UNIVERSITY OF CALIFORNIA

Santa Barbara

Large Scale Total Synthesis Towards (–)-Muironolide A

&

Asymmetric Chemistry of Carboxylic Acids Using Chiral Lithium Amides as Non-Covalent Chiral Auxiliaries

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

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Professor Craig J. Hawker

December 2019

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October 2019

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PUBLICATIONS

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2. **Yu, K.**; Lu, P.; Jackson, J. J.; Nguyen, T. D.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian, A. "Lithium Enolates in the Enantioselective

Construction of Tetrasubstituted Carbon Centers with Chiral Lithium Amides as Noncovalent Stereodirecting Auxiliaries" *J. Am. Chem. Soc.* **2017**, *139*, 527-533.

3. Zhu, R.; **Yu, K.**; Gu, Z. "N-Bromoacetamide-mediated Domino Cyclization and Elimination of Homoallylic Trichloroacetimidates: a Novel Approach Toward the Synthesis of 1-Bromo-2-amino-3-butene Derivatives" *Org. Biomol. Chem.* **2014**, *12*, 6653-6660.

4. Xie, Y.; **Yu, K.**; Gu, Z. "Stereoselective Synthesis of 1,3-Amino Alcohols by the Pd-Catalyzed Cyclization of Trichloroacetimidates" *J. Org. Chem.* **2014**, *79*, 1289-1302.

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ABSTRACT

Large Scale Total Synthesis Towards (–)-Muironolide A

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Asymmetric Chemistry of Carboxylic Acids Using Chiral Lithium Amides as Non-Covalent Chiral Auxiliaries

By

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In order to enable detailed biological studies with the naturally occurring enantiomer and test the feasibility of our synthetic route, a large scale synthesis towards (–)-muironolide A was carried out. A series of optimizations on the synthesis of different fragments were achieved, including the diene amine and chlorocyclopropyl ketide. A newly designed chiral terpyridine was tested as a ligand in the key intramolecular Diels-Alder reaction.

In another research area of mine, chiral lithium amides derived from C_2-symmetric tetraamines, acting as non-covalent chiral auxiliaries, provide a pathway to generate tetrasubstituted and quaternary carbon centers directly through the α-functionalization of carboxylic acids. All chiral amines can be easily recovered by acid-base extraction with no loss of enantiomeric purity. Crystallographic, spectroscopic and computational studies elucidated the structure of an enediolate-lithium amide mixed aggregate as the origin of stereoselectivity. Using a similar aggregation process, the alkylation of β,γ-unsaturated carboxylic acid was also

achieved with both high enantio- and regioselectivity. This method was attempted as a key step to establish the chirality in the concise synthesis of (–)-morphine, and resulted in a competing conjugate addition of dienoic acid in the presence of an activated alkyl halide. Inspired by the competition reaction, a method of enantioselective Michael-initiated ring closure was developed. Carbocyclic compounds can be synthesized in good to excellent stereoselectivities, providing a streamlined approach to the construction of densely functionalized cycloalkanes.

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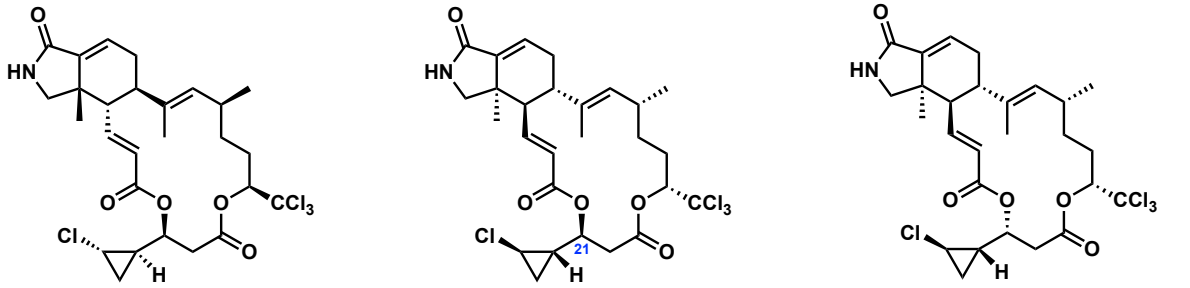
Chapter 1. Large-Scale Total Synthesis Towards (–)-Muironolide A

1.1 Introduction

In 2009, Molinski group reported the first isolation of a remarkable marine natural product, muironolide A (**1-1**), from the sponge of the *Phorbas* species in 90 μg (152 nmol) scale.[1] The primary bioactivity study presented the polyketide possessed cytotoxic activity against the HCT-116 solid colon tumor cell line (IC_{50} 96.5 μg/mL) and antifungal activity against *Cryptococcus neoformans* (MIC 16 μg/mL).

By using the lately developed nanoscale NMR techniques[2], the structure of muironolide A was determined (**1-2**) as a fascinating tetrachlorinated structure of a 16-membered diester lactone with a hexahydro-1H-isoindolone, a trichlorocarbinol ester, and chlorocylcopropane subunits.



1-1
(–)-muironolide A
(natural enantiomer)

1-2
C21-*epi*-(+)-muironolide A
(originally assigned by Molinski)

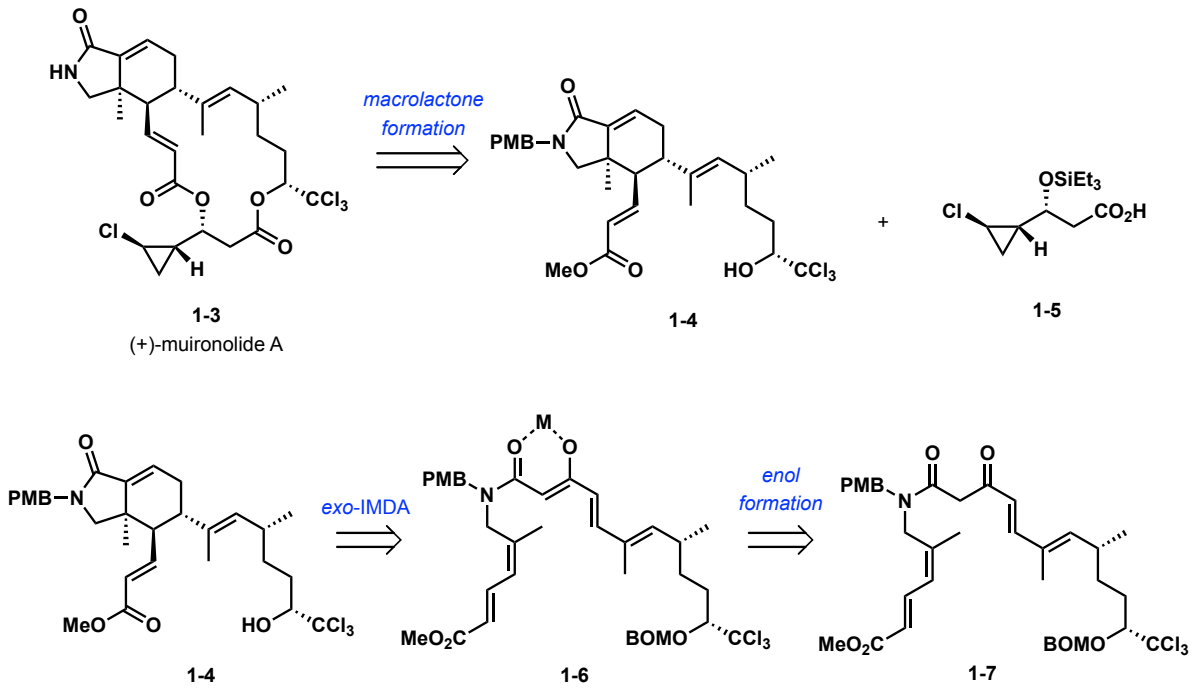
1-3
(+)-muironolide A
(synthesized and revised by Zakarian)

Figure 1-1. Natural and originally assigned structures of muironolide A

In 2015, Zakarian group introduced the first total synthesis towards muironolide A.[3] In the report, both molecules with originally assigned (**1-2**) and revised structures (**1-3**) were

synthesized, showing that the stereochemistry of C21 in **1-2** was assigned oppositely by Molinski and (–)-enantiomer (**1-1**) is naturally abundant.

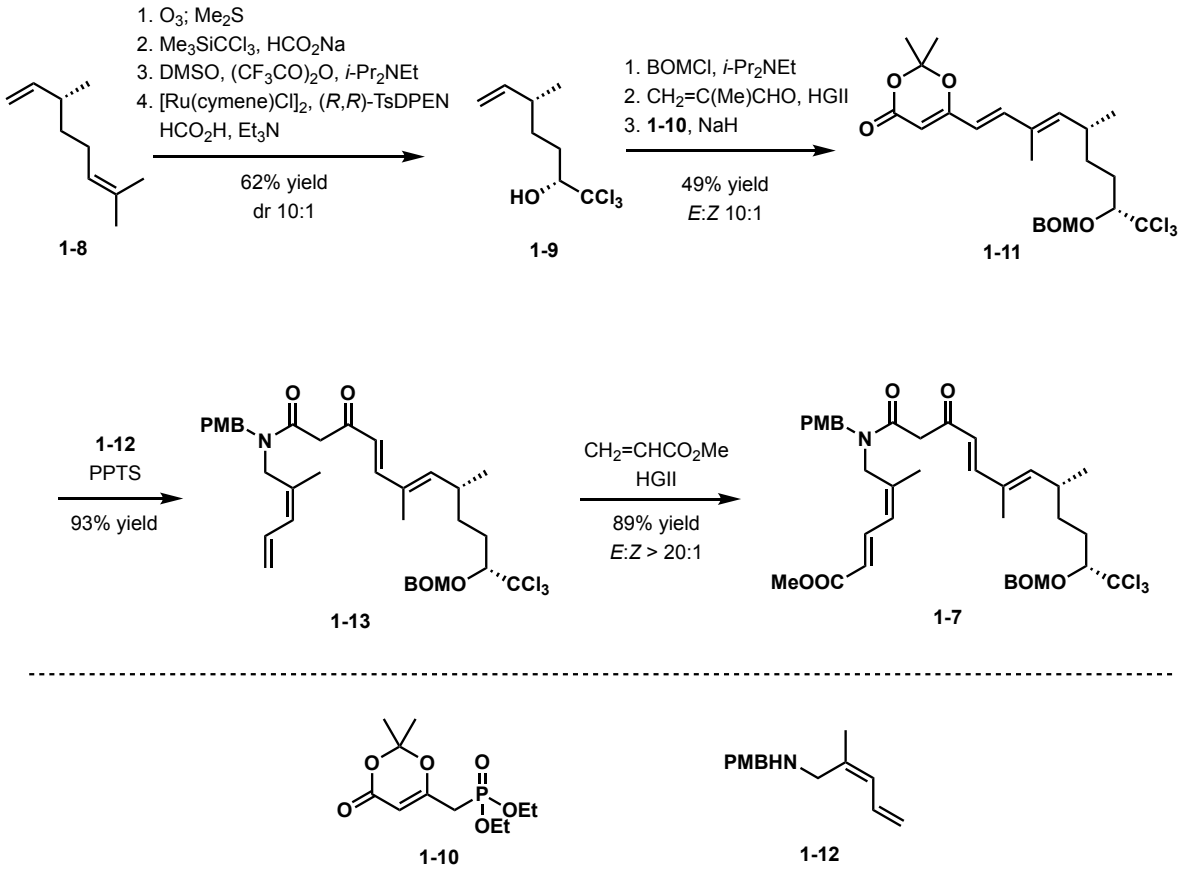
In our 2015 total synthesis, the 16-membered macrolactone of muironolide A was designed to be constructed in the late stage between trichlorocarbinol (**1-4**) and the chlorocylcopropane ketide (CCK, **1-5**) acid. To generate **1-4**, a key *exo*-selective lanthanide-catalyzed intramolecular Diels-Alder (IMDA) reaction of β-ketoamide **1-7**, through an enolate chelate **1-6**, was applied in the construction of hexahydro-1*H*-isoindolone moiety.



Scheme 1-1. Retrosynthetic design of Zakarian's synthesis towards (+)-muironolide A

Starting from commercially available (+)-citronellene (**1-8**), trichlorocarbinol **1-9** was generated in 62% yield and 10:1 diastereomeric ratio, in a sequence of selective ozonolysis, addition of trimethyl(trichloromethyl)silane, Swern oxidation and asymmetric transfer hydrogenation. The following benzyloxymethylation, cross-metathesis with methacrolein and olefination with phosphate **1-10** provided the dioxinone **1-11** in 49% yield with 10:1 *E*:*Z*-

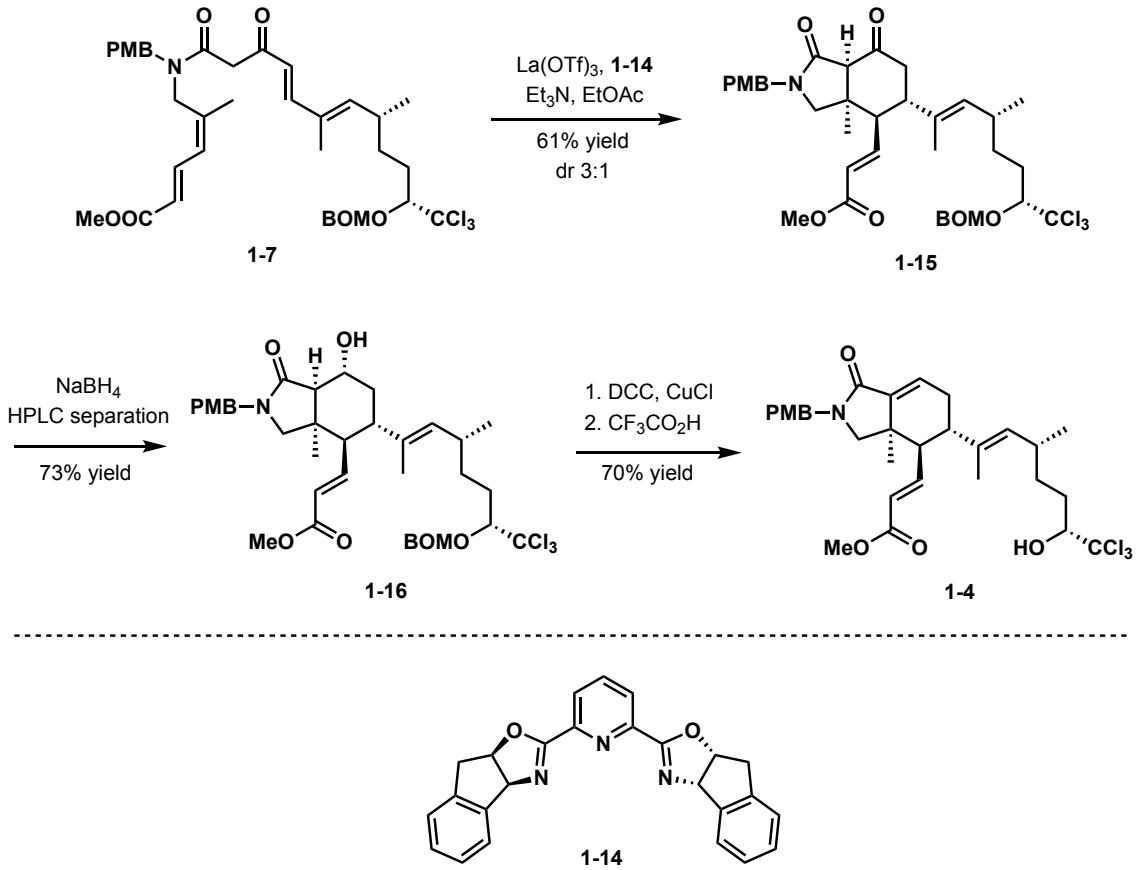
selectivity. Refluxing the toluene solution of **1-11** and diene amine **1-12** afforded 93% yield of the amide **1-13**, which was then converted to the IMDA precursor **1-7** as a single *E*-isomer by another cross-metathesis with methyl acrylate.



Scheme 1-2. Synthesis of IMDA precursor 1-7

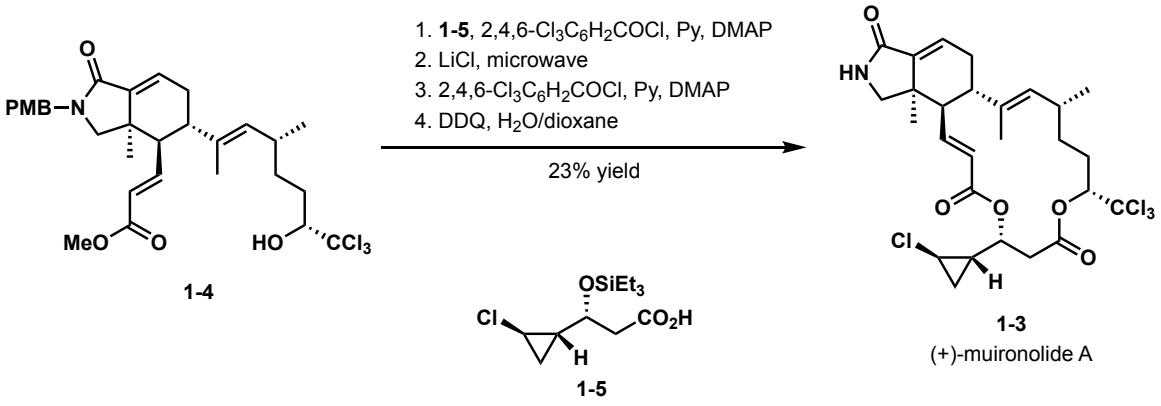
After a significantly detailed study on the intramolecular Diels-Alder reaction[4], the *exo*-selective asymmetric cyclization of β-ketoamide **1-7** was carried out with lanthanide and PYBOX ligand **1-14**, providing 61% yield of a 3:1 diastereomer mixture of isoindolone **1-15**. Reduction with sodium borohydride followed with a necessary preparative HPLC separation afforded 73% yield of desired diastereomer **1-16**, together with 21% yield of undesired isomer.

Trichlorocarbinol **1-4** was then obtained via dehydration of **1-16** with DCC and CuCl, followed by treating with trifluoroacetic acid.



Scheme 1-3. Synthesis of trichlorocarbinol 1-4 via IMDA reaction

The end game to (+)-muironolide A was carried out as follow: 1) esterification of the coupling between trichlorocarbinol **1-4** and CCK acid **1-5** under Yamaguchi conditions; 2) cleavage of the methyl ester and the silyl ether with LiCl under microwave irradiation at 170 ºC; 3) ring closure with an intramolecular Yamaguchi esterification; 4) removal of parамethoxybenzyl group with DDQ oxidation. As the result, (+)-muironolide A, with a revised structure (**1-3**), was enantioselectively synthesized in 25 mg as white solids, of which ^{13}C-NMR data matched with that reported for the natural substance.



Scheme 1-4. End game with macrolactonization with CCK acid 1-5

In Molinski's primary study of naturally isolated muironolide A, with the extremely small amount (90 μg), saying "nearly extinct", only fragmented studies on its bioactivity were reported.[1] In our 2015 total synthesis, 25 mg of (+)-muironolide A was obtained, which was confirmed enantiomeric to the natural sample. Thus, for a further thorough biostudy on the natural enantiomer, we would like to synthesis grams of (–)-muironolide A, and also this project could prove the feasibility of our synthetic design and methods in the larger scale.

Though no change was applied on the synthetic strategy in general, to scale up the total synthesis of (–)-muironolide A, abundant efforts were necessarily to be done:

1) Preparation of (–)-citronellene in high chemical and enantiomeric purity.
2) Optimization of the preparation of diene amine **1-12**.
3) Synthesis of CCK acid with correct optical property.
4) Optimization of the exo-IMDA reaction.

In the following discussion, details will be demonstrated in the achievement of the first three points mentioned above. Multi-gram scale synthesis towards the IMDA precursor will be gone

through in detail. Also, the *exo*-IMDA reaction with a new type of terpyridine ligand will be illustrated.

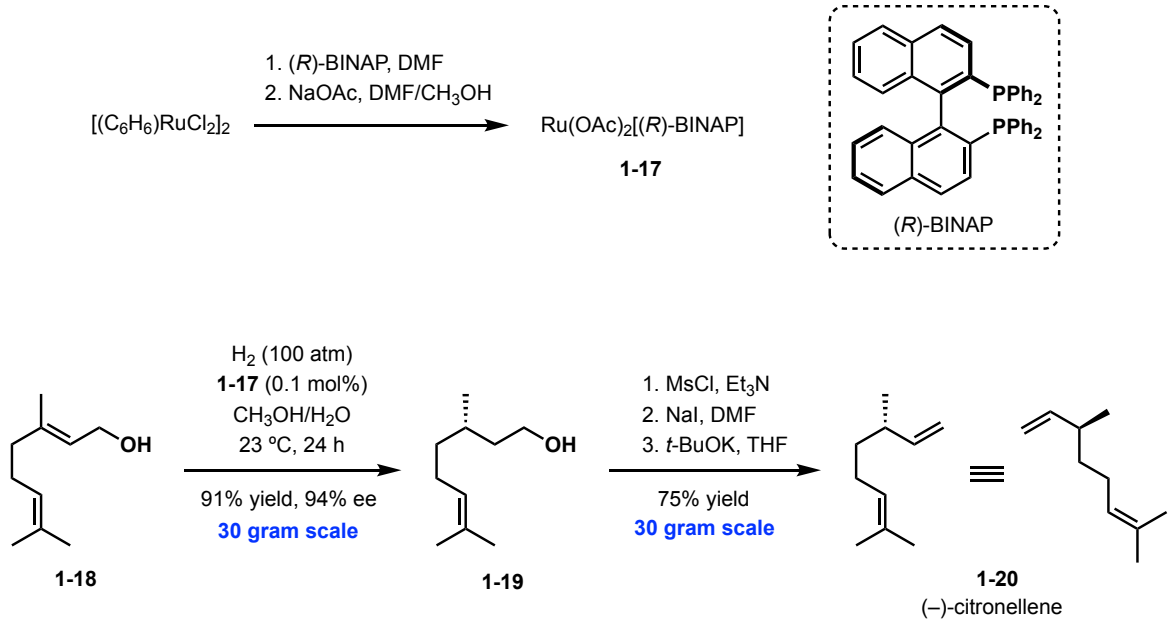
1.2 Preparation of (–)-Citronellene

Optically pure citronellene was the very first starting material in the total synthesis. To finally synthesize 2~5 grams of (–)-muironolide A, considering the further optimization in the later steps, around 100 grams of (–)-citronellene were required. Not like its enantiomer, the commercially available (–)-citronellene has rather lower quality: the chemical purity was only ~90% and the optical purity was ~85%. Therefore, it is necessary to freshly synthesize (–)-citronellene with high chemical and enantioselective purity in hundreds gram scale.

In 1995, Noyori *et. al.* introduced an asymmetric hydrogenation of allylic alcohols using chiral BINAP-Ru complexes (**1-17**).[5] Following the Noyori's method, in our practice, the chiral ruthenium complex **1-17**, was synthesized from the ligand exchange between benzeneruthenium(II) chloride dimer and (*R*)-BINAP, followed by the addition of sodium acetate, affording 2.3 grams of prouduct as fine yellow powdery crystals. BINAP-Ru complex can be oxidized in the presence of air, much more rapidly if it stays in solution. Therefore, the fresh made **1-17** was stored in glovebox and all procedure involved with this complex had to be carried out with thoroughly degassed solvents.

Geraniol (**1-18**), with 0.1 mol% of chiral catalyst **1-17** in methanol solution, was treated with hydrogen at 100 atm pressure in autoclave in 30-gram scale. After 24-hour hydrogenation at room temperature, (*S*)-citronellol (**1-19**) was obtained in 78-91% yield with up to 94% ee. The following sequential mesylation, iodination and elimination provided up to 75% yield of (–)-citronellene (**1-20**) in 30-gram scale, with no significant decay of the optical purity.

Combining all the batches of the home-made products, 113 grams of **1-20** was synthesized with 91% enantiomeric excess.



Scheme 1-5. Large-scale synthesis of (–)-citronellene

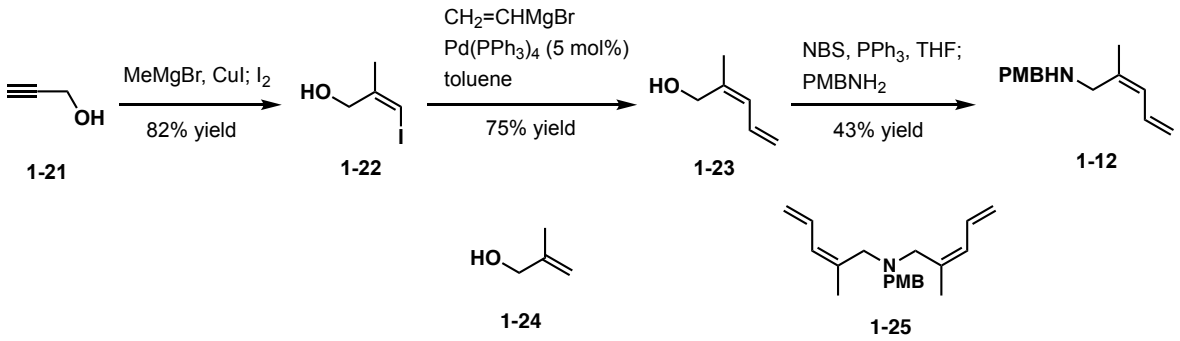
1.3 Optimization of the Preparation of Diene Amine 1-12

1.3.1 Original Synthesis of Diene Amine 1-12

In our original synthesis, PMB-protected diene amine **1-12** was prepared from propargyl alcohol (**1-21**) over three steps in gram scale.[4a] (*Z*)-3-Iodo-2-methylprop-2-en-1-ol (**1-22**) was synthesized in 82% yield via the copper-catalyzed methylmagnesation of propargyl alcohol followed by the iodine quench. Kumada coupling[6] with vinylmagnesium bromide[7] in toluene at room temperature afforded 75% yield of (*Z*)-2-methylpenta-2,4-dien-1-ol (**1-23**), and one-pot Appel reaction-amination provided **1-12** in 43% yield.

In the Kumada coupling, the reduced compound, 2-methylprop-2-en-1-ol (**1-24**), was generated as byproduct, which shared the similar polarity with **1-23** and became a trouble in

the purification, especially when the synthesis scale increased. In the following elaboration of the hydroxy group, the yield was only 43% due to the formation of the byproduct, dialkylated PMB-amine **1-25** (up to 16% yield). Also, a more convenient procedure needed to be developed for the purification of **1-12**, especially for the large-scale synthesis.

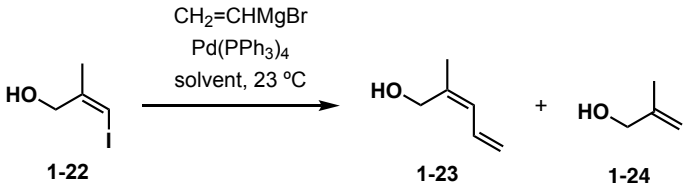


Scheme 1-6. Original synthesis of diene amine 1-12

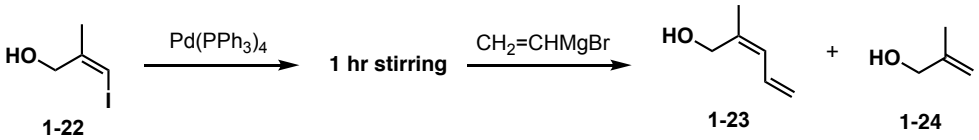
1.3.2 Optimization of Kumada Coupling

The optimization of Kumada coupling was carried out as shown in Table 1-1. In the original procedure, $Pd(PPh_3)_4$ was firstly added into the toluene solution of iodoallylic alcohol **1-22** and the resultant solution was stirred for 1 hour. Vinylmagnesium bromide (2.0 equiv.) was then added to the reaction mixture to finish the coupling. In one-gram scale reaction, 68% yield of ideal product **1-23** was isolated after 2-hour reaction, with a fully conversion of **1-22**, while from the crude ^{1}H-NMR, the ratio between **1-23** and **1-24** was 4.0:1 (entry 1). Decreasing palladium loading to 1 mol% slowed down the reaction (entry 2): 2-hour coupling afforded 41% yield of **1-23** and 11% recovery of substrate **1-22**. The ratio between 1-23 and 1-24 dropped to 2.2:1, showing that the occupation of **1-24** would increase with using smaller catalyst loading.

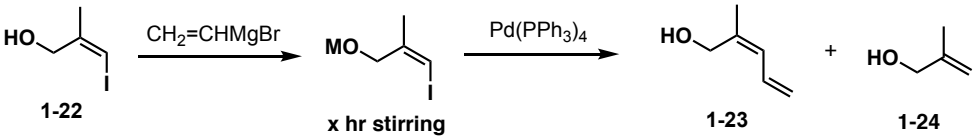
Table 1-1. Optimization of Kumada coupling towards 1-23[a]



Sequence A



Sequence B



Sequence A

entry	equiv. of Grignard reagent	cat. loading (mol%)	solvent	ratio (**1-23**:**1-24**)	isolated yield of **1-23**
1	2.0	5.0	toluene	4.0:1	68%
2	2.0	1.0	toluene	2.2:1	41%
3	2.0	1.0	THF	3.3:1	68%
4	2.5	1.0	THF	3.7:1	75%
5	2.5	0.5	THF	2.5:1	52%

Sequence B

entry	equiv. of Grignard reagent	cat. loading (mol%)	solvent	pre-stirring (x hr)	ratio (**1-23**:**1-24**)[b]	isolated yield of **1-23**
6	2.5	1.0	THF	2	4.8:1	80%
7	2.5	1.0	THF	6	9.0:1	88%
8	2.5	1.0	THF	12	9.0:1	83%
9[c]	**2.5**	**1.0**	**THF**	**6**	**9.1:1**	**90%**
10[d]	1.5	1.0	THF	2	2.2:1	-
11[e]	1.5	1.0	THF	2	1.4:1	-

[a] Experiments were performed on a 5.0 mmol scale. [b] The ratio between **1-23** and **1-24** was determined by crude ^{1}H-NMR. [c] Experiment was performed on a 40 mmol scale (8 g of **1-22**). [d] 1.0 equiv. of *i*-Pr_2NLi was added with vinylmagnesium bromide. [e] 1.0 equiv. of NaH was added with vinylmagnesium bromide.

Maintaining the catalyst loading as 1 mol%, when THF was used as solvent instead of toluene, the substrate could be converted completely in 2 hours with 68% yield of **1-23** (entry 3). Slight increase on the equivalent of vinylmagnesium bromide (2.5 equiv.) kept improving on the result (entry 4, 75% yield, **1-23**:**1-24** = 3.7:1), while lower catalyst loading to 0.5 mol% decreased the ratio between the coupled product and reduced product (entry 5).

The sequence of adding substrates and catalyst was noticed to be vital to the generation of **1-24**. Instead of pre-stirring with palladium catalyst (**sequence A**), iodoallylic alcohol **1-22** was firstly treated with vinylmagnesium bromide with a significant time of stirring at room temperature, before the addition of the catalyst to carry out the coupling (**sequence B**). With

2.5 equiv. of Grignard reagent and 2-hour pre-stirring, the coupling in one-gram scale afforded 80% yield of **1-23** (entry 6). The formation of **1-24** got further limited by increasing the time of pre-stirring of two substrates to 6 hours (entry 7, 88% yield, **1-23**:**1-24** = 9.0:1). Interestingly, higher yield and ratio was noticed when the coupling was carried out in 8.0 g scale (entry 9). Using other bases like LDA or NaH for the deprotonation in the pre-stirring, together with 1.5 equivalent of vinylmagnesium bromide, provided dramatic decrease on the ratio between **1-23** and **1-24**, 2.2:1 and 1.4:1, respectively.

1.3.3 Optimization of Amination with Paramethoxybenzyl Amine

There were three problems in the original conversion from diene alcohol **1-23** to PMB-protected diene amine **1-12**: First, it was hard to be removed triphenylphosphine oxide, the byproduct of Appel reaction, after the one-pot procedure; Second, the dialkylated product **1-25** was formed in the amination, sharing the similar polarity with ideal product **1-12**; Third, the excess amount of paramethoxybenzyl amine ($PMBNH_2$) was also close with **1-12**, and needed to be removed via some other method instead of column chromatography.

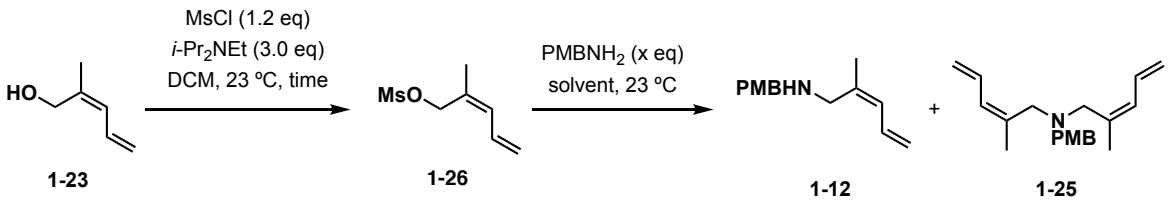
To avoid dealing with triphenylphosphine oxide, mesylation was chosen for generating the leaving group for the following amination. After four-hour stirring with methanesulfonyl chloride and diisopropylethylamine in DCM at room temperature, 2.0 equiv. of $PMBNH_2$ was added and the resultant mixture was quenched by saturated $NaHCO_3$ aqueous solution after 12 hours, affording 51% yield of **1-12** and 16% yield of byproduct **1-25** (entry 1). Direct filtration to remove the precipitate from the reaction mixture during workup provided almost identical result (entry 2). Shortening the mesylation time to 30 min did not affect result significantly

(entry 3), while increase on the amount of $PMBNH_2$ (3.0 equiv.) improved the yield of **1-12** by around 10% (entry 4), but the dialkylation of $PMBNH_2$ still yielded around 15%.

Screening on the solvent system for the amination[8] demonstrated that more polar aprotic solvent did good limitation on the dialkylation: using DCM/THF (1:1) mixed solvent for the amination limited the yield of **1-25** to 9%, while the yield of **1-12** was maintained as 56% (entry 5). The yield of dialkylated product got suppressed to 4% when *N*-methyl-2-pyrrolidone (NMP) was applied in the solvent system (DCM/NMP 4:1, entry 6). Notice that freshly distilled NMP was required for the amination to avoid the competition with the hydrolysis of **1-26** back to **1-23** by the moisture in the solvent.

Excess of $PMBNH_2$ could be partially removed by the basic workup with 1M NaOH aqueous washing, which eased the isolation of target diene amine from the crude mixture: 75% yield of amine **1-12** was obtained in test scale (entry 7). In larger scale synthesis, the yield of **1-12** was 70% (entry 8).

Table 1-2. Optimization of amination with $PMBNH_2$[a]



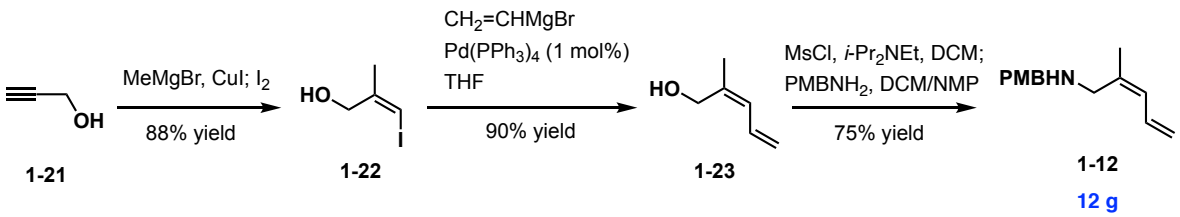
entry	mesylation time	equiv. of $PMBNH_2$	amination solvent	isolated yield of 1-12	isolated yield of 1-25
1[b]	4 h	2.0	DCM	51%	16%
2[c]	4 h	2.0	DCM	50%	16%
3[b]	30 min	2.0	DCM	46%	15%

4[b]	30 min	3.0	DCM	56%	15%
5[b]	30 min	3.0	DCM/THF (1:1)	56%	9%
6[b]	30 min	3.0	DCM/NMP (4:1)	62%	4%
7[d]	30 min	3.0	DCM/NMP (4:1)	75%	4%
8[d,e]	30 min	3.0	DCM/NMP (4:1)	70%	-

[a] Experiments were performed on a 2.0 mmol scale. [b] The reaction mixture was worked up with saturated $NaHCO_3$ aqueous solution. [c] The salt precipitate was directly filtrated during the workup instead of using any basic aqueous solution. [d] The reaction mixture was worked up with 1M NaOH aqueous solution. [e] Experiment was performed on a 71 mmol scale (7 g of **1-23**).

1.3.4 Optimized Large-Scale Synthesis of Diene Amine 1-12

Based on the above optimization, the large-scale synthesis of diene amine **1-12** was proceeded with good results: Copper-catalyzed methylmagnesation of propargyl alcohol followed by iodination afforded 88% yield of **1-22** in 30 gram scale; Kumada coupling with optimized sequence of adding substrates provided 90% yield of diene alcohol **1-23** in 15 gram scale; the elaboration of hydroxy group with $PMBNH_2$ was carried out in 7 gram scale, yielding 75% of **1-12**. Finally, 12 grams of PMB-protected diene amine **1-12** was synthesized, ready for the generation of β-keto amide **1-13**.



Scheme 1-7. Large-scale synthesis of diene amine 1-12

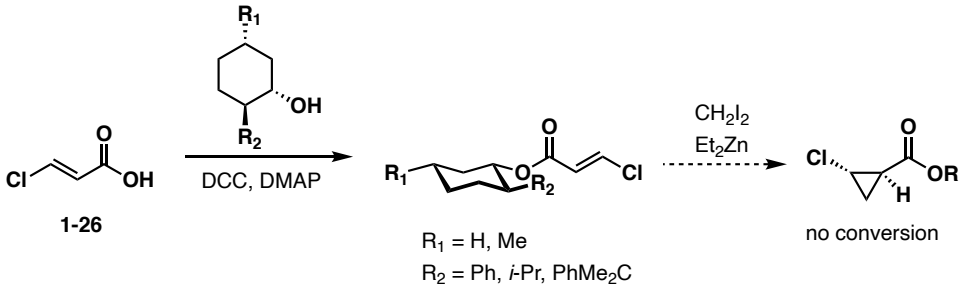
1.4 Synthesis of Chlorocyclopropyl Ketide Acid

Due to the unsuccess on the direct asymmetric cyclopropanation[9] of (*E*)-3-chloroacrylic acid (**1-26**)[10] with chiral auxiliaries (Scheme 1-8a), our effort was focusing on the optimization of the original synthesis of CCK acid and around 8 grams of target compound (**1-33**) with correct chirality was successfully obtained.

The synthesis started with the reactions obtaining chiral β-hydroxy ester **1-28**.[11] The aldol reaction of the acrolein with the lithiated *tert*-butyl acetate afforded 93% yield of racemic *tert*-butyl 3-hydroxypent-4-enoate. Enzymatic resolution of the β-hydroxy ester was accomplished by stirring with vinyl acetate and PS Amano lipase in pentane with molecular sieves at 30 ºC, yielding 48% of **1-28** and up to 97% ee.

The diastereoselective Simmons-Smith cyclopropanation [12] of **1-28** with chlorodiiodomethane and diethylzinc with an optimized condition at –55 ºC for 24 hours provided the chlorocylcopropane **1-29** in 75% yield and 8:1 dr. Comparing to the same step in the original synthesis, the yield and dr value were both increased from 50% and 5:1, respectively. The reversal of the stereochemistry of the β-hydroxy group was carried out by a sequential Jones oxidation and asymmetric reduction. The asymmetric reduction [13] with $[Ru(cymene)Cl_2]_2$ and (*S*,*S*)-TsDPEN afforded the CCK unit **1-31** with the desired stereochemistry in 73% yield and 22:1 dr, which was an excellent improvement from the original reduction, especially on diastereoselectivity (original dr 5:1). The CCK acid **1-33** was finally synthesized by a removal of *tert*-butyl group and silylation with chlorotriethylsilane in 85% yield over two steps.

a. Unsuccess asymmetric cyclopropanation

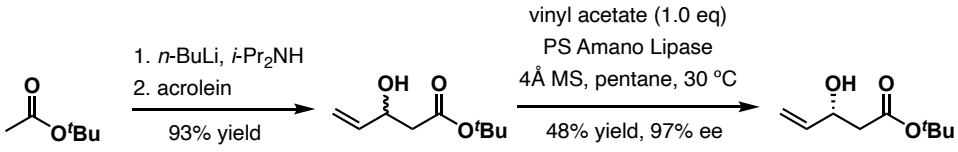


1-26

R_1 = H, Me
R_2 = Ph, *i*-Pr, $PhMe_2C$

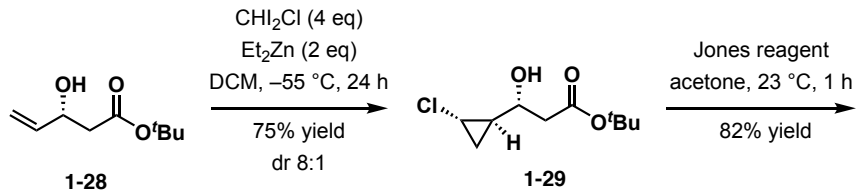
no conversion

b. Preparation of chiral hydroxy pentenoate

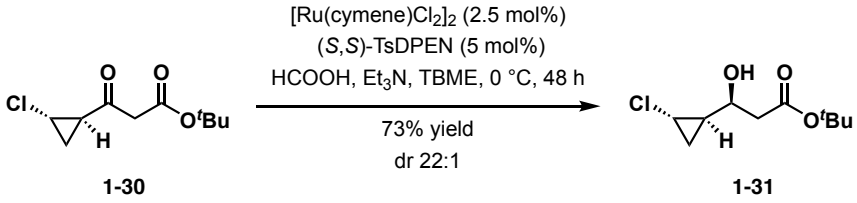


1-27 (±)-1-28 1-28

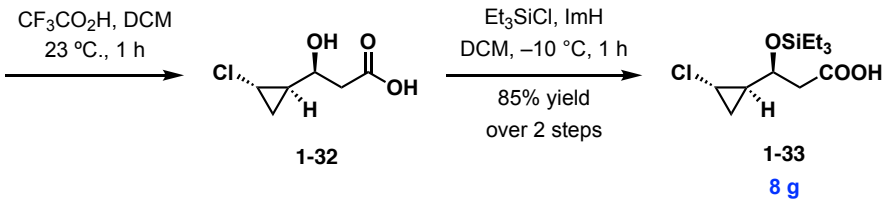
c. Preparation of CCK unit



1-28 1-29



1-30 1-31



1-32 1-33

8 g

Scheme 1-8. Synthesis of CCK acid

All steps mentioned above were proceeded in 4 ~ 10 gram scale, and in total, 8 grams of CCK acid **1-33** was synthesized, which was stored as a solution of benzene frozen at –20 ºC to avoid the possible racemization.

1.5 Synthesis of IMDA Precursor

Multigram scale synthesis towards the IMDA precursor, β-keto amide, is demonstrated in Scheme 1-9. The synthetic route was generally followed the published one, but several steps were optimized to fit the feasibility of the larger scale. Also, some notable details in this synthesis will be pointed out.

The freshly distilled (–)-citronellene was bubbled with ozone at –78 ºC in DCM and quenched with dimethyl sulfide. The crude of the ozonolysis was purified via fractional distillation to remove Me_2S and DCM, and the residue was directly used into the next step. In the presence of catalytic amount of sodium formate, the addition of trimethyl(trichloromethyl)silane onto the aldehyde in DMF at room temperature delivered the diastereomeric mixture **1-34**. Notice that trimethyl(trichloromethyl)silane could be synthesized in 80% yield in 20 gram scale, but the yield dropped dramatically when the scale kept increase. Both reactions could be accomplished in 30 gram scale, and the total yield of **1-34** was 81%.

Swern oxidation of **1-34** with DMSO/$(CF_3CO)_2O$ afforded the trichloromethyl ketone with no side reaction in 83% yield. Interestingly, the oxidation could not be fully finished in large-scale, and around 10% of substrate alcohol could be recovered after the column chromatography. The following asymmetric hydrogen transfer[13] was carried out with deducted amount of catalyst: both ruthenium complex and chiral ligand was used one tenth of the original catalyst loading. With an extended reaction time at 0 ºC, 0.25 mol% $[Ru(cymene)Cl_2]_2$

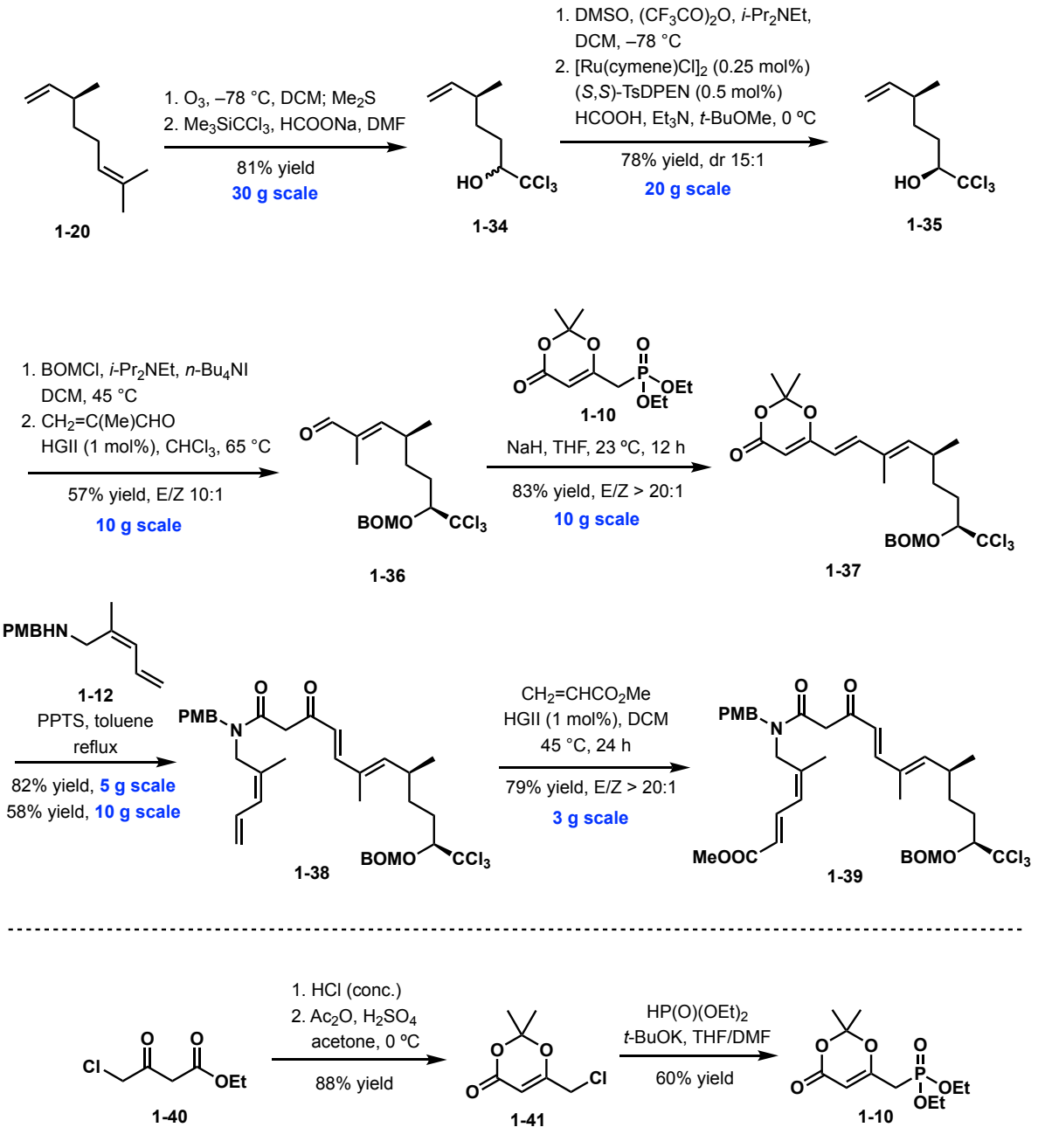
and 0.5 mol% (*S*,*S*)-TsDPEN finished the 20 gram scale of reduction with a near-quantitative yield of the chiral trichlorocarbinol **1-35** with an improved diastereoselectivity (dr 15:1).

Benzyloxymethylation was carried out smoothly at 45 ºC when the scale increased to 10 grams, with around 90% yield, followed by the cross-metathesis with methacrolein catalyzed by Hoveyda-Grubbs II catalyst (HGII). The optimization on the metathesis demonstrated the yield and *E*/*Z*-selectivity would not be affected when the catalyst loading limited from 3 mol% to 1 mol%, resulting 63% yield of aldehyde **1-36** (79% brsm) with 10:1 *E*-selectivity in 10 gram scale. However, when the catalyst loading decreased to 0.5 mol%, we noticed that a significant increase on the formation of possible dimerization of substrate.

Horner-Wadsworth-Emmons reaction of aldehyde **1-36** and dioxinone phosphonate **1-10** was accomplished in 10 gram scale with sodium hydride as base in THF, affording 83% yield of the dioxinone **1-37** and excellent *E*-selectivity (*E*/*Z* >20:1). Dioxinone phosphonate **1-10** was prepared from the commercially available ethyl 4-chloro-3-oxobutanoate (**1-40**). Overnight hydrolysis with concentrated hydrochloric acid delivered 91% yield of 4-chloro-3-oxobutanoic acid, which was then condensed with acetone in the presence of acetic anhydride and sulfuric acid, affording chlorodioxinone **1-41** in almost quantitative yield. Deprotonated by potassium *tert*-butoxide[14], diethylphosphite reacted with **1-41**, and 60% of phosphonate **1-10** was obtained. The rather low yield is due to the hard isolation of target compound from the crude with different type of phosphites.

The solution of dioxinone **1-37** and PMB-protected diene amine **1-12** in toluene was under reflux with catalytic amount of pyridinium *p*-toluenesulfonate (PPTS), and 82% yield of β-keto amide **1-38** was obtained in 5 gram scale. Surprisingly, the yield dropped sharply when the reaction scale increased (58% yield, 10 g scale). All the rest of dioxinone was noticed as

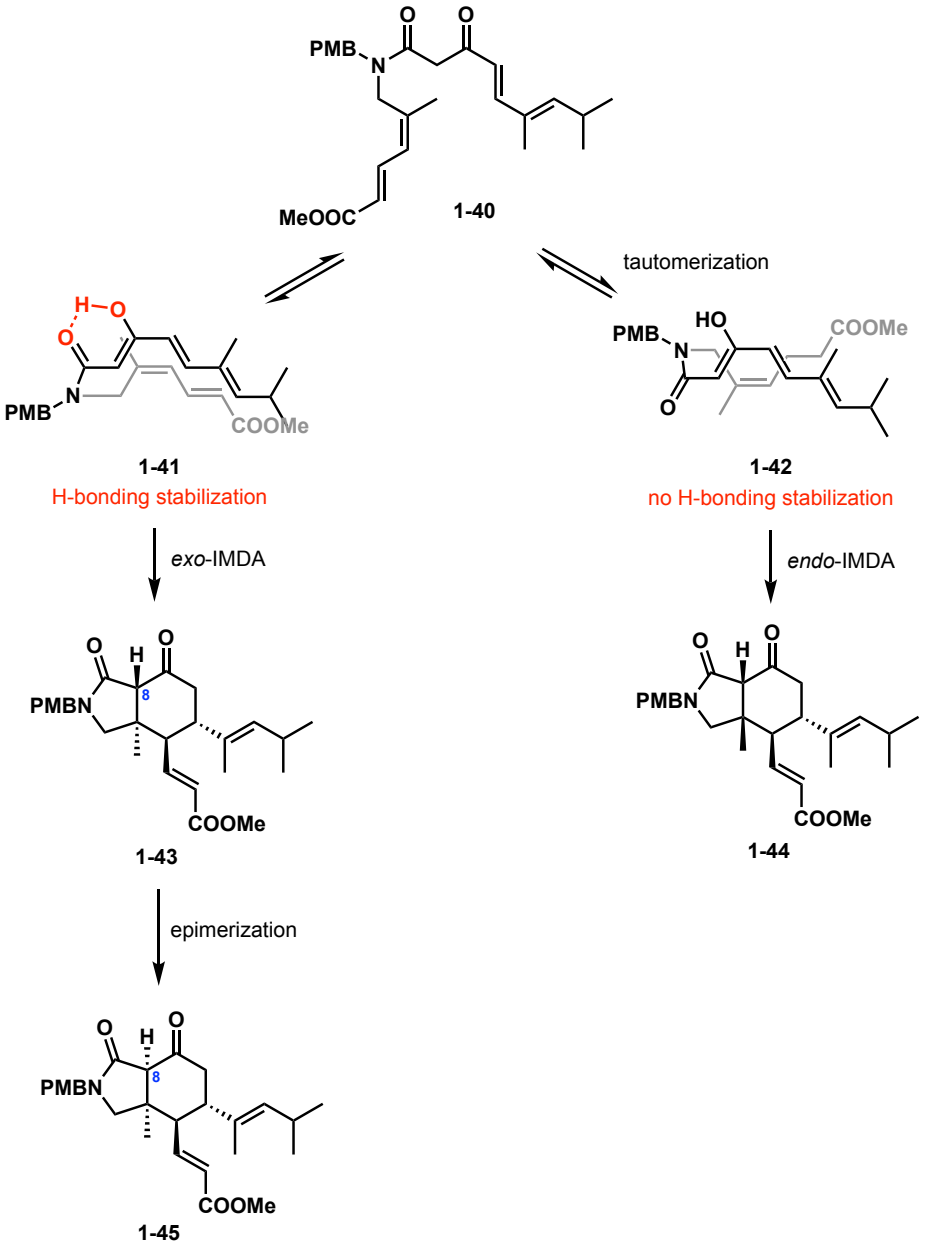
decomposition after further heating. The synthesis of IMDA precursor **1-39**, was completed by the optimized cross-metathesis with methyl acrylate and low catalyst loading of Hoveyda-Grubbs II catalyst (1 mol%). After a series of effort, there are around 7 grams of IMDA precursor **1-39** and 18 grams of its precursor **1-38** in store.



Scheme 1-9. Synthesis of IMDA precursor 1-39

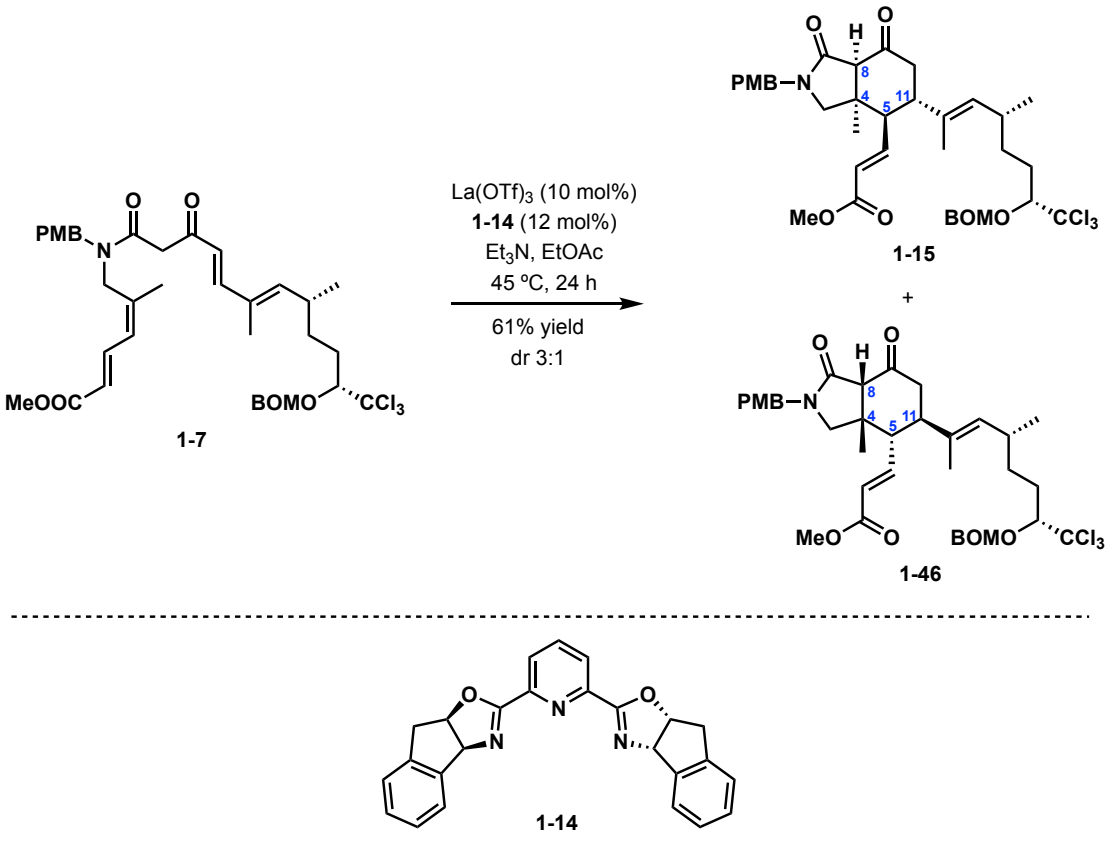
1.6 Efforts on the Improvement of IMDA Reaction and Late Stage

After obtaining desired stereoisomer of β-keto amide **1-39**, a further investigation on the asymmetric intramolecular Diels-Alder (IMDA) reaction was performed.



Scheme 1-10. Model study of IMDA reaction

In previous model study of the IMDA reaction[4a], the high *exo*-selectivity for the construction of the hexahydro-1*H*-isoindolone ring system had been demonstrated. We found that the thermal cycloaddition of **1-40** can be performed by heating the substrate at 110 ºC in toluene with no existence of additive, resulting over 20:1 diastereocontrol favoring on the *exo*-IMDA product. As shown in Scheme 1-10, the β-keto amide can tautomerize to the hydroxy diene intermediate, which got stabilized by intramolecular hydrogen-bonding (**1-41**) and went through the *exo*-cyclization. The following C8-epimerization afforded desired cycloadduct **1-45** with the desired stereochemistry, while the disfavored *endo*-product **1-44** had to be generated with a disruption of the hydrogen bond (**1-42**).

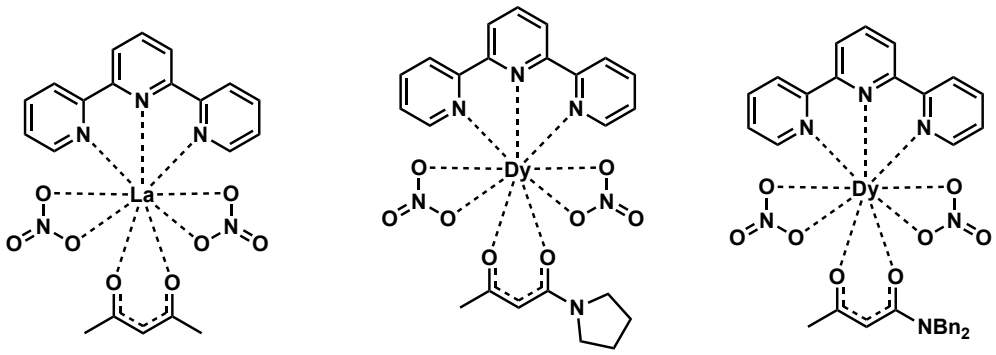


Scheme 1-11. Asymmetric IMDA reaction with La(OTf)$_3$ and chiral PYBOX 1-14

We also disclosed chelated enolate with lanthanide could also catalyzed the *exo*-IMDA cyclization with excellent diastereoselectivity (dr >20:1), and a screen of chiral ligand (including PYBOX, BOX, BINOL, chiral amides, etc.) revealed that the stereoselectivity on C4,C5,C8,C11 can be achieved at a moderate level.[4b] In the practical synthesis of (+)-muironolide A[3], by being treated with 10 mol% $La(OTf)_3$, 12 mol% of PYBOX ligand **1-14**, and triethylamine in ethyl acetate at 45 ºC for 24 hours, β-keto amide **1-7** converted to cyclized product **1-15**, as a 3:1 inseparable mixture with its C4,C5,C8,C11-diastereomer (Scheme 1-11). It is very necessary to improve the diastereoselectivity of *exo*-cyclization because of the inseparable diastereomers, of which the reduction products had to be separated by preparative HPLC, not feasible or efficient for the multigram scale synthesis with the technique in our group. Thus, a new type of chiral ligand for *exo*-IMDA reaction is required for the later synthesis towards (–)-muironolide A.

2,2':6',2"-Terpyridine has been described as a type of ligand coordinating with lanthanide.[15] Typically, Fukuda group[15a,c] have introduced the lanthanide complexes with terpyridine and β-oxo carbonyl compound, $Ln(terpy)(acac)(NO_3)_2$ (like **1-47**), and our group[4b] demonstrated the X-ray crystallographic study on the nonsymmetric heteroleptic complexes of lanthanides with β-oxo carbonyl compounds (**1-48** and **1-49**), suggesting the chiral terpyridine might be a good target in the development of *exo*-IMDA reaction.

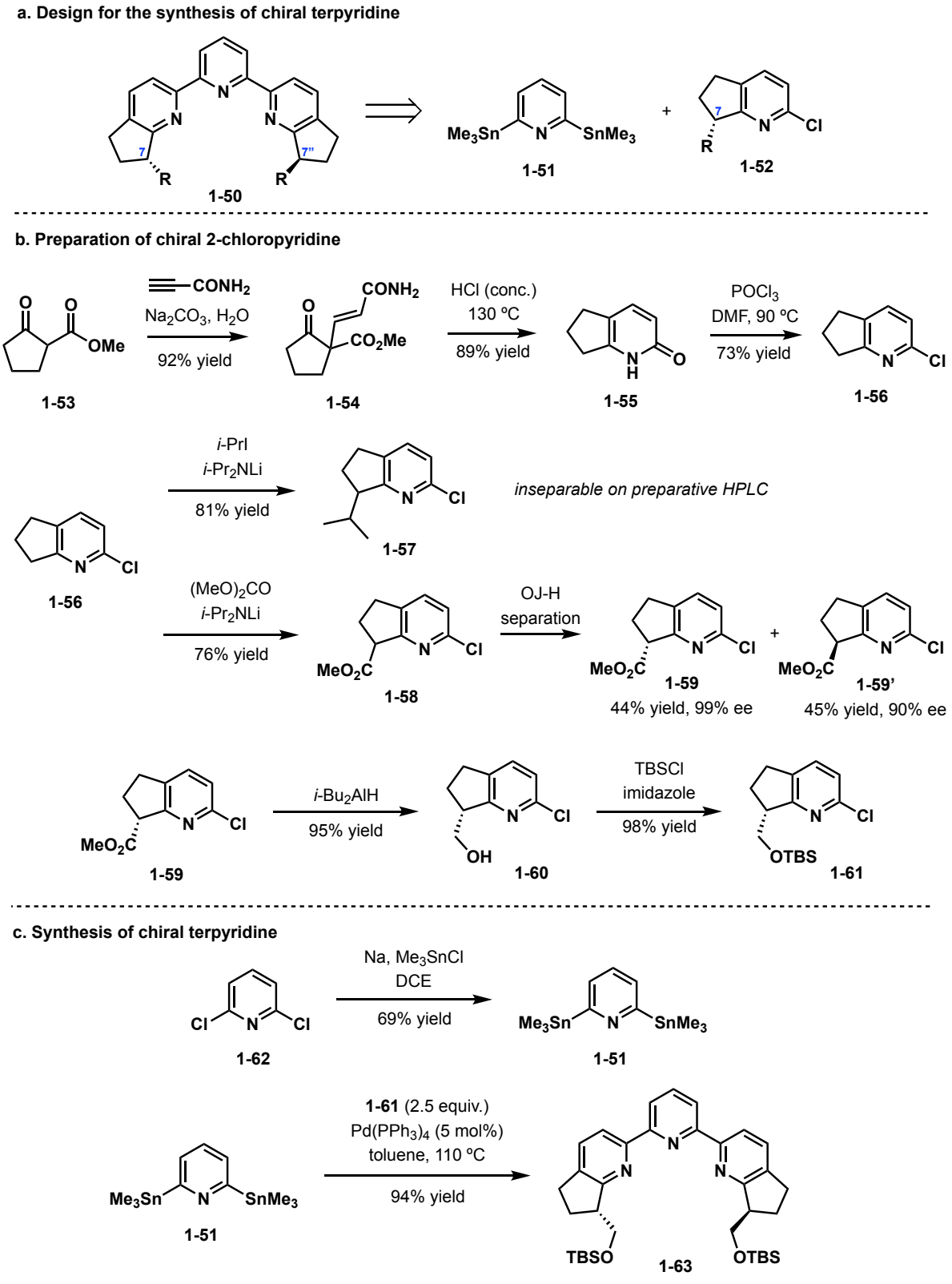
As designed, the substitution on the 7 and 7" positions of the chiral terpyridine **1-50** would control the stereoselectivity of the reaction which β-oxo carbonyl compounds attend. After a through screening on the common coupling conditions, **1-50** was designed to be synthesized through Stille coupling[16] between of 2,6-bis(trimethylstannyl)pyridine (**1-51**)[17] and 2.5 equivalents of 2-chloropyridine **1-52** (Scheme 1-13a).



Scheme 1-12. Complexes of lanthanides with β-oxo carbonyl compounds

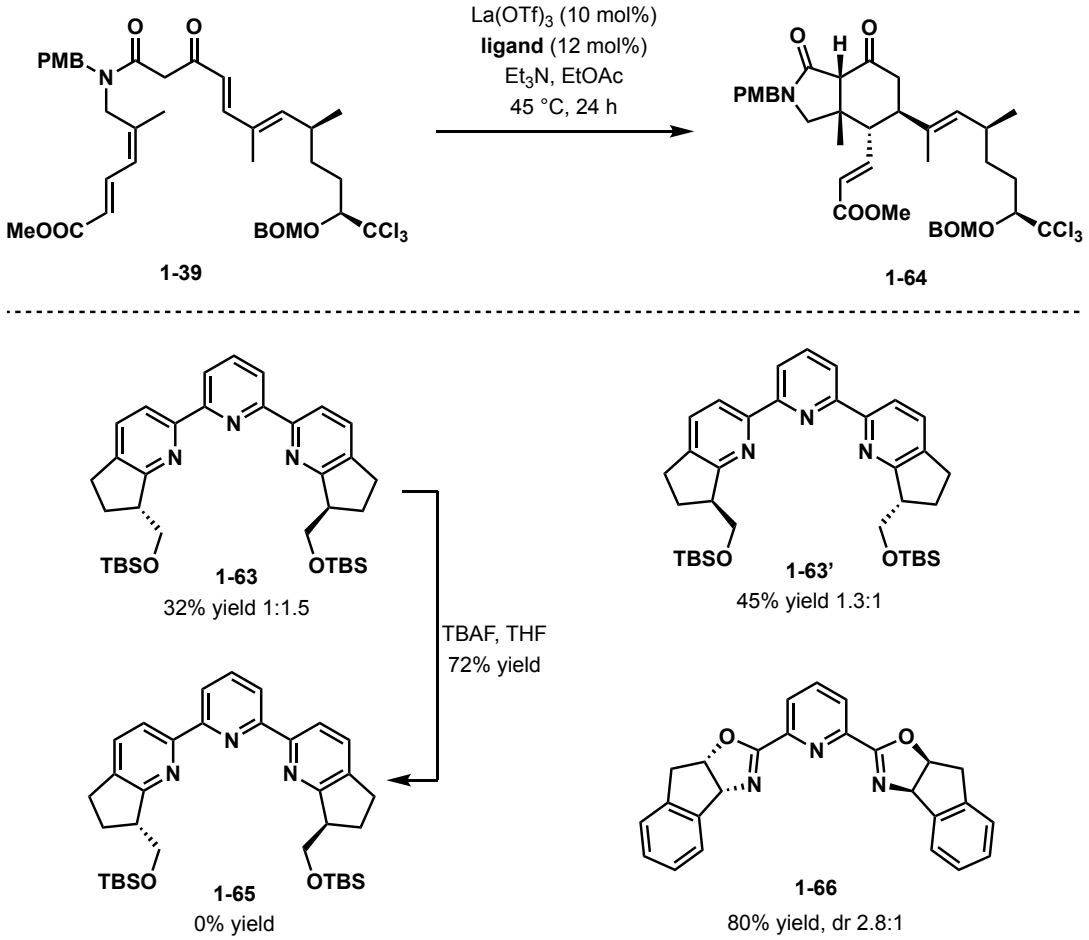
The preparation of **1-52** started from methyl 2-oxocyclopentanecarboxylate (**1-53**), which underwent a Michael addition with propiolamide in basic aqueous solution, affording 92% yield of amide **1-54**. The following intramolecular condensation was performed at 130 ºC in sealed tube with concentrated hydrochloric acid, and provided the 2-pyridinone **1-55** in 89% yield. 2-Chloropyridine **1-56** was obtained by treating **1-55** with $POCl_3$. The modification of 7-position of **1-56** was performed by the deprotonation of LDA following the treatment with electrophile: isopropylation of 7-position with 2-iodopropane afforded **1-57** in 81% yield. However, 7-isopropylpyridine **1-57** could not be separated via chiral columns. 7-Methoxycarbonylpyridine **1-58** was prepared with dimethyl carbonate as electrophile in 76% yield, and the following separation with preparative HPLC using OJ-H column afforded the two isolated enantiomers **1-59** and **1-59'** in 44% and 45% yield, respectively. The following reduction and silylation delivered 93% yield of 2-chloropyridine **1-61**, ready for Stille coupling.

2,6-Bis(trimethylstannyl) pyridine (**1-51**) was synthesized in multigram scale via the reaction between 2,6-dichloropyridine and sodium trimethylstannide, generated *in situ* from sodium and trimethyltin chloride.[17]



Scheme 1-13. Synthesis of chiral terpyridine

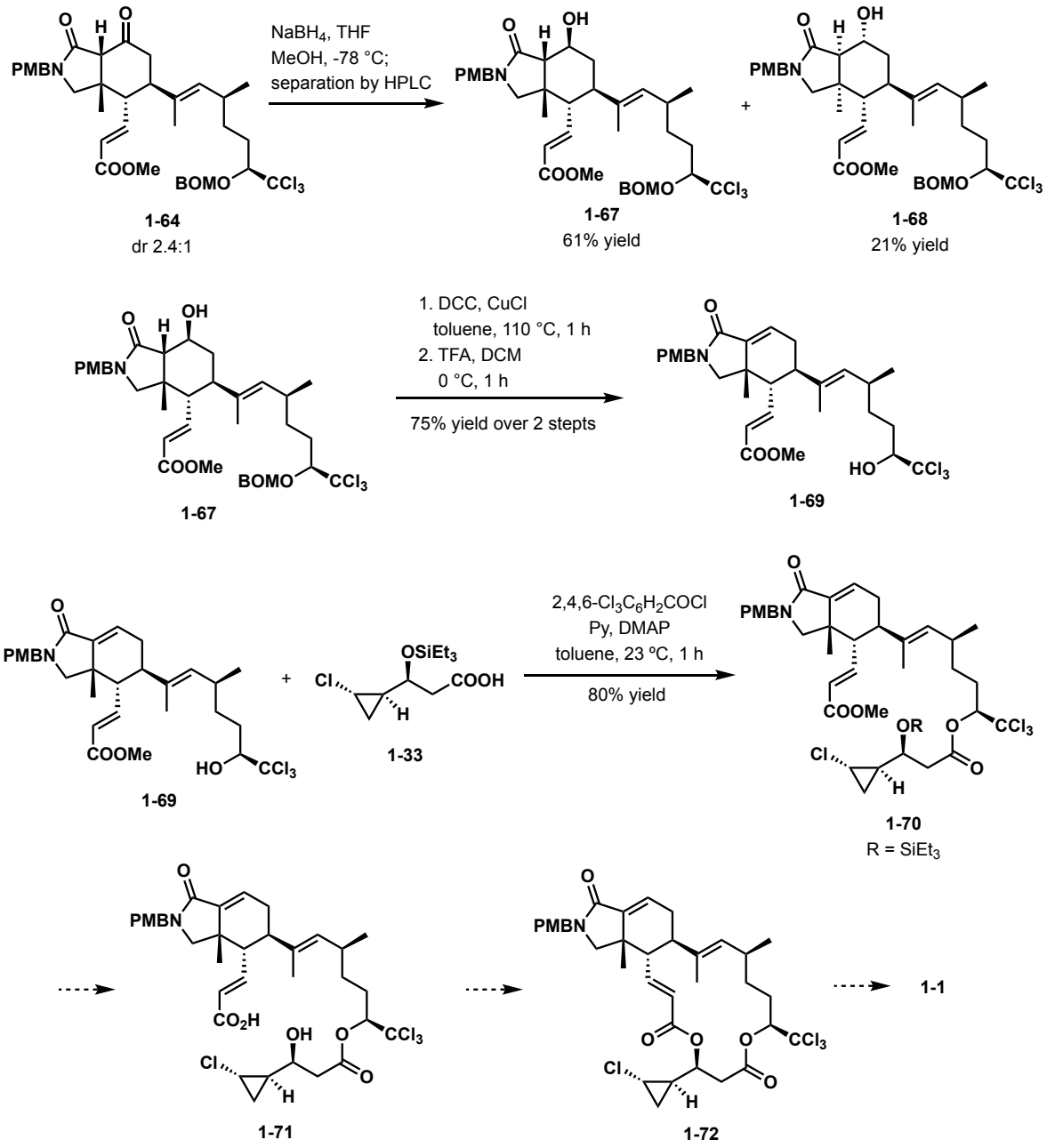
The Stille coupling between **1-51** and **1-52** was then carried out with 5 mol% of $Pd(PPh_3)_4$ in toluene at 110 ºC, and 94% yield of chiral terpyridine **1-63** was finally isolated.



Scheme 1-14. IMDA reaction of β-keto amide 1-39

Notice that the absolute configurations of **1-59** and **1-59'** were uncertain. Therefore, both of the enantiomers were applied in the synthesis and tests of terpyridine ligands (**1-63**, **1-63'**). The attempt of using the chiral terpyridine ligands **1-63** and **1-63'** with $La(OTf)_3$ in the IMDA reaction of β-keto amide **1-39** only delivered **1-64** in low diastereoselectivities (dr 1:1.5 and 1.3:1, respectively). Another terpyridine derived from **1-63** was also examined as the ligand (**1-65**), but resulted no formation of **1-64** after 24 hours, which possibly due to the further

chelation of the free hydroxy groups with lanthanide, jeopardizing the ideal cyclization. The investigation aiming highly selective IMDA reaction had to be suspended because of the data demonstrated above, and the cyclization of **1-39** was carried out with $La(OTf)_3$ and PYBOX ligand **1-66**, resulting desired product **1-64** in 80% yield and 2.8:1 dr.



Scheme 1-15. Late stage of the synthesis after IMDA reaction

The continuous synthesis towards (–)-muironolide A was performed hundreds milligrams scale. The mixture of IMDA product **1-64** (dr 2.4:1) was reduced by sodium borohydride, and the resultant mixture got isolated by preparative HPLC, yielding 61% of the desired isomer **1-67** and 21% of its diastereomer **1-68**. Trichlorocarbinol **1-69** was then afforded in 75% yield through sequential dehydration and cleavage of BOM group. Esterification of **1-69** with CCK acid **1-33** using the Yamaguchi condition delivered 80% yield of ester **1-70**. However, the later synthesis towards (–)-muironolide A was not finished because 1) the one-pot cleavage of the methyl ester and the triethylsilyl ether have not been optimized, since it is hard to carry out microwave irradiation in gram scale using our equipment; 2) we have not improved the ring closure to **1-72**, which went through another Yamaguchi esterification in the original synthesis (50% yield).

1.7 Conclusion

Great efforts have been done in the large-scale total synthesis towards (–)-muironolide A. Over 100 grams of non-commercially available (–)-citronellene was synthesized in excellent chemical and optical purity. The syntheses of PMB-protected diene amine and chlorocyclopropyl ketide acid have been thoroughly investigated and optimized, and multiple grams of these two synthetic subunits were prepared. After slight modification on the detailed procedures, all steps towards the IMDA precursor can be performed as well as the original in both yield and stereoselectivity in multigram scale. A new type of chiral terpyridine was synthesized, but its application in the IMDA reaction did not improve the moderate diastereoselectivity. The continuous synthesis provided the condensed product with full carbon

skeleton. The final synthesis to (–)-muironolide A yet suspended due to the further optimizations of macrolactonization need to be down in the late stage.

1.8 References

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(8) No removal of solvent was carried out after mesylation, and other solvents (like THF, NMP) were directly added to the reaction mixture right before the addition of $PMBNH_2$. That is why all types of solvent system in the screening were mixtures with DCM.

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(14) The yield of **1-10** was always lower than 50% if sodium hydride was used as base.

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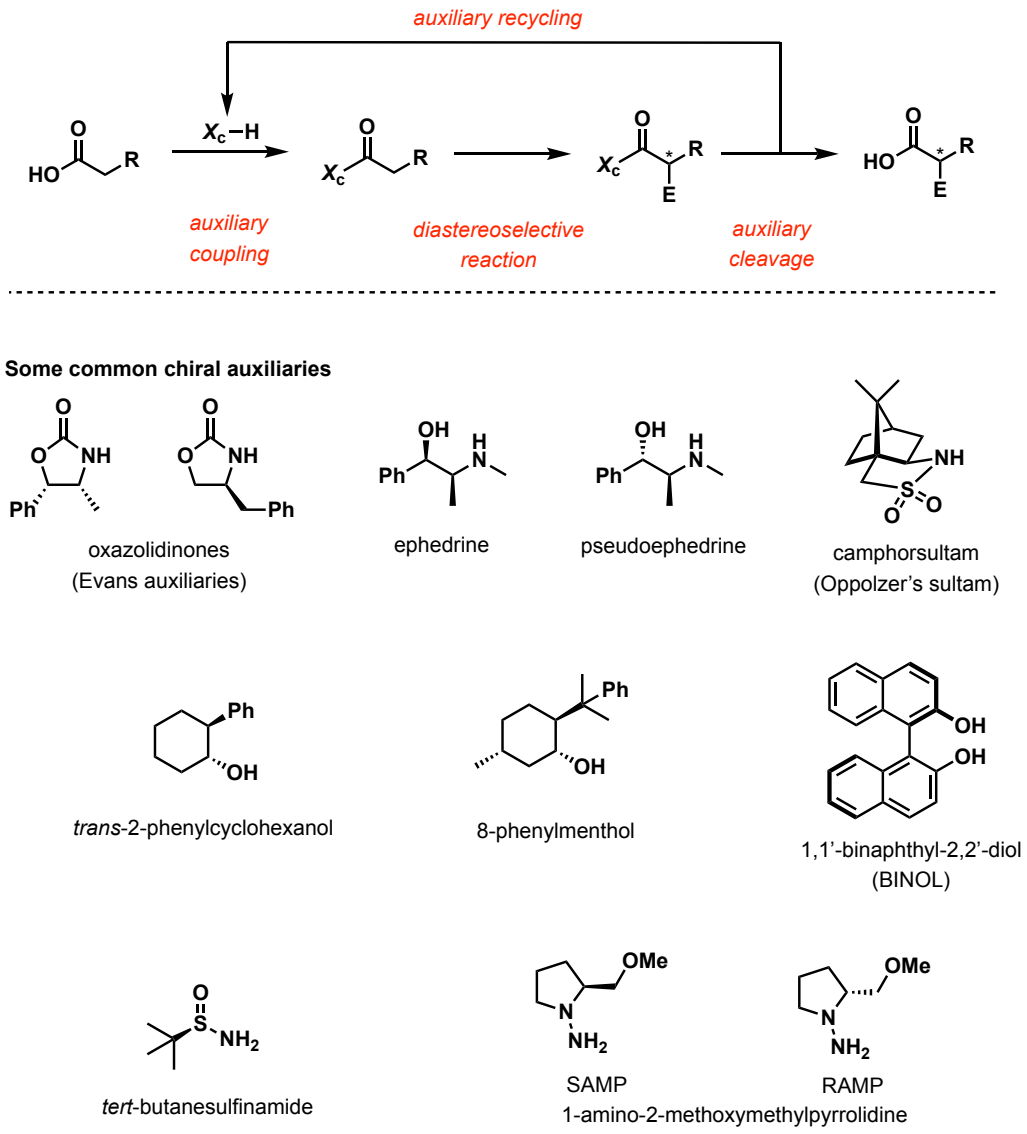
Chapter 2. Introduction to Asymmetric Chemistry Using Chiral Lithium Amides as Non-Covalent Chiral Auxiliaries

2.1 Covalent Chiral Auxiliaries

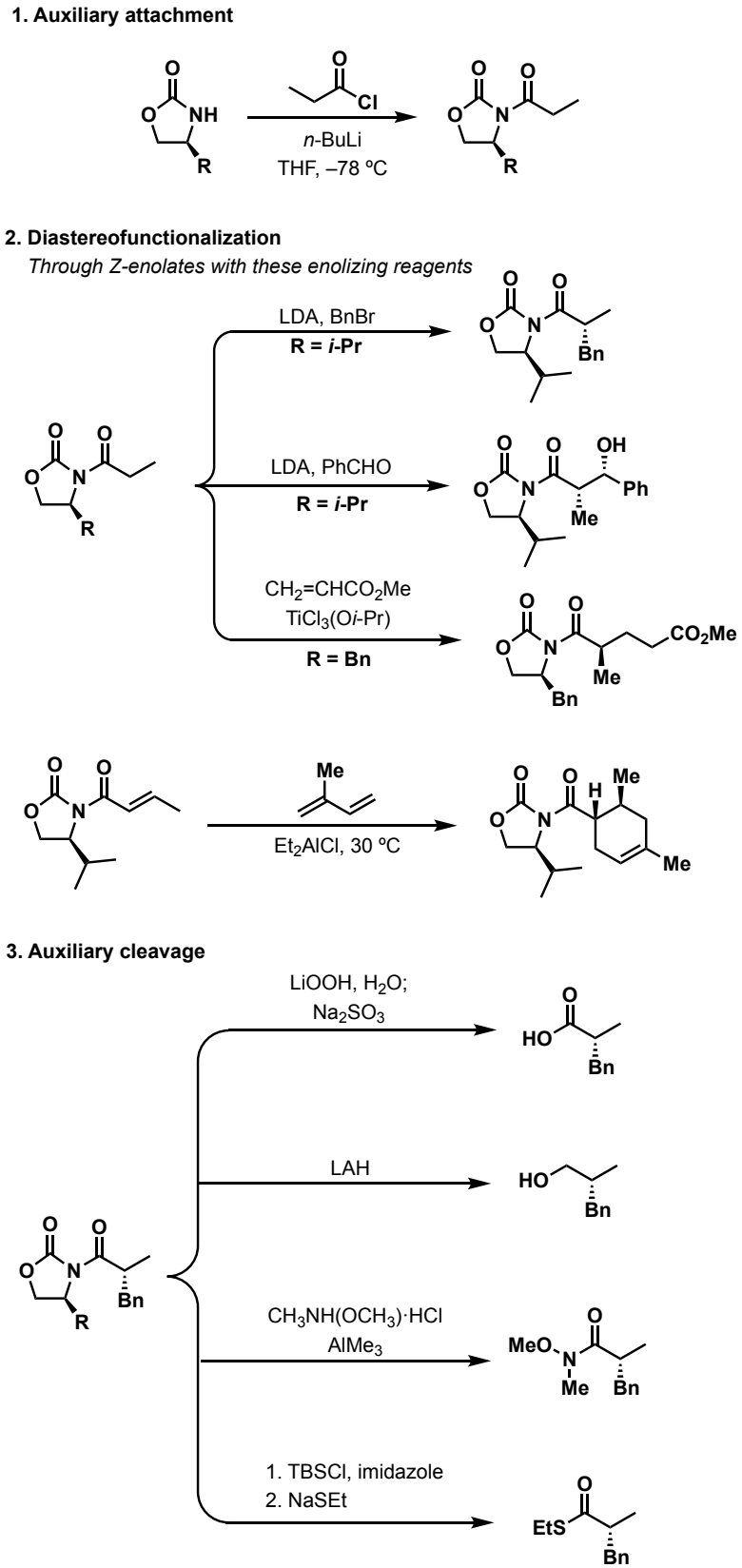
The stereoselective construction of carbon-carbon bonds is a central goal of organic synthesis.[1] Stoichiometric equivalents of chiral auxiliaries are applied to influence the stereochemistry of a reaction through a ***covalently*** bonded auxiliary-substrate template.[2] Despite the relatively poor diastereoselection at the very beginning of this research area during the mid-twentieth century, chiral auxiliaries nowadays have turned to a kind of powerful reagents to induce the chirality, and have been efficiently utilized in the academic and industrial area since 8-phenylmenthol was introduced by E. J. Corey in 1975.[3]

A general covalent chiral auxiliary approaching the stereoselectivity for α-functionalization is summarized in Scheme 2-1. In this process, a covalent bond is first constructed between the substrate and the stoichiometric equivalent of chiral auxiliary, followed by a stepwise *"targeted"* diastereoselective functionalization. Usually, the unequal diastereomeric products need to be separated before the cleavage of the auxiliary unit, so that the desired enantiomerically pure product will be finally afforded. Also, at the same time with generating the ideal product, the issue of recovery or recycling the chiral auxiliary itself is also need to be emphatically considered, especially in the large-scale asymmetric syntheses.[4]



Scheme 2-1. Diastereoselective functionalization with covalent chiral auxiliaries

Besides 8-phenylmenthol, by far there have been introduced numerous covalent chiral auxiliaries commonly used in the stereoselective functionalization at the α-position of the carbonyl compounds, like oxazolidinones (Evans auxiliaries), [5] pseudoephedrines, [6] camphorsultam (Oppolzer's sultam),[7] *trans*-2-phenylcyclohexanol,[8] and 1,1'-binaphthyl-2,2'-diol (BINOL), [9] *tert*-butanesulfinamide, [10] (*S*/*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP).[11]



Scheme 2-2. General process of oxazolidinone auxiliary

Oxazolidinones,[5] popularized by D. A. Evans, are possibly the most famous kind of covalent chiral auxiliaries and are shown as an example for the sequence of the covalent chiral auxiliary chemistry (Scheme 2-2). Due to the steric hindrances derived from the 4-position (sometimes 5-position as well) of oxazolidinones, the substrate acids can be transformed through alkylation,[5e] aldol reaction,[5a,12] conjugate addition,[5b] and Diels-Alder reactions[5c,5d] to the desired product in high enantio- and diastereoselectivity within three steps: 1) The substrate, usually carboxylic acid or corresponding acyl chloride, attaches with the lithiated oxazolidine. 2) The purified chiral amide is then treated with enolization reagent (*i*-Pr_2NLi, $NaN(Si(CH_3)_3)_2$, $TiCl_4$, etc.) to generate one significant dominant enolate conformer and followed by the sterically directed functionalization. 3) Lithium hydroperoxide is applied in the hydrolysis to cleave the oxazolidinone unit to afford the carboxylic acid as product, or there are a variety of transformations developed to remove the auxiliary generating other synthetically useful functional groups. In general, the oxazolidinones can be recovered and purified after the cleavage through column chromatography.

Although plentiful covalent chiral auxiliaries have been broadly utilized and giving the good to excellent stereoselectivity in the asymmetric chemistry, a significant issue need to be considered, especially for the large-scale synthesis,[4] that is stepwise route of using covalent chiral auxiliary. As shown in the previous introduction, at least three individual steps are required to finally construct one or more chiral centers, while only the second diastereoselective reaction is the *real* reaction ensuring the stereochemistry due to the chiral environment derived from the auxiliary. In this process, another two steps, auxiliary attachment and cleavage, increase the total steps of the synthesis, require the further purification (particularly on the separation of the diastereomers in the auxiliary attachment step) and result

in much lower atom economy and higher production of the wastes. Also, chemists have to spend efforts on evaluating the procedure for the recovery and recycling of the chiral auxiliaries. Despite the mainly used auxiliaries can be capable of disassociating from the product with the maintenance of their chirality, the isolation of them from the ideal products as well as their purification might be troublesome, especially when the synthesis scale goes up.

2.2 Chiral Lithium Amides as Noncovalent Chiral Auxiliaries

2.2.1 Early Study on Chiral Lithium Amides

Lithium amide bases derived from chiral amines have been acting as a type of chiral source in asymmetric synthesis over the last few decades (Figure 2-1).[13] These compounds form aggregates with organolithium reagents and induce stereoselectivity without being covalently bound to the substrate. They can be treated as noncovalent, or "traceless", chiral auxiliaries. In the following discussion, we will focus on the historical and recent applications of Koga type chiral lithium amides.

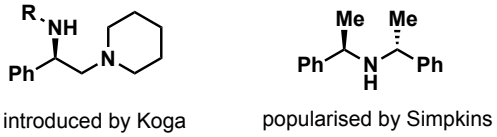
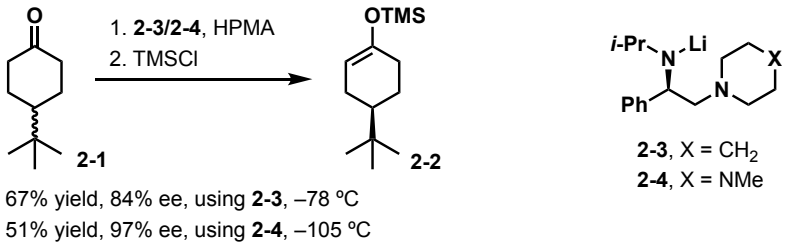


Figure 2-1. Common chiral amines for chiral lithium amides

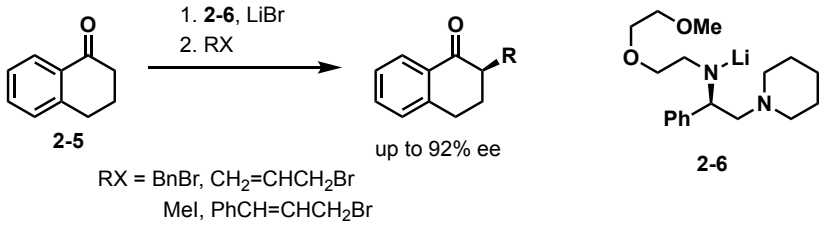
In 1986, chiral bases from 1,2-diamine, introduced by Koga, have been applied successfully in the enantioselective deprotonation and alkylation of prochiral cyclic prochiral ketones.[14] It was reported an asymmetric deprotonation of 4-*tert*-butylcylohexanone (**2-1**) at –78 ºC with lithiated diamine (**2-3**) in the presence of hexamethylphosphoramide (HMPA) (2.0 equiv.). The following silylation with 5.0 equivalents of trimethyl chloride (TMSCl) afforded moderate

to 67% yield of chiral enol silane **2-2** with 84% ee. The ee could be increased up to 97% when the lithiation was carried out at –105 ºC with another similar chiral lithium amide (**2-4**) and 1.0 equivalent of HMPA, while the yield dropped to 51%.



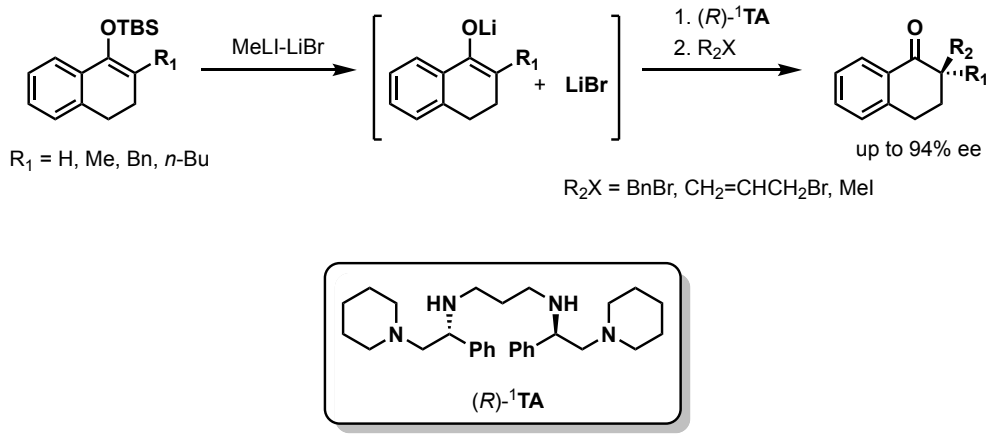
Scheme 2-3. Asymmetric enolization of prochiral ketones with lithiated chiral diamine

During this time, Koga group also reported an enantioselective alkylation of ketones using chiral lithium amide.[15] Up to 92% enantiomeric excess at the α-position of 1-tetralone (**2-5**) was realized by first forming the lithium enolate together with the chiral lithium amide **2-6** in the presence of lithium bromide, followed by treatment with alkyl halides.



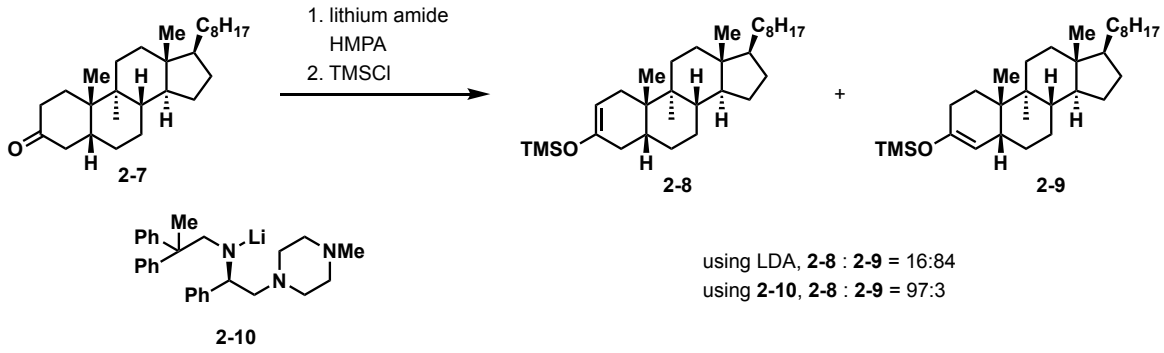
Scheme 2-4. Asymmetric α-alkylation of ketones with lithiated chiral diamine

In a subsequent study, C_2-symmetric chiral tetraamine (*R*)-[1]**TA**, reported by Koga as well, could direct the same approach, by generating the lithium enolate-chiral secondary amine-LiBr complex, to the alkylated 1-tetralones in higher enantioselectivity (up to 94% ee) with moderate to good yields.[16]



Scheme 2-5. C_2-symmetric chiral tetraamine in asymmetric α-alkylation of ketones

Besides, they reported using chiral base **2-10** in the regioselective enolization of certain 3-keto steroid **2-7**.[17] An opposite and much higher regioselectivity (97:3) was observed when **2-10** was applied with HMPA, comparing to using lithium diisopropylamide (LDA).

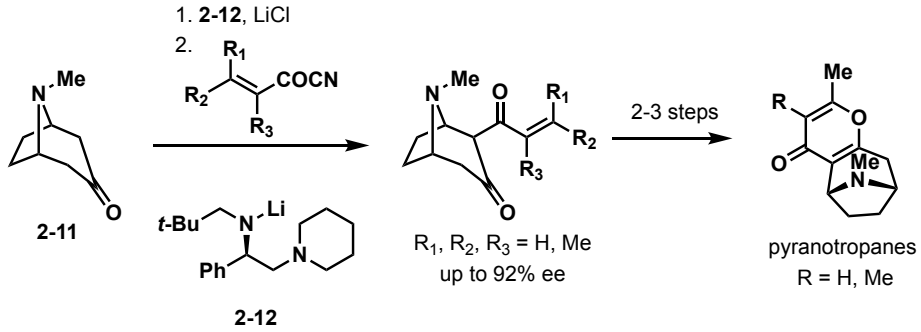


Scheme 2-6. Early application of chiral lithium amide in regioselective enolization

2.2.2 Early Applications of Koga's Chiral Lithium Amides in Total Synthesis.

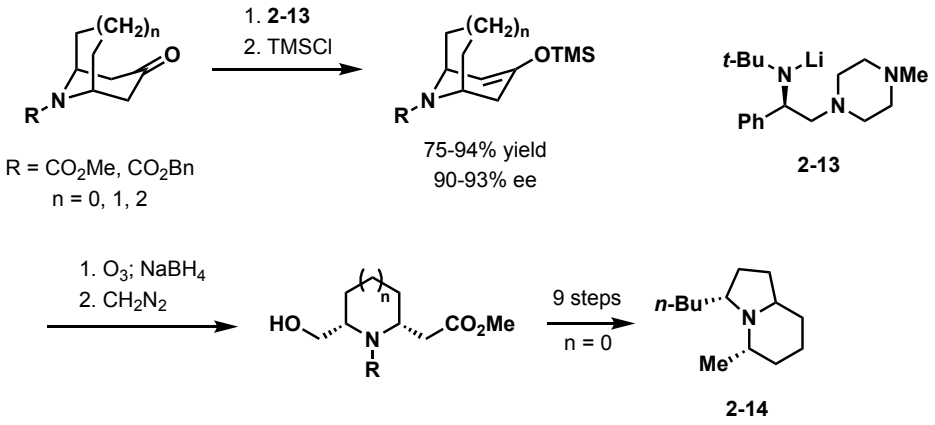
Closely following the released asymmetric methodology, the Koga type chiral lithium amides started to be applied in a series of total syntheses, like reiswigin A, indolizidine and tropinone alkaloids.

In 1994, Majewski *et al.* introduced a synthesis of tropane alkaloids via enantioselective deprotonation strategy. [18] The prochiral substrate, tropinone (**2-11**), was deprotonated asymmetrically by lithiated neopentyl diamine (**2-12**) with lithium chloride. Treatment of acyl cyanide (*i.e.* crotonyl cyanide, tigloyl cyanide, cinnamoyl cyanide and senecioyl cyanide) afforded 1,3-diketone in up to 92% ee. The resulted product could be easily converted into pyranotropanes within another 2-3 steps.



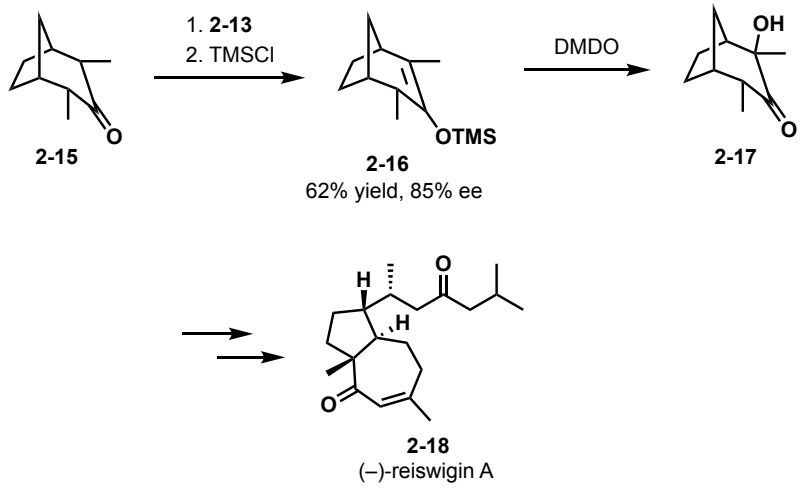
Scheme 2-7. Application of Koga's chiral lithium amides in synthesis of pyranotropanes

In 1997, Koga's chiral lithium amide **2-13** was applied in the asymmetric enolization of methyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate. [19] The followed silylation with TMSCl at –100 ºC afforded silyl enol ether in one pot with 75-94% yield and 90-93% ee. Ozonalysis and subsequent esterification with diazomethane gave the chiral α,α'-bifunctionalized *cis*-disubstituted pyrrolidine (n=0), piperidine (n=1) and hexahydroazepine (n=2). Specifically, optically pure indolizidines can be synthesized through the chiral pyrrolidine over 9 steps.



Scheme 2-7. Application of Koga's chiral lithium amides in synthesis of indolizidines

MaGee *et al.* also reported an enantioselective deprotonation of 2,4-dimethylbicyclo[3.2.1]octan-3-one (**2-15**), as a model study for the total synthesis of (–)-reiswigin A (**2-18**), using the same chiral lithium amide **2-13** introduced right above.[20] The enantioselective enolization yielded 62% of desired enol ether with 85% ee, which was then oxidized by dimethyldioxirane (DMDO) furnishing α-hydroxy ketone **2-17** in 72% yield as a single stereoisomer.



Scheme 2-7. Application of Koga's chiral lithium amides in synthesis of (–)-reiswigin A

2.2.3 Limitations and Prospects

The majority of early methodologies and applications of the Koga' chiral lithium amides were mainly focusing on the prochiral ketones as the substrate. Narrow substrate scope and too specific reaction conditions for different reactions were the severe limitations for chemists to apply this type of chiral lithium amide in asymmetric synthesis.

Carboxylic acids are used as abundant, inexpensive, and versatile precursors of enediolates. The resulting products contain a carboxy group in free form, readily available for further conversion to amines, alcohols, esters, amides, nitriles, as well as a variety of heterocyclic compounds.[21] Asymmetric functionalizations of carboxylic acids are of fundamental importance in chemical synthesis. The covalent-auxiliary-based methodology has dominated in the area as described hereinbefore, but it requires three-stage process. Without covalently bonding to the stereodirecting unit, single step towards the asymmetry with chiral lithium amide can be an excellent alternative.

2.3 Asymmetric Reactions of Carboxylic Acids with Chiral Lithium Amides

2.3.1 Direct Enantioselective Alkylation of Arylacetic Acids

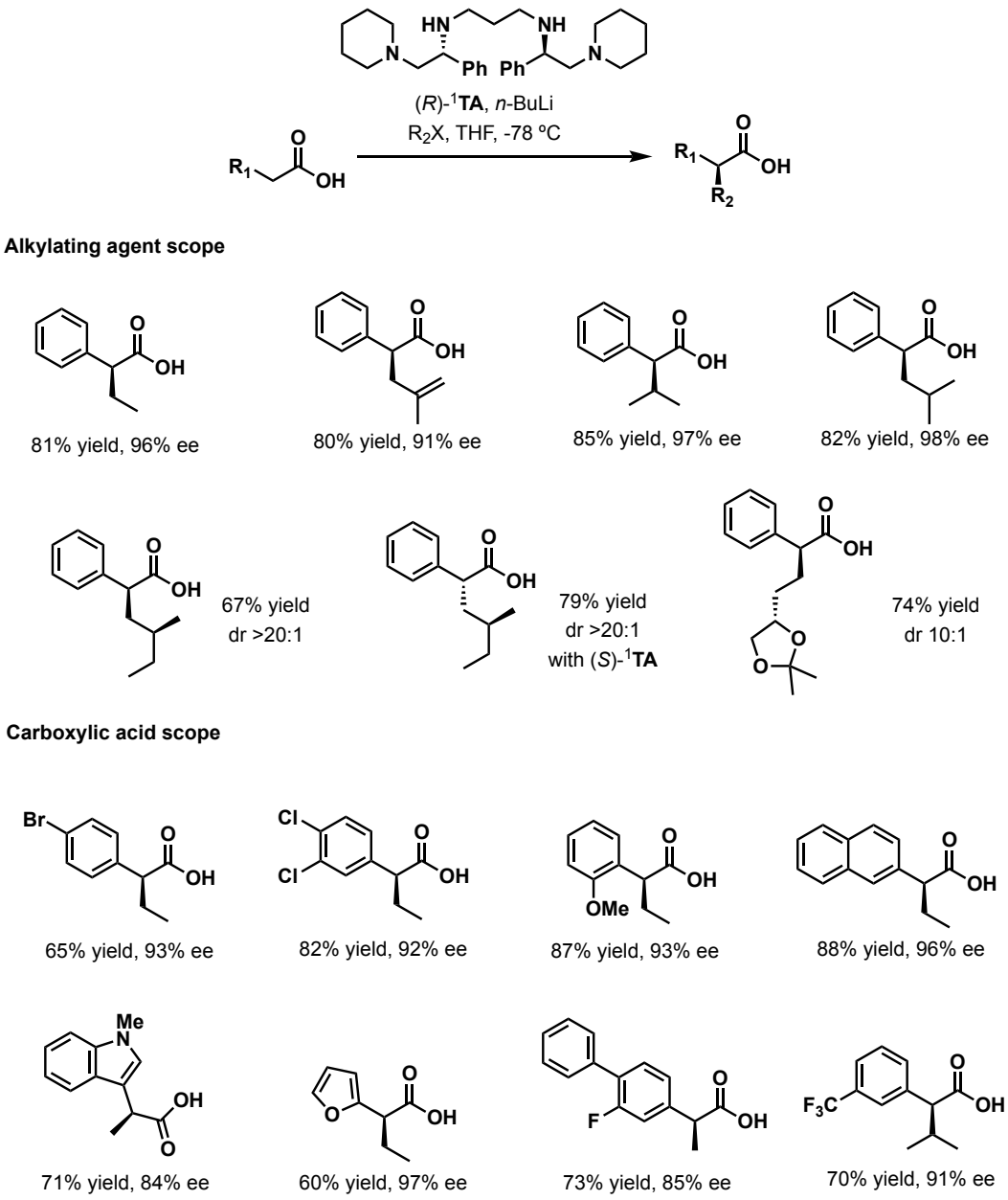
In 2011, Zakarian group introduced a direct, highly enantioselective alkylation of aryl- and heteroarylacetic acids via enediolates using a readily available chiral lithium amide as a stereodirecting reagent.[22] Around 40 cases showed considerable generality for activated, unactivated, and functionalized alkylating agents, and as well as aryl/heteroaryl carboxylic acids, with good to excellent yields and high enantioselectivities.

As shown in Scheme 2-8, high enantioselectivity is maintained with a broad range of primary and more hindered secondary alkyl halides (>80% yield, >90% ee). High lithium amide-controlled diastereoselectivity was also realized with chiral alkyl iodides. Highly diastereoselective alkylations with (*S*)-1-iodo-2-methylbutane were achieved with (*R*)-^{1}**TA** or (*S*)- ^{1}**TA** resulting with >20:1 diastereomeric ratio (dr). Alkylation with (*S*)-2,2-dimtheyl-4-iodoethyldioxolane provided the expected product in 74% yield and 91% dr. Significantly, the same alkylations carried out with LDA afforded 1:1 mixture of diastereomers.

The scope of aryl- and heteroarylacetic acids were also resulted in good to excellent enantioselectivity. Uniformly, the clean alkylation process was carried out with different substrates. Substituents on the phenyl group barely affect the chirality, while the heteroaryl units, such like pyridyl, indolyl, furanyl and thiophenyl, were all proved to be good on substrates with over 60% yield and 84% ee.

In general, the reaction is carried out as follow in 0.7–0.8 mmol scale: 4.0 equiv. of *n*-butyllithium was added dropwise 1.0 equiv. of arylacetic acid and 1.03 equiv. of C_2-symmetric chiral tetraamine, (*R*)-^{1}**TA** in THF at 0 ºC, and the resultant reaction mixture was kept stirring at 0 ºC for 15 min for lithiation-aggregation, followed by being cooled to –78 ºC. The alkylating agent (1.0–4.0 equiv.) was added either in neat or as 1M THF solution at –78 ºC over 10 min, and the resulting mixture would be quenched in another 0 –80 min by THF/MeOH (3:1, 8.0 equiv. of MeOH), then followed by the acid workup and extraction.

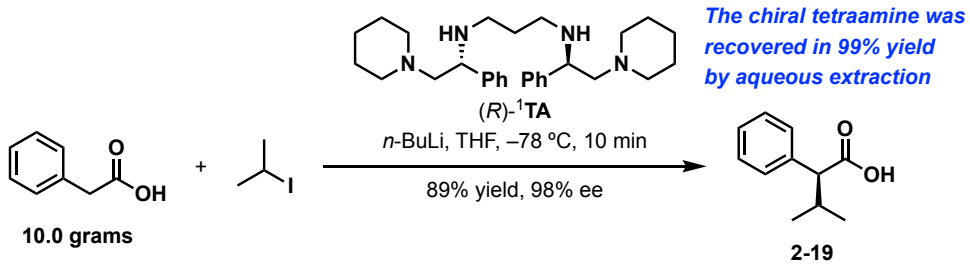
Direct alkylation of 10 grams of phenylacetic acid with 2-iodopropane was demonstrated. Excellent result was maintained and even improved slightly in the large scale (Scheme 2-9, 89% yield, 98% ee), while a practically simple recovery of chiral tetraamine was also introduced with near quantitative recovery.



Scheme 2-8. Enantioselective alkylation of arylacetic acids with chiral lithium amides

One thing needs to be highlighted is the quality of *n*-butyllithium is very vital to the level of enantioselectivities, not only of this alkylation, but also of all other asymmetric reactions in the later discussion. We believe that it is due to the presence of ionic lithium contaminants (*i.e.* *n*BuOLi, LiOH, etc.) in aged reagent bottles, which has been confirmed by the observation of

drastically lower enantioselectivities in the controlled tests with lithium *n*-butoxide or lithium bromide.



Scheme 2-9. Multigram scale direct enantioselective alkylation

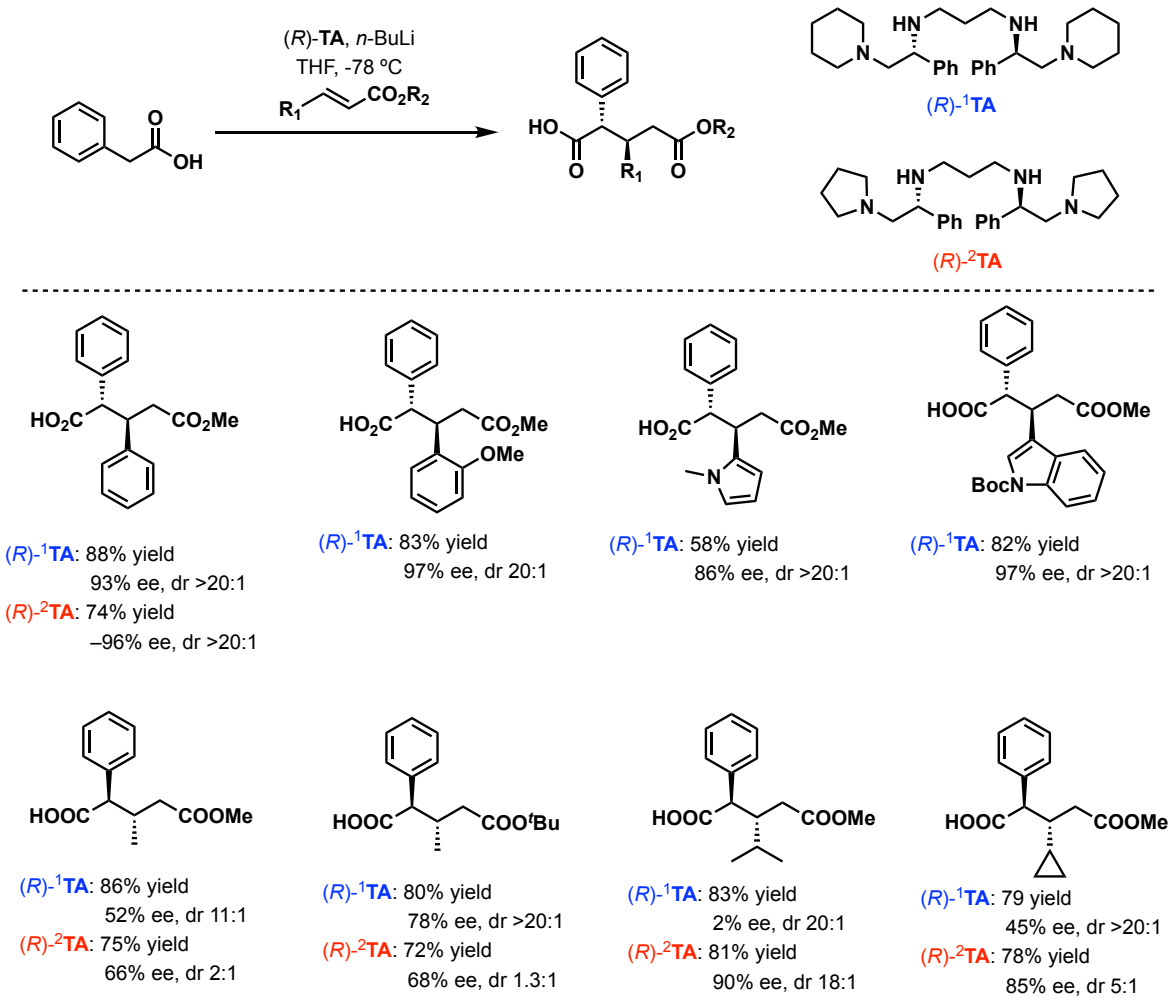
2.3.2 Direct Enantioselective Conjugate Addition of Carboxylic Acids

Following the similar protocol of the lithiation-aggregation and functionalization, direct enantioselective methodology of conjugate addition of carboxylic acids was released in 2015 by Zakarian group.[23] The method provides a high stereocontrol in both the relative and absolute sense, again, showing the utility of chiral lithium amides as traceless noncovalent auxiliaries for asymmetric synthesis.

More than 30 cases were demonstrated with high enantioselectivities, diastereoselectivities, and a broad compatibility on the different Michael acceptors (α,β-unsaturated esters) and Michael donors (arylacetic acids). Both piperidine base (*R*)-^{1}**TA** and pyrrolidine base (*R*)-^{2}**TA** are applied in the investigations of this methodology, showing competitively good stereocontrol.

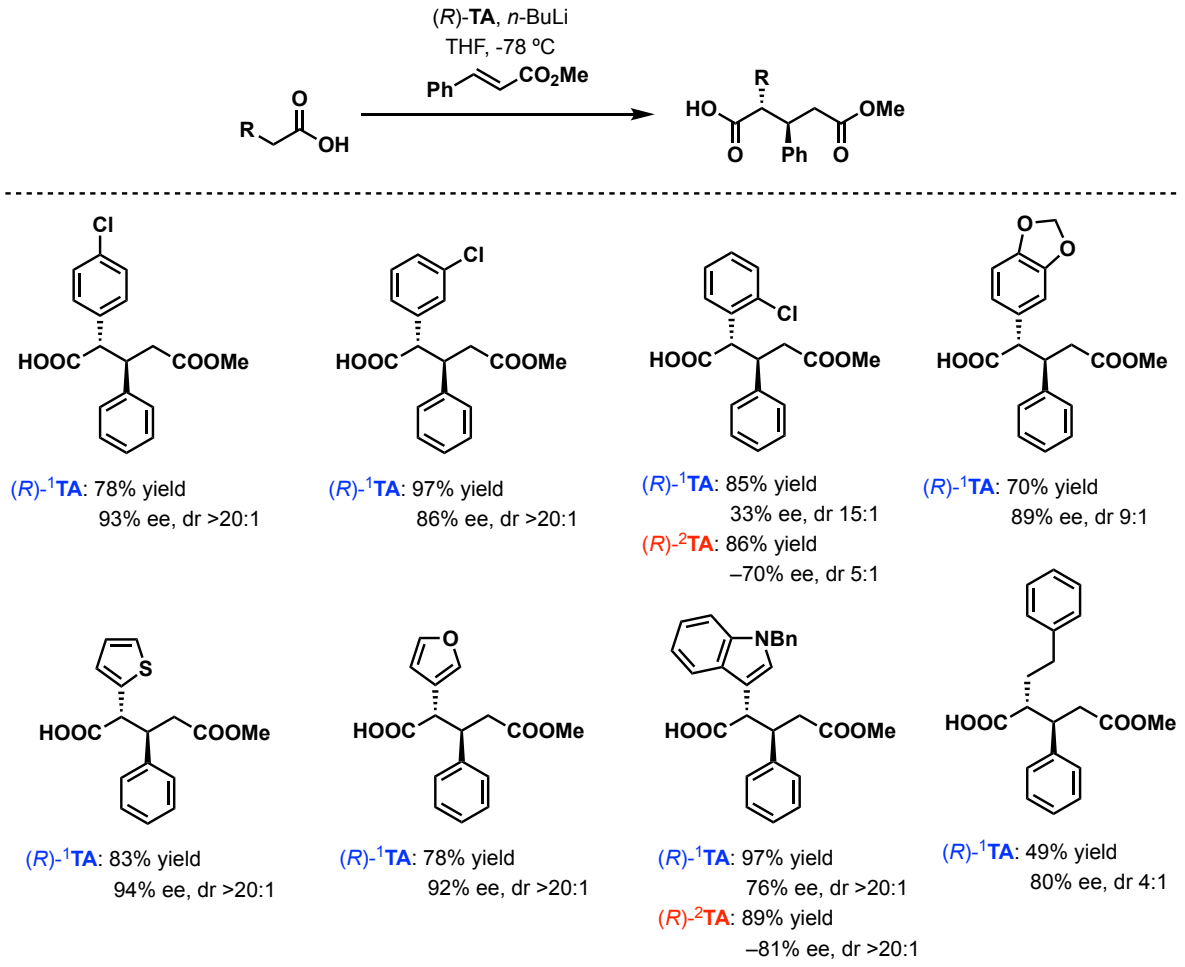
Aryl and heteroaryl α,β-unsaturated esters practiced very well with phenylacetic acid, generally affording over 86% ee and over 20:1 diastereoselectivity (Scheme 2-10). Interestingly, the absolute configuration turned opposite when aliphatic α,β-unsaturated esters got applied. The enantioselectivities of using piperidine or pyrrolidine base were varied

dramatically, and the esters with either primary or secondary aliphatic groups provided moderate to excellent stereocontrol.



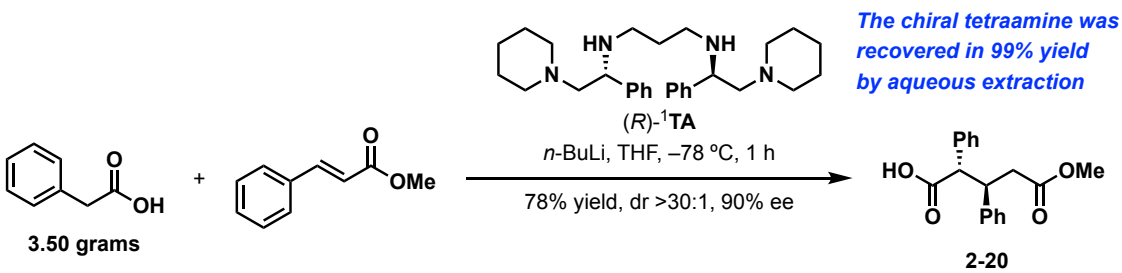
Scheme 2-10. Partial scope of Michael acceptors for enantioselective conjugate addition

The partial scope of carboxylic acids as Michael donors is shown in Scheme 2-11. Variation of the position of the chlorine on the phenyl ring afforded 70–93% ee. The heteroarylacetic acids also provided good to excellent stereoselectivity. Aliphatic carboxylic acid was the first time joined in the scope of this type of methodology: 4-phenylbutyric acid together with methyl crotonate also provided a rather high ee of 80% with 4:1 dr and 49% yield.



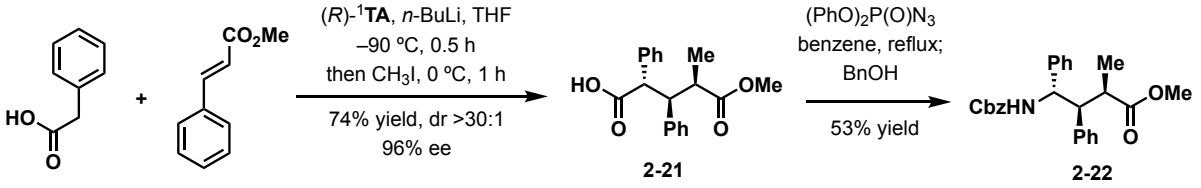
Scheme 2-11. Partial scope of carboxylic acids for enantioselective conjugate addition

Also, a large-scale conjugated addition was performed at –78 ºC on 26 mmol scale, yielding 78% of the adducted product **2-20** as one diastereomer in 90% ee, also with 99% recovery of chiral tetraamine.



Scheme 2-12. Multigram scale direct conjugate addition

Additionally, a further secondary functionalization in one-pot was illustrated. Methylation on the α-position of the ester with iodomethane right after the conjugate addition, which generated three consecutive tertiary stereocenters (**2-21**) with excellent stereoselectivity (96% ee, >30:1 dr) in 74% yield. Besides, a subsequent Curtius rearrangement to **2-22** indicates the versatility of free carboxyl group in the more complex synthesis.

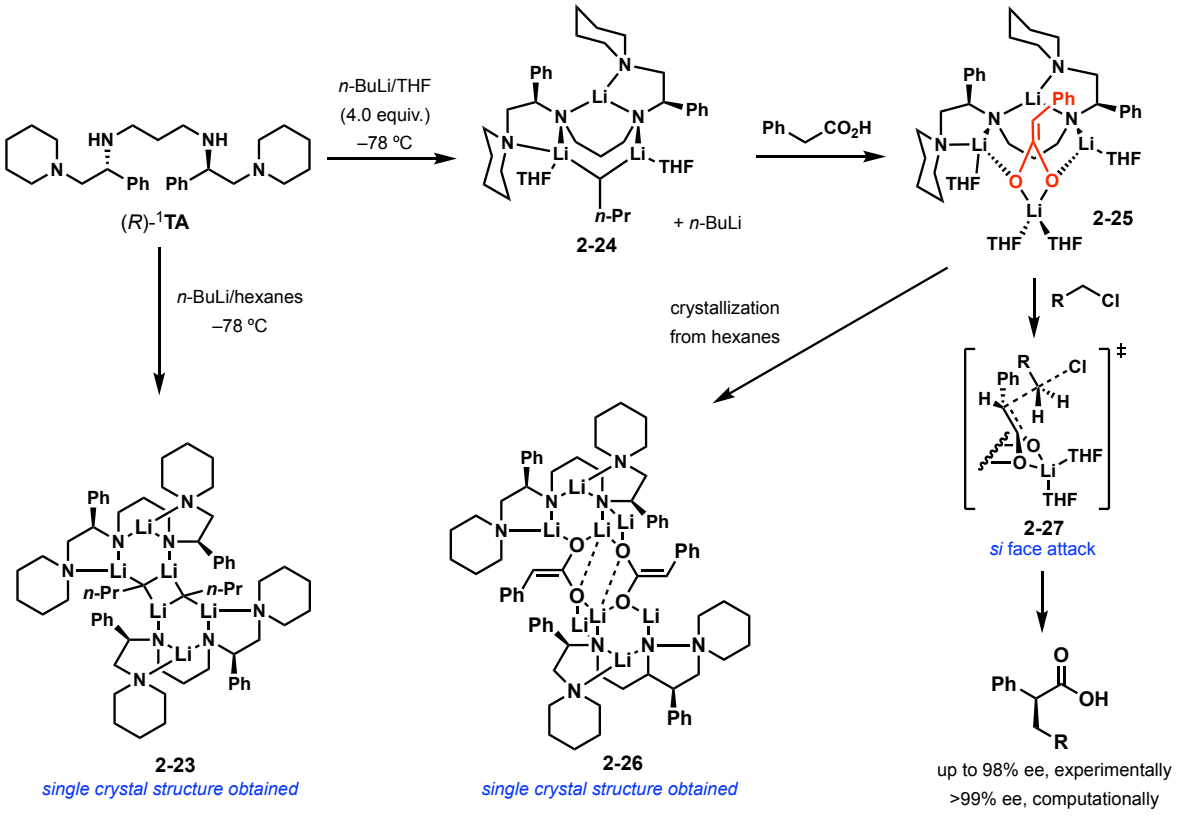


Scheme 2-13. One-pot sequential Enantioselective conjugate addition-methylation

2.3.3 Enediolate-Dilithium Amide Mixed Aggregates in the Enantioselective Functionalization of Arylacetic Acids

Based on a combination of X-ray crystallography, ^{6}Li, ^{15}N, and ^{13}C NMR spectroscopies, and density functional theory (DFT) computations, a systematic analysis of the generation of the enediolate-dilithium amide mixed aggregates got illustrated.[24]

Without any coordinating solvent molecule as ligand (*i.e.* THF), dilithiated amide and *n*-BuLi affords a crystalline mixed aggregate in a hexalithiated form **2-23** (Scheme 2-14) shown by X-ray crystallography, while in the THF solution, the mixed aggregate would maintain as a trilithio *n*-butyllithium-dilithiated amide (**2-24**). Adding other equivalent of phenylacetic acid affords asymmetric tetralithiated tetrasolvated aggregate (**2-25**), which is the key structure indicating the high stereocontrol. Another type of single crystal was obtained by crystallization from hexanes with a small amount of added THF as a light yellow powder in 48% yield. An octalithio structure (**2-26**) was confirmed by X-ray diffraction.

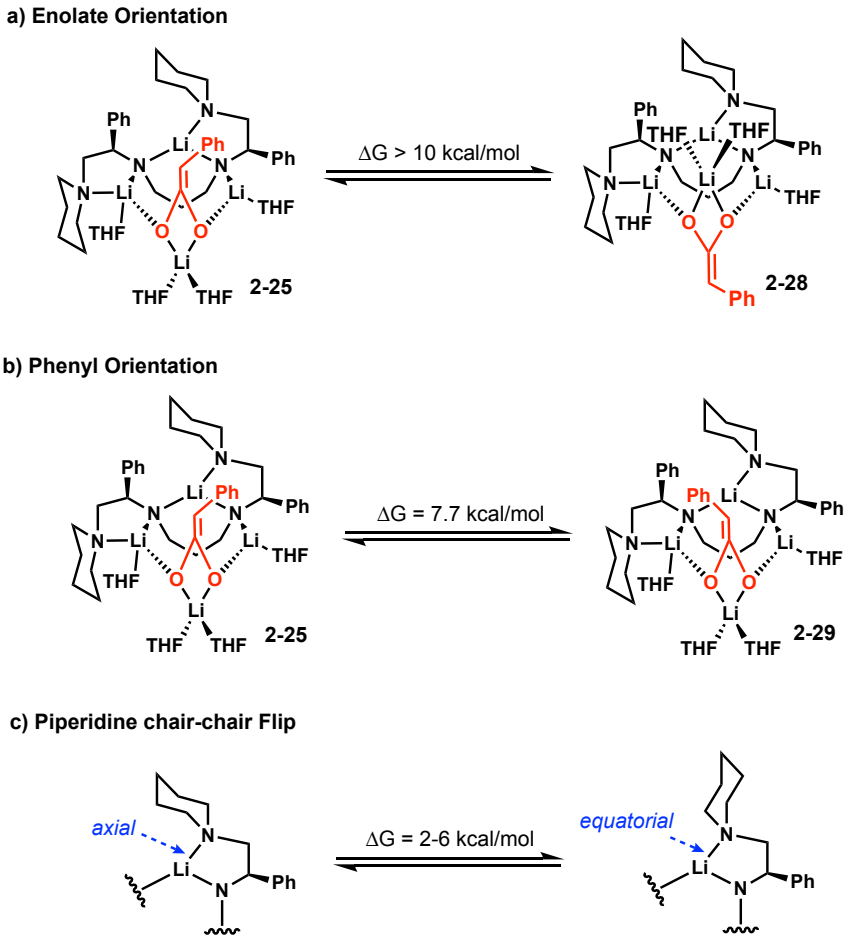


Scheme 2-14. Mixed aggregates with chiral lithium amides and enediolates

NMR spectroscopic studies, specifically, imply four different types of lithium and nitrogen as 1:1:1:1 ratio in the enediolate-dilithium amide mixed aggregates. Li-N Coupling constants have been assigned clearly and shown the difference between primary Li-N linkages of the lithium amide moieties (larger, 3.6-5.6 Hz) and dative Li-N linkages deriving from chelation by the piperidino moieties (smaller, 1.9-2.2 Hz).[25]

The DFT computations were carried out at B3LYP/6-31G(d) level with single-point calculations at the MP2 level of theory.[26] By using the methyl chloride as electrophile in the computation, it shows a dramatic preference ($\Delta\Delta G^{\ddagger}$ = –6.4 kcal/mol) for *si* face attack (**2-27**, Scheme 2-14) comparing with attacking from the *re* face in the transition structure,

suggesting >99% enantiomeric excess, which is consistent with the experimental result, up to 98% ee of the same stereochemistry.



Scheme 2-15. Details about mixed lithium aggregates 2-25

Besides the details mentioned above, several important variables of the solvated mixed aggregates **2-25** need to be highlighted by the DFT calculation:

1. Enolate Orientation. The enolate orients the way demonstrated as **2-25** with >10 kcal/mol favored over the other orientation (**2-28**), due to the more sterically hindered disolvated lithium (Scheme 2-15a).

2. Phenyl Orientation. The orientation of phenyl (aryl/heteroaryl) group of the enediolate is vital to the stereocontrol. A 7.7 kcal/mol preference was observed for **2-25** over the other orientation (**2-29**, Scheme 2-15b).

3. Piperidine Chair-Chair Flip. Piperidine moieties on the tetraamine keep the chair conformer as shown in the scheme, which also proves the preference found in the crystallographic structure. The difference between the favored and the other chair conformers is 2.0-6.0 kcal/mol (Scheme 2-15c).

4. Solvation. The tetrasolvation state is 7.1 kcal/mol favored over the trisolvate.

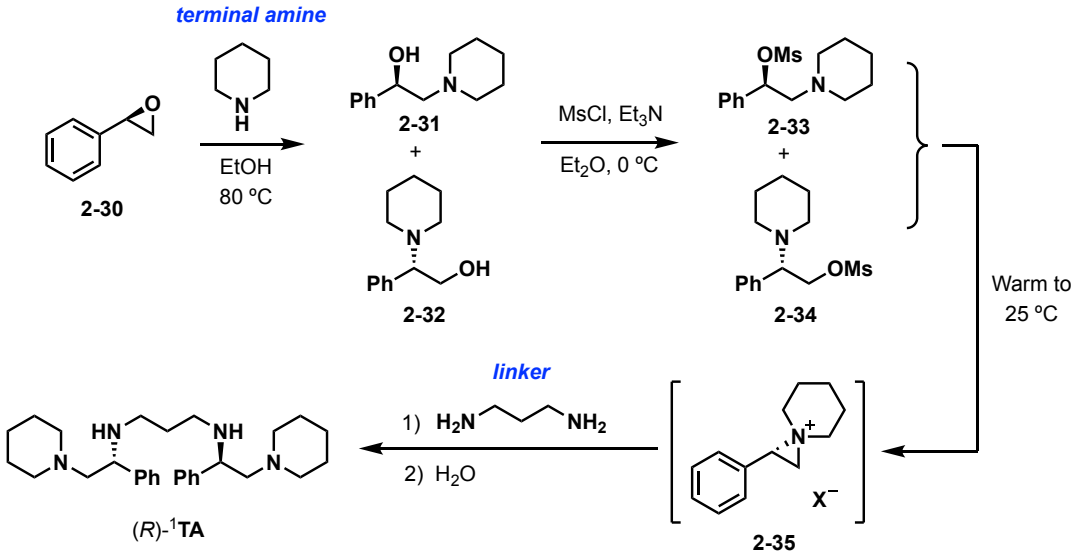
2.4 Preparation of Chiral Koga-type Tetraamines

2.4.1 Synthetic Route

A simple and practical method to prepare chiral tetraamine, (*R*)-^{1}**TA**, in one pot was firstly reported by O'Brien.[27] After that, an efficient multi-kilogram-scale synthetic process for the base was introduced by Amgen, *Inc.*, in which (*R*)-^{1}**TA** can be easily produced as crystalline solid without chromatography in high yield and excellent enantiomeric purity.[28]

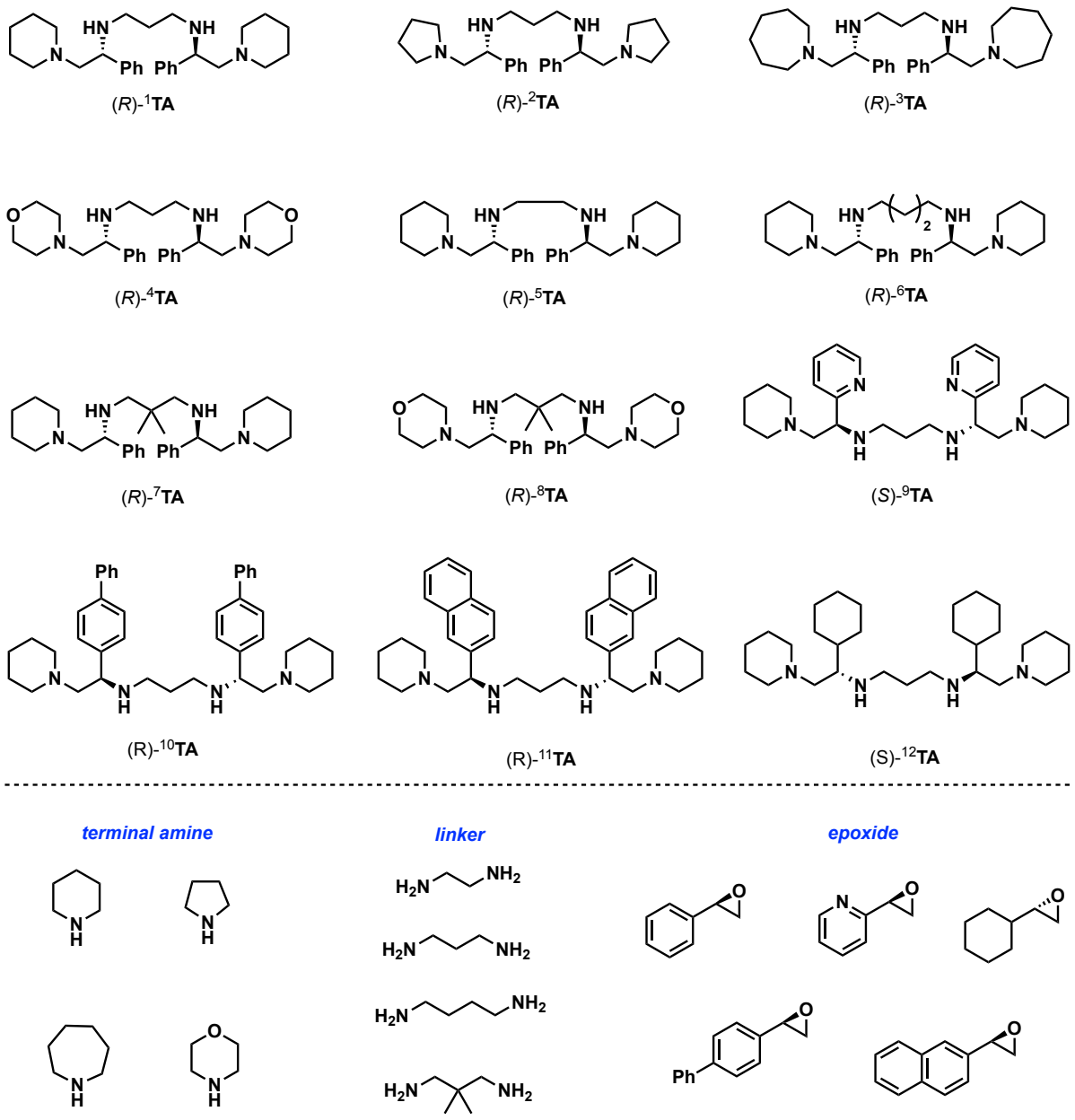
As shown in the Scheme 2-16, ring-opening of the commercially available enantiomerically pure (*R*)-styrene oxide (**2-30**) using piperidine (as the "*terminal amine*") resulted a 1:1 mixture of aminoalcohol **2-31** and **2-32**, and the concentrated crude was applied in the mesylation at 0 ºC. The resultant solution of the mixed mesylate **2-33** and **2-34** in diethyl ether was then warmed up to room temperature, generating the aziridinium **2-35** *in situ*, followed by the addition of the 1,3-diaminopropane (as the "*linker*") and water respectively to afford the chiral Koga tetraamine, (*R*)-^{1}**TA**, as light yellow solid. The product can be easily purified by

recrystallization from isopropanol and water, with 70% yield and 99.9% chiral purity in 1.3 kilogram-scale.[28]



Scheme 2-16. One-pot preparation of (*R*)-^{1}TA from (*R*)-styrene oxide

Based on this synthetic approach to (*R*)-^{1}**TA**, our group have established a library of chiral tetraamines[22,23] with different kinds of *terminal amines*, *linkers* and other substitutions to replace the phenyl groups (Scheme 2-17). Besides piperidine as the *terminal amine*, we also employed pyrrolidine, azepane and morpholine (^{2}**TA** – ^{4}**TA**) for the possible screening on the different ring sizes and their corresponding electrical properties. As for the *linker*, to differentiate the size/range of the linkage part, we also utilized 1,2-diaminoethane and 1,4-diaminobutane, as well as 2,2-dimethyl-1,3-diaminopropane to test the effect of the bulkiness on the *linker* (^{5}**TA** – ^{8}**TA**). Other than styrene oxide, various chiral aromatic or aliphatic epoxides also applied in the synthesis towards building this library. From pyrid-2-yl-, (1,1'-biphenyl)-4-yl-, naphthalen-2-yl-, and cyclohexyloxiranes diverse chiral tetraamines (^{9}**TA** – ^{12}**TA**) were made to testify their chirality inducing properties in the following reactions.

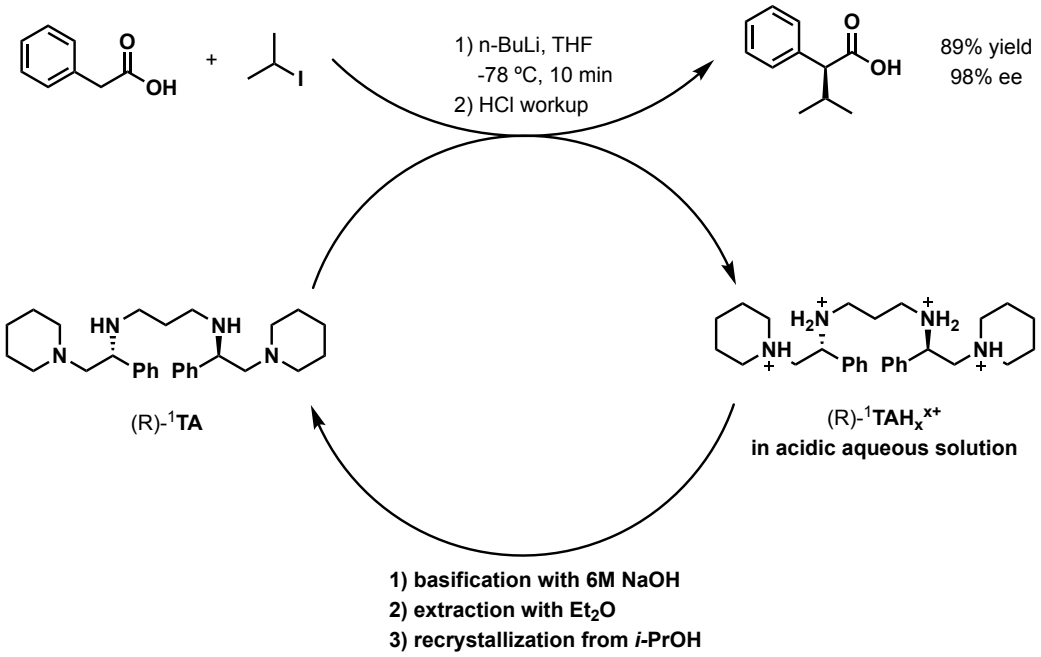


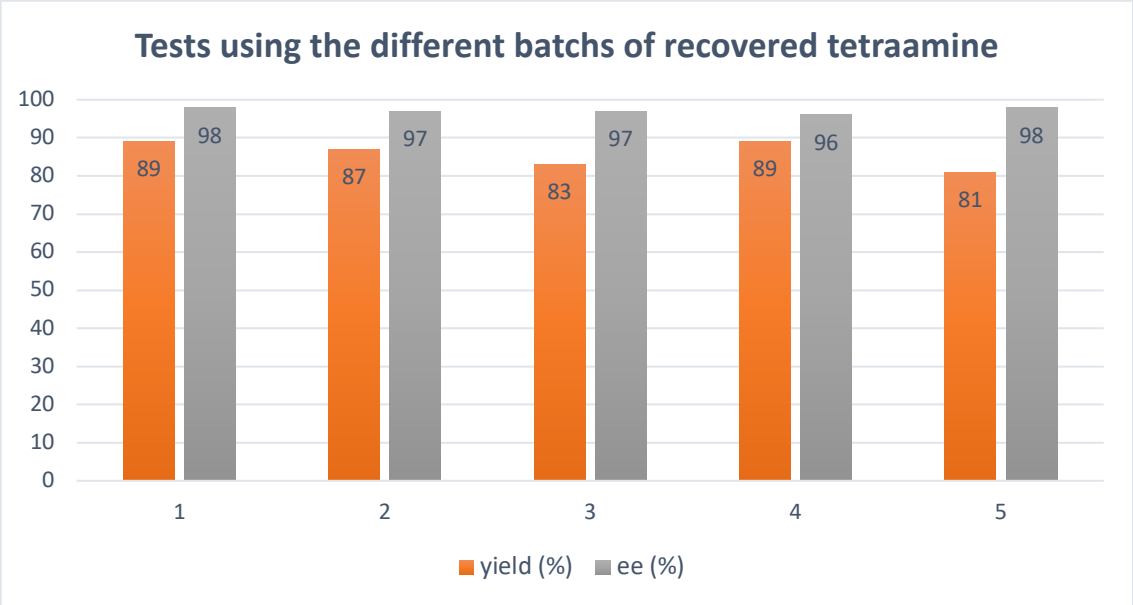
Scheme 2-17. Main library of chiral tetraamines in Zakarian group

2.4.2 Recovery of the Chiral Amines

The chiral amine was recovered by a simple extraction with aqueous HCl in nearly quantitative yield. As showed in the Scheme 2-18, taking the 10-gram scale isopropylation of phenylacetic acid as example, after the 1M hydrochloric acid workup (pH = 1), chiral

tetraamine would totally protonated and extracted in the acidic aqueous phase. Then, the aqueous extract got basified to pH=14 with 6M NaOH, when it was obvious to see a significant amount of white/light pink precipitate crushed out from the light yellow aqueous solution.





Scheme 2-18. Recovery of chiral tetraamine

After cooling, the simple extraction with diethyl ether would be performed. The choice of organic solvent for the extraction is important due to the solubility and the solidification of the recovered chiral amine. After the concentration and dryness, the quantitively recovered chiral amine stayed as light yellow solid, which either can be directly used (entry 3) or recrystallized with isopropanol (entry 1, 2, 4) with maintenance of its quality.

During the study of asymmetric methodologies, usually the acidic aqueous extract of every reaction was stocked and the chiral amine got recovered together. No significant decrease on either yield or stereocontrol efficiency of the chiral amine was noticed after it stayed in the acidic aqueous solution for 6 months (entry 5).

2.5 Recent applications of the Koga's Chiral Lithium Amides in Total Syntheses

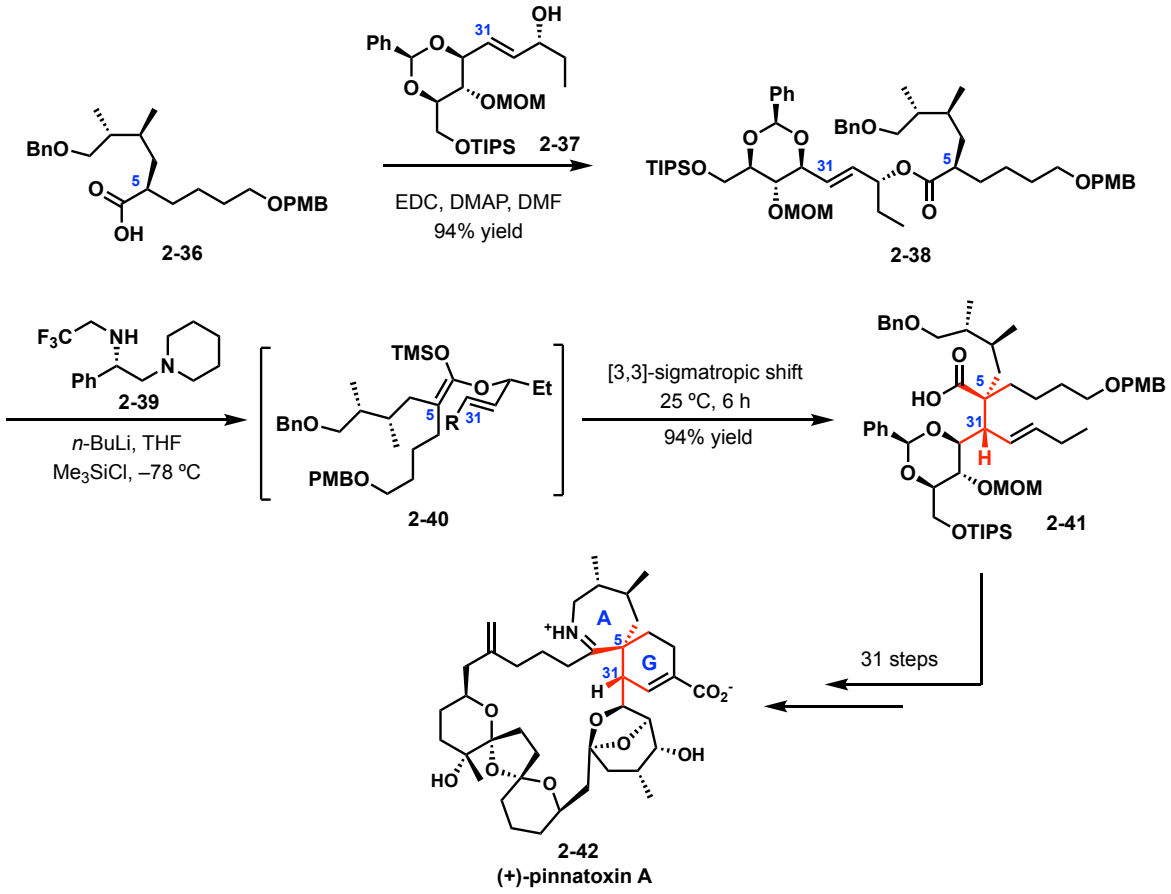
2.5.1 Application in the Total Synthesis of (+)-Pinnatoxin A

Pinnatoxin A (**2-42**) was first isolated by Uemura *et al*. from 45 kg of the viscera of *Pinna muricata* collected in Okinawa, Japan, and described the its gross structure, which is comprised of a 27-memebered carbocycle incorporating a unique A, G-spiroimine.[29] The biosynthetic route to the natural product proposed by Uemura pointed the cyclohexene (ring G) is established through intramolecular Diels-Alder cycloaddition, and it served as the basis for the pioneering total synthesis of (–)-pinnatoxin A by Kishi *et al*.[30]

In 2008, Zakarian group published a total synthesis of (+)-pinnatoxin A in a different strategy[31] which was the assembly of the ring G with a diastereomeric Ireland-Claisen rearrangement to efficiently construct two challenging stereogenic centers, C5 and C31. In the previous study, it had been noticed that chiral lithium amides derived from Koga bases could

stereoselectively controlled the enolization and, furthermore, Ireland-Claisen rearrangement of α-branched esters.[32]

In Zakarian's synthesis, the Ireland-Claisen precursor, ester **2-38**, was formed from the esterification of carboxylic acid **2-36**, generated from (*S*)-citronellic acid,[33] and allylic alcohol **2-37** using EDC in the presence of DMAP. Then in the key step, the ester **2-38** was subjected to stereoselective enolization using chiral Koga-type chiral lithium amide generated from **2-39**. The resulting lithium enolate was intercepted as silyl ketene acetal **2-40**, which underwent a highly diastereoselective [3,3]-sigmatropic shift delivering carboxylic acid **2-41** in 94% yield.



Scheme 2-19. Application of chiral lithium amide in total synthesis of (+)-pinnatoxin A

2.5.2 Application in the Total Synthesis of (+)-Dragmacidin D

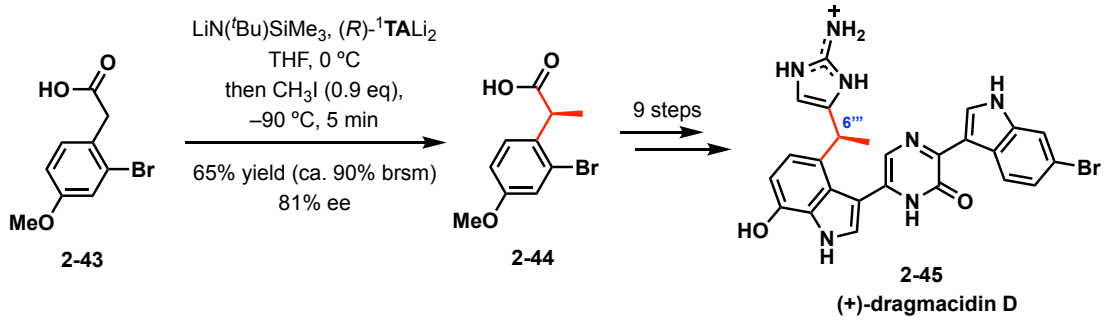
Dragmacidin D (**2-45**) is one of heterocyclic bis(indole) natural products isolated from deep-water Caribbean sponges of the *Dragmacidon* and *Spongosorites* genera, being found, along with dragmacidin E, as a potent inhibitor of the serine/threonine phosphatases PP1 and PP2A.[34]

In 2015, Zakarian group introduced an asymmetric synthesis of (+)-dragmacidin D completed in 10 steps,[35] which is much shorter than the previous asymmetric total synthesis (26 steps, Jia and Capon, 2015 [36]). This concise synthesis was enabled by a direct early-stage enantioselective alkylation of commercially available 4-methoxy-2-bromophenylacetic acid (**2-43**), with a C_2-symmetric tetraamine and lithium *N*-(trimethylsilyl)-*tert*-butylamide as the enolization reagent.

Though it was based on our published methodology,[22] a large effort was applied on succeeding the asymmetric alkylation. Acid **2-43** was a challenging substrate in the initial studies. Using either *n*-BuLi or lithium diisopropylamide (LDA) as the enolization reagents, α-methylation with methyl iodide only led to decomposition of the starting material, due to a possible lithiation of the arene C-H bond of the substrate acid. Lithium bis(trimethylsilyl)amide (LiHMDS) together with lithiated C_2-symmetric tetraamine provided 67% yield of totally racemized **2-44**, because of the higher acidity of $(Me_3Si)_2NH$ (pK_a = 26) led to protonation of (*R*)-^{1}**TA**Li_2, preventing the formation of chiral mix lithium aggregates.

After investigating a series of readily available amines, *t*Bu(Me_3Si)NH (pK_a = 26) showed a right balance between steric bulk to prevent arene lithiation and basicity (pK_a = 37 for *i*-Pr_2NH). LiN(*t*Bu)$SiMe_3$ together with lithiated tetraamine led to 65% yield of **2-44** with 81% enantiomeric excess in 4.7-gram scale.

The stereochemistry of the asymmetric alkylation for **2-44** was solid, and strongly supports the assignment of its sole stereogenic center as *S* configuration at the 6''' position, which is consistent with the original prediction by Stoltz[34] and other members of the dragmacidin family of natural products.



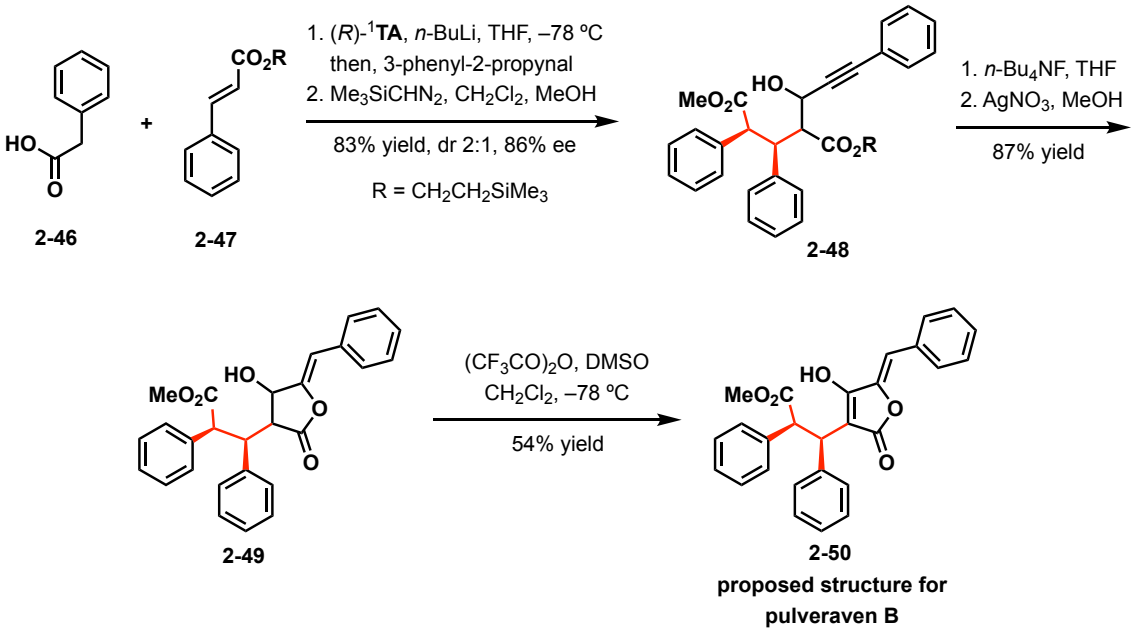
Scheme 2-20. Application of chiral lithium amide in synthesis of (+)-dragmacidin D

2.5.3 Application in the Total Synthesis of Pulveraven B

Pulveraven B was reported as a constituent of the edible mushroom *Pulveroboletus ravenelii* in 2003.[37] It showed selective inhibition of carcinogen-induced pre-neoplastic lesion formation in mouse mammary organ culture (IC_{50} = 0.8 μM). Based on the methodology of enantioselective conjugate addition between the arylacetic acids and α,β-unsaturated esters, our group introduced a total synthetic route to pulveraven B with a high enantioselectivity in 5 steps.[23]

As showed in the Scheme 2-21, after the asymmetric Michael addition of 2-(trimethylsilyl)ethyl cinnamate (**2-47**) onto phenylacetic acid, the initial conjugate adduct was subjected *in situ* to aldol coupling with 3-phenyl-2-propyanal, yielding a 2:1 mixture of aldol products **2-48** with 86% ee for both diastereomers (83% yield). γ-Lactone **2-49** was afforded by a cleavage of the trimethylsilylethyl ester with *n*-Bu_4NF followed by a Ag-catalyzed

cyclization. Swern oxidation of **2-49** yielded the tetronic acid with a structure **2-50** proposed for pulveraven B, of which the optical rotation and NMR spectral data, though, did not match those reported for the natural product.



Scheme 2-21. Application of chiral lithium amide in total synthesis of pulveraven B

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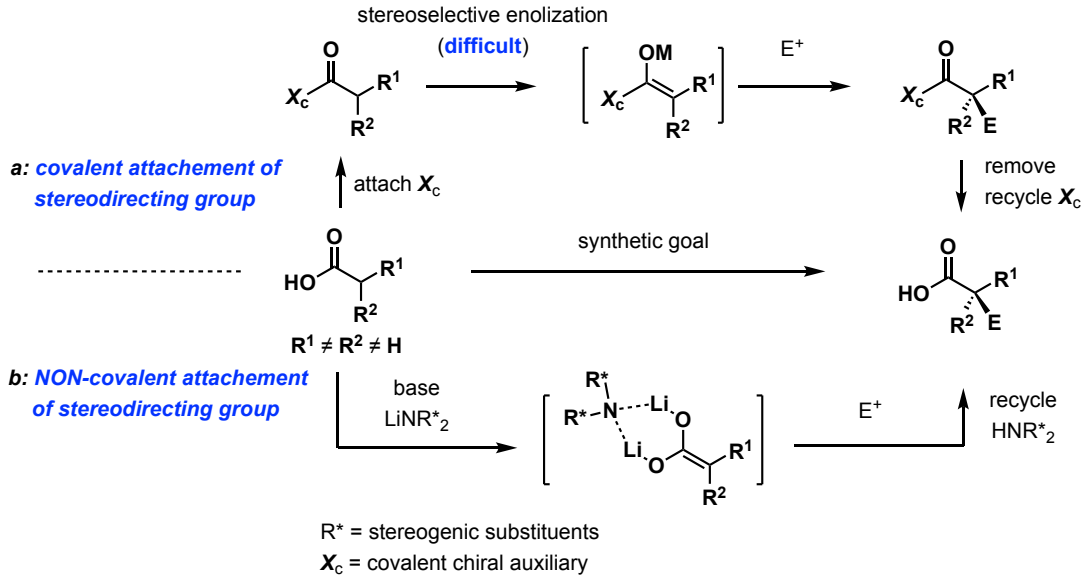
Chapter 3. Lithium Enolates in the Enantioselective Construction of Tetrasubstituted Carbon Centers with Chiral Lithium Amides as Noncovalent Stereodirecting Auxiliaries

3.1 Introduction

The generation of stereogenic quaternary carbon centers is an everlasting challenging in organic chemistry.[1] Lithium enolates are ubiquitous reactive intermediates that form the basis of many powerful asymmetric transformations, including these quaternizations. Contemporary methods for the practical stereoselective transformation of lithium enolates derived from carboxylic acids are dominated by the use of covalently bound stereodirecting chiral auxiliaries [2] and self-regenerating stereocenters. [3] However, the allylic strain [4] in the enolizations of oxazolidinone- and *N*-alkylephedrine-based auxiliaries precludes the simple generation of the fully substituted enolates required for the formation of tetrasubstituted sp^3 carbon stereocenters (Scheme 3-1, pathway a).[5]



Scheme 3-1. Enantioselective construction of tetrasubstituted carbon center

As demonstrated in Chapter 2, non-covalent stereodirecting auxiliaries offer considerable advantages for the enantioselective α-functionalization of arylacetic acids.[6] Formed *in situ*, they temporarily bound to the reactive intermediate and can be recovered quantitatively by a simple aqueous workup procedure. The well-documented and structurally defined aggregates comprising lithium enolates and lithium amides translate this general concept into practice.[7] Generating enediolates[8] with tightly bounding to chiral lithium amides, as we designed, a highly stereoselective enolization would form and undergo an asymmetric functionalization of α-branched carboxylic acids (Scheme 3-1, pathway b). Herein, we describe a practical protocol that enables highly enantioselective construction of tetrasubstituted carbon centers with chiral lithium amides, including a facile and quantitative recovery of a tetraamine auxiliary in nearly pure form through simple aqueous extraction.

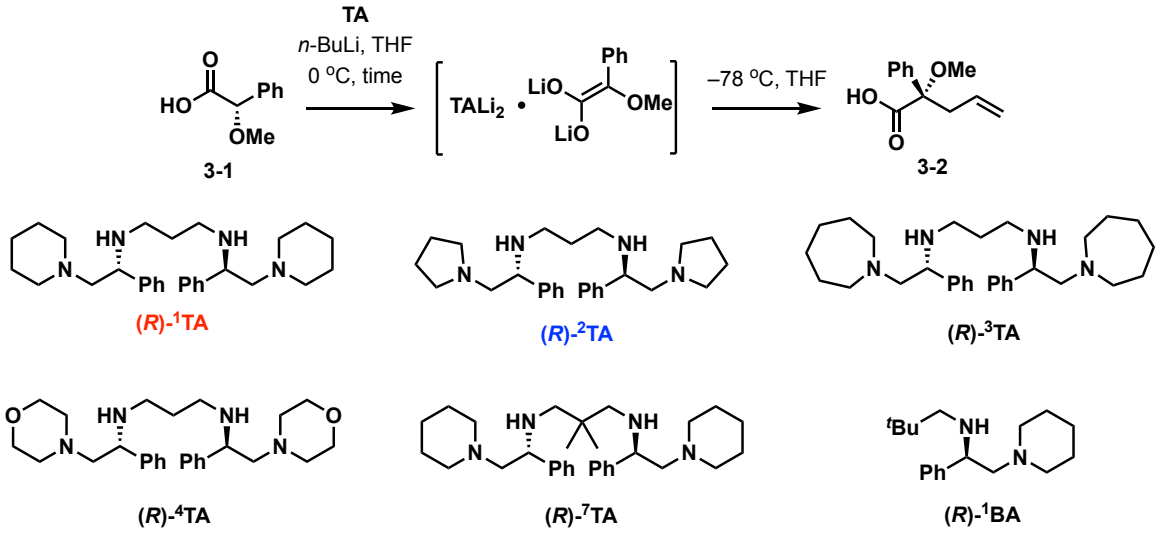
3.2 Optimization of Enantioselective Alkylation of α-Methoxyphenylacetic Acid

The alkylation of α-methoxy phenylacetic acid (2-methoxy-2-phenylacetic acid, **3-1**) with allyl bromide was carried out for the optimization of this enantioselective methodology (Table 3-1). The temperature and time of aggregation are critical parameters influencing enantiocontrol.

Originally, the *S*-enantiomer of the substrate acid was applied in the optimization in 0.50 mmol scale. *n*-Butyllithium (4.0 equiv) was added to the THF solution of substrate and piperidine base (*R*)-[1]**TA** at 0 ºC and the following aggregation time was 30 min. Allyl bromide (4.0 equiv) was then added at –78 ºC over 10 min and the solution was kept stirring for another 5 hours before quenched, resulting **3-2** with 76% yield and 81% ee (entry 1). 2.0 Equivalent of diisopropylamine was used to generate lithium diisopropylamide (2.0 equiv) *in situ* during the

initial lithiation and did not affect dramatically on the result (79% yield, 77% ee, entry 2). Lower aggregation temperature (–20 ºC) led to lower enantioselectivity (65% ee, entry 3). The vary on the lithiation-aggregation time affected enantiomeric excess to a certain extent: the ee of the yielded quaternary acid was positively related to the aggregation time in the range of 15 min to 2 h at 0 ºC (entry 4,5). The time-dependent stereoselectivity correlates with the slow formation of mixed aggregates describe below. Similar strong correlations for lithium enolate aging and stereoselectivity have been documented previously.[9]

Table 3-1. Identification of optimal chiral lithium amides for the enantioselective allylation of (*S*)- α-methoxyphenylacetic acid.[a]



entry	aggregation time (h)	(*R*)-TA	yield (%)	ee (%)
1	0.5	**^{1}TA**	76	81
2[b]	0.5	**^{1}TA**	79	77
3[c]	0.5	**^{1}TA**	79	65

4	0.25	[1]**TA**	77	78
5	2	[1]**TA**	78	83
6	0.5	[2]**TA**	74	84
7	0.5	[3]**TA**	73	77
8	0.5	[4]**TA**	77	84
9	0.5	[7]**TA**	60	10
10	0.5	[1]**BA**	66	53
11	**2**	[2]**TA**	**79**	**89**
12	2	[4]**TA**	76	86
13[d]	2	[2]**TA**	76	89

[a] *n*-BuLi, (*S*)- α-methoxyphenylacetic acid (0.50 mmol), and (*R*)-**TA** were combined at 0 °C in THF. After the indicated aggregate formation time, allyl bromide was added at –78 °C over 10 min. Enantiomeric excesses were measured using chiral HPLC analysis. All results are corrected to bases with the *R* configuration shown. [b] *i*-Pr_2NH (2 equiv) was used together with tetraamine. [c] The mixed aggregate was formed at –20 °C. [d] (±)-α-Methoxyphenylacetic acid was used.

Besides piperidine tetraamine (*R*)-[1]**TA**, other chiral base with different *terminal amine* in our library were tested with aggregation at 0 ºC for 30 min (entry 6–8). Pyrrolidine tetraamine (*R*)-[2]**TA** and morpholine tetraamine (*R*)-[4]**TA** provided relatively higher stereocontrol (84% ee for both), while azepane tetraamine (*R*)-[3]**TA** afforded similar enantioselectivity (77% ee). The ee value decreased dramatically when geminal dimethyl tetraamine (*R*)-[7]**TA** was used as chiral lithium amide precursor, in which only 10% ee was measured and the yield dropped relatively

to 60% after 5-hour allylation (entry 9). Koga type chiral neopentyl bisamine (*R*)-^{1}**BA** was also examined in the optimization, resulting with 66% yield of allylated acid in 53% ee.

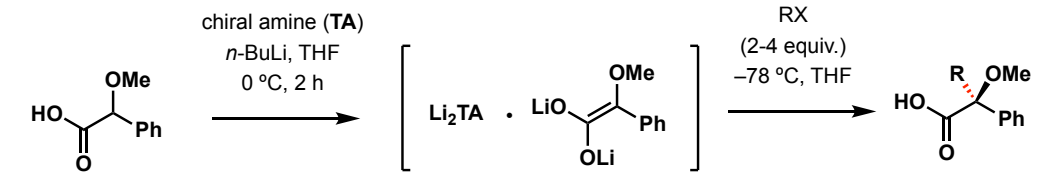
Pyrrolidine base (*R*)-^{2}**TA** and morpholine base (*R*)-^{4}**TA** were also tested with a longer aggregation time to 2 hours at 0 ºC, and increasing ee's are found in both tests, 89% and 86% ee, respectively (entry 11–12). The time-dependent stereocontrol correlates with the slow formation of mixed aggregates described below. No significant difference on the result was noticed when the racemic α-methoxyphenylacetic acid was also tested comparing with its enantiomerically pure isomer (76% yield, 89% ee, entry 13), which made us select the racemic α-alkoxy carboxylic acids for the future study due to the easier access of corresponding starting materials.

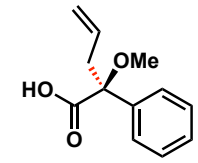
Based on the above study of screening conditions of aggregation, ^{1}**TA** and ^{2}**TA** were decided to be applied as chiral amine for the substrate scope study. The reactive aggregate was generated by incubating the carboxylic acid substrate, the chiral amine (1:1 molar ratio), and 4.0 equiv. of alkyllithium reagent in tetrahydrofuran (THF) at 0 ºC for 2h. The later functionalizations were carried out at –78 ºC unless noted otherwise.

3.3 Asymmetric Alkylation Reactions

With the optimal conditions for the generation of mix aggregates, a survey showed that chiral amines ^{1}**TA** and ^{2}**TA** promoted the alkylation of α-alkoxy carboxylic acids with a variety of reactive alkyl halides in good yields and excellent enantioselectivities.

Table 3-2. Scope of alkylating agents in the enantioselective alkylations for the construction of tetrasubstituted carbon centers [a]

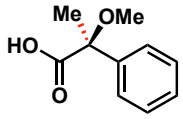




3-2

[1]TA: 78% yield, 83% ee

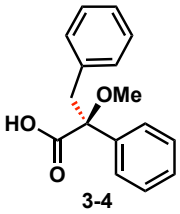
[2]TA: 79% yield, **89% ee**



3-3

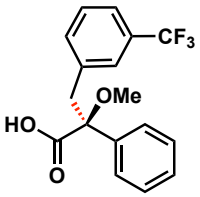
[1]TA: 77% yield, **97% ee**

[2]TA: 78% yield, 93% ee



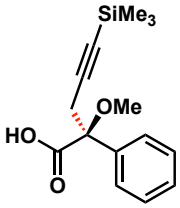
3-4

[2]TA: 70% yield, **94% ee**



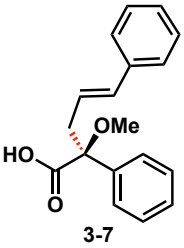
3-5

[2]TA: 89% yield, **84% ee**



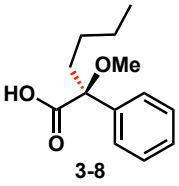
3-6

[2]TA: 72% yield, **89% ee**



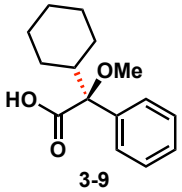
3-7

[2]TA: 61% yield, **85% ee**



3-8

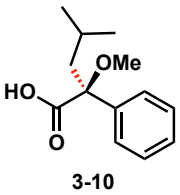
[2]TA: 70% yield, **89% ee**[b]



3-9

[1]TA: 70% yield, 80% ee[c]

[2]TA: 69% yield, **91% ee**[c]



3-10

[2]TA: 23% yield, **53% ee**[d]

[a] Experiments were performed on a 0.50 mmol scale. All results are corrected to bases with the *R* configuration shown.[b] Alkylation was conducted at –40 ºC. [c] 3-Bromocyclohexene was used as the reagent, followed by hydrogenation. [d] Alkylation was conducted at –20 ºC.

Besides the allyl bromide showed in the previous study, other active alkyl halides were tested in the scope (Table 3-2), including iodomethane (**3-3**, **[1]TA**, 97% ee; **[2]TA**, 93% ee), benzylic bromides (**3-4**, **[2]TA**, 94% ee; **3-5**, **[2]TA**, 84% ee), alkynyl bromide (**3-6**, **[2]TA**, 89% ee),

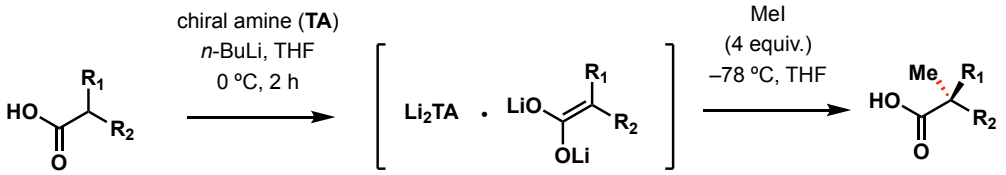
and cinnamyl bromide (**3-7**, **^{2}TA**, 85% ee). Less reactive haloalkanes such as 1-iodobutane required a lightly elevated temperature of –40 ºC but still afforded good yield and selectivity (**3-8**, **^{2}TA**, 70% yield, 89% ee). Remarkably, 3-bromocyclohexene with subsequent hydrogenation provided cyclohexyl-substituted **3-9** in 91% ee using **^{2}TA**. Bulkier electrophile decelerated the progress of the alkylation: only 23% yield of **3-10** was obtained in 53% ee after the alkylation was carried out for 5 hours at –20 ºC.

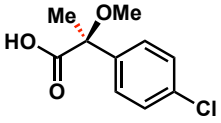
Investigation of the scope of carboxylic acid substrates was also carried out, focusing on methylation with iodomethane emblematically — an important transformation because hydrogen-to-methyl substitution is valuable during drug discovery (Table 3-3). Varying the position of the chloro-substituent on the phenyl group provided a notable impact on enantioselectivity. With (*R*)-**^{1}TA** as the non-covalent auxiliary, 4-chloro- and 3-chloro-substituted products **3-11** and **3-12** were obtained in 90% ee and 84% respectively, while a significant reduction on enantioselectivity to 75% ee was observed for (*S*)-2-(2-chlorophenyl)-2-methoxypropinoic acid **3-13**. The stereocontrol could be easily restored to 84% ee by switching the chiral auxiliary to **^{2}TA**, with a slight drop of the yield to 51%. Heteroaromatic acid also provided excellent result: 2-methoxy-2-(thiophen-2-yl)acetic acid afforded the corresponding tetrasubstituted product **3-14** in 80% yield and 94% ee with **^{2}TA**. Importantly, aliphatic 2-methoxy carboxylic acids were also suitable substrates, affording **3-15** in 91% ee and **3-16** in 85% ee. In these cases, *n*-butyllithium had to be replaced with *sec*-butyllithium to prevent 1,2-addition of the organolithium reagent to the carboxy group.

An unexpected reduction in enantioselectivity to 79% ee was observed in the case of methylation of *O*-methoxymethyl mandelic acid with **^{1}TA** as the stereodirecting reagent, while

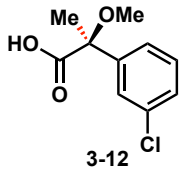
the ee value could be raised up to 88% when ^{2}**TA** was used (**3-17**). The methoxymethyl (MOM) group was readily hydrolyzed with HCl in methanol to the free alcohol in 88% yield.

Table 3-3. Scope of substrate acids in the enantioselective alkylations for the construction of tetrasubstituted and quaternary carbon centers [a]

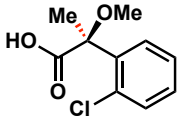




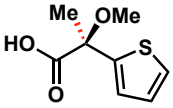
3-11
^{1}TA: 84% yield, **90% ee**



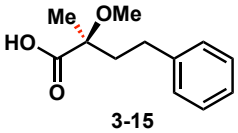
3-12
^{1}TA: 69% yield, **84% ee**



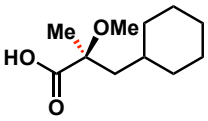
3-13
^{1}TA: 68% yield, 75% ee
^{2}TA: 51% yield, **84% ee**



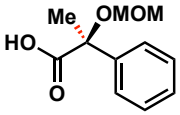
3-14
^{1}TA: 84% yield, 88% ee
^{2}TA: 80% yield, **94% ee**



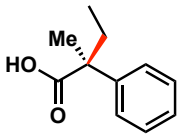
3-15
^{1}TA: 75% yield, **91% ee**[b]



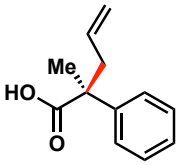
3-16
^{1}TA: 75% yield, **85% ee**[b]



3-17
^{1}TA: 70% yield, 79% ee
^{2}TA: 54% yield, **88% ee**



3-18
^{1}TA: 72% yield, **90% ee**



3-19
^{1}TA: 80% yield, **86% ee**

[a] Experiments were performed on a 0.50 mmol scale. All results are corrected to bases with the *R* configuration shown. [b] *sec*-Butyllithium was used instead of *n*-butyllithium.

A direct enantioselective construction of all-carbon quaternary centers was also illustrated in the substrate scope: the ethylation and allylation of 2-phenylpropionic acid afforded **3-18** and **3-19** in 90% and 86% ee, respectively. A slight modification was applied on the reaction conditions: the aggregation was carried with **^{1}TA** as stereodirecting reagent at room temperature (23 ºC) for 1 hour, and the alkylation with corresponding alkyl halide, iodoethane or allylbromide, was quenched immediately after the 10-min addition. Notably, the facial selectivity in now reversed in the resulting compounds, with the opposite absolute configuration.

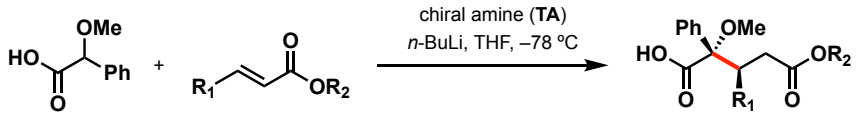
3.4 Asymmetric Conjugate Addition

Another common transformation available to lithium enolates is conjugate addition to α,β-unsaturated esters (Michael addition). Two or more stereogenic centers can potentially be created in this powerful carbon-carbon bond-forming process. Non-covalent lithium amide auxiliaries were found enabling highly enantio- and diastereoselective conjugate additions in good to excellent chemical yields, affording products with adjacent tetrasubstituted and trisubstituted stereogenic carbon centers.

The scope of α,β-unsaturated esters was carried out with α-methoxyphenylacetic acid as the Michael donor in 0.50 mmol scale (Table 3-4). The use of chiral tetraamine (*R*)-**^{1}TA** and ethyl cinnamate afforded adduct **3-20** in 96% ee as a single diastereomer. Similarly, functionalized products, **3-21**, **3-22** and **3-23**, have also been prepared in high stereoselectivity (93-97% ee, dr >20:1) from methyl crotonate, ethyl 4,4,4-trifluorocrotonate, and *tert*-butyl (*E*)-3-cyclopropylacrylate, respectively. A variety of heteroaryl-substituted acrylates were also suitable as Michael acceptors, and the reactions of 3-indolyl (**3-24**), 2-furyl (**3-25**), and 3-

pyridinyl acrylates (**3-26**) afforded the corresponding products in 92-98% ee and >20:1 diastereomeric ratio. With no terminal substitution, the Michael addition of *n*-butyl acrylate provided the tetrasubstituted carboxylic acid **3-27** in 75% ee with **^{1}TA**, while the ee value was increased to 92% when the chiral amine replaced with **^{2}TA**.

Table 3-4. Scope of unsaturated esters in the enantioselective conjugate additions for the construction of tri- and tetrasubstituted carbon centers [a]



3-20
^{1}TA: 77% yield
dr >20:1, **96% ee**

3-21
^{1}TA: 84% yield
dr >20:1, **94% ee**
4.1 gram scale
98% recovery of (*R*)-^{1}TA

3-22
^{1}TA: 66% yield
dr >20:1, **95% ee**

3-23
^{1}TA: 86% yield
dr >20:1, **97% ee**

3-24
^{1}TA: 58% yield
dr >20:1, **96% ee**[b]

3-25
^{1}TA: 58% yield
dr >20:1, **98% ee**

3-26
^{1}TA: 55% yield
dr >20:1, **93% ee**[b]

3-27
^{1}TA: 53% yield, 75% ee[b]
^{2}TA: 39% yield, **92% ee**[b]

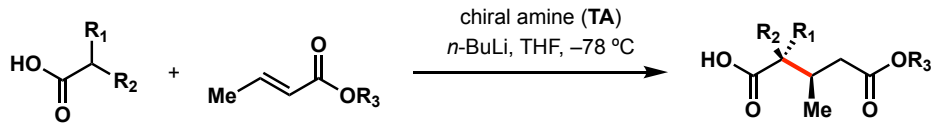
[a] Experiments were performed on a 0.50 mmol scale. All results are corrected to bases with the *R* configuration shown. [b] Isolated yield after methyl ester formation.

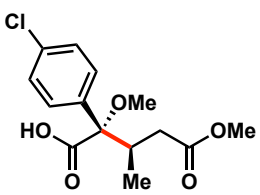
A large-scale conjugate addition was carried out using 4.1 grams of racemic α-methoxyphenylacetic acid and 1.0 equivalent of methyl crotonate with (*R*)-**^{1}TA** as non-covalent chiral auxiliary, obtaining 84% yield of **3-21** in 94% ee and >20:1 dr. Also, the chiral amine was recovered in 98% yield via acid-base extraction.

The effect of substituent variation in 2-methoxy-2-arylacetic acids were then under investigation. (Table 3-5) As in the previous alkylation study, comparing to 4-chloro (**3-28**, 93% ee, dr >20:1) and 3-chloro (**3-29**, 86% ee, dr >20:1) congers with **^{1}TA**, stereoselectivities decreased with 2-(2-chlorophenyl)-2-methoxyacetic acid (**3-30**, 78% ee, dr 10:1). High enantioselectivity (91% ee) was restored with **^{2}TA** as stereodirecting auxiliary. The conjugate addition of 2-methoxy-2(thiophen-2-yl)acetic acid to methyl crotonate afforded 66% yield of functionalized acid **3-31** with high enantio- and diastereoselectivity (97% ee, dr >20:1). More strikingly, aliphatic 2-methoxy carboxylic acids delivered the corresponding adducts with methyl crotonate in excellent enantioselectivity and good diastereoselectivity under the modified condition.

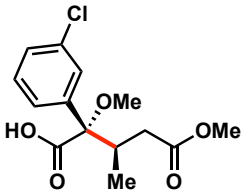
Using a combination of *i*-Pr_2NLi and (*R*)-Li_2^{1}**TA**, from 3-cyclohexyl-2-methoxypropionic acid, 2-methoxy-4-phenylbutyric acid, and 2-methoxypropionic acid, respectively, Michael addition products, **3-32**, **3-33** and **3-34**, have been accessed in 89-98% ee with a 7:1 to 10:1 diastereomeric ratio in good yields. Besides the 2-methoxy carboxylic acids, some other acids with different alkoxy groups were suitable in the conjugate addition. A reaction of tetrahydropyran-2-carboxylic acid and benzyl crotonate afforded product **3-35** in 74% yield and 98% ee as a single diastereomer. Addition of the more versatile methoxymethyl (MOM) derivative with standard procedure also afforded 69% yield of **3-36** in >20:1 dr with a slight decrease on the enantiocontrol (86% ee).

Table 3-5. Scope of substrate acids in the enantioselective conjugate additions for the construction of tetrasubstituted carbon centers [a]

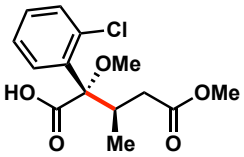




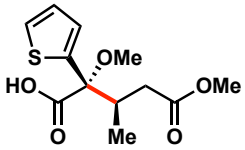
3-28
[1]TA: 79% yield
dr >20:1, **93% ee**



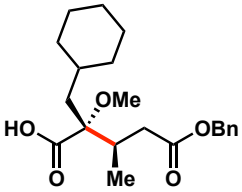
3-29
[1]TA: 54% yield
dr >20:1, **86% ee**



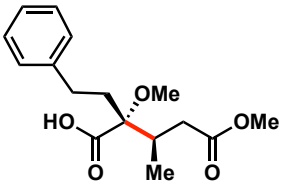
3-30
[1]TA: 47% yield, dr 10:1, 78% ee[b]
[2]TA: 46% yield, dr 10:1, **91% ee**[b]



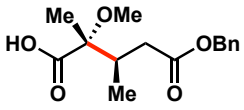
3-31
[1]TA: 66% yield
dr >20:1, **97% ee**



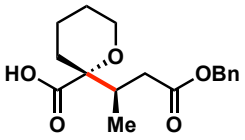
3-32
[1]TA: 67% yield
dr 10:1, **98% ee**[c]



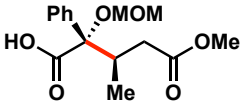
3-33
[1]TA: 72% yield
dr 10:1, **94% ee**[c]



3-34
[1]TA: 69% yield
dr 7:1, **90% ee**[c]



3-35
[1]TA: 74% yield
dr >20:1, **98% ee**[c]



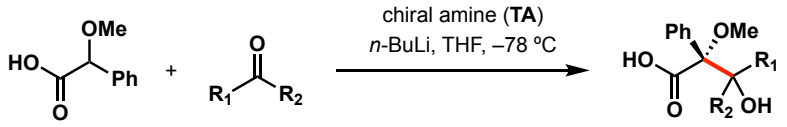
3-36
[1]TA: 69% yield, dr >20:1, **86% ee**
[2]TA: 66% yield, dr 17:1, 83% ee

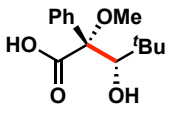
[a] Experiments were performed on a 0.50 mmol scale. All results are corrected to bases with the *R* configuration shown. [b] Isolated yield after methyl ester formation. [c] *i*-Pr_2NLi (2.0 equiv) was used for enediolate formation.

3.5 Asymmetric Aldol Reaction

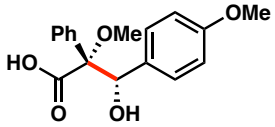
Aldol reaction is the third transformation common to lithium enolates. In this study, a survey of aldol reactions was also under investigation and revealing that moderate to good yields and stereoselectivities could be obtained by the noncovalent lithium amides (Table 3-6).

Table 3-6. Scope of aldehydes/ketones in the enantioselective aldol reactions for the construction of tetrasubstituted carbon centers [a]

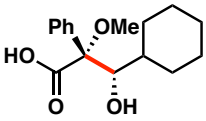




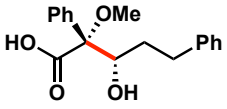
3-37
[1]TA: 60% yield, dr 10:1, 50% ee[b]
[2]TA: 64% yield, dr 13:1, **89% ee**[b]



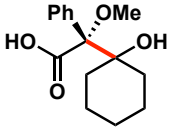
3-38
[1]TA: 47% yield, dr 7:1, 40% ee[b]
[2]TA: 34% yield, dr 6:1, **56% ee**[b]



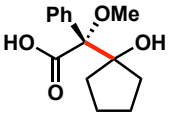
3-39
[1]TA: 45% yield, dr 8:1, 49% ee[b]
[2]TA: 50% yield, dr 8:1, **63% ee**[b]



3-40
[1]TA: 51% yield, dr 1.5:1, 9/**80% ee**[b]
[2]TA: 52% yield, dr 1:1, 51/71% ee[b]



3-41
[1]TA: 84% yield, 77% ee
[2]TA: 88% yield, 77% ee
[4]TA: 68% yield, **80% ee**



3-42
[1]TA: 46% yield, 26% ee
[2]TA: 69% yield, **60% ee**

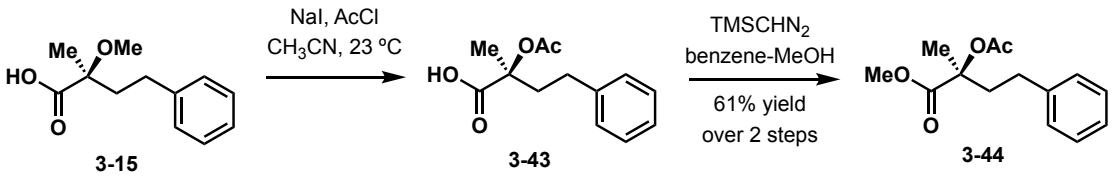
[a] Experiments were performed on a 0.50 mmol scale. All results are corrected to bases with the *R* configuration shown. [b] Isolated yield after methyl ester formation.

Aldol addition of α-methoxyphenylacetic acid to pivalaldehyde furnished 64% yield of β-hydroxy carboxylic acid **3-37** in 89% ee and 13:1 dr using [2]**TA** as the stereodirecting auxiliary,

while a lower stereoselectivity was observed with ^{1}**TA** both on relative and absolute control. Similarly, ^{2}**TA** provided higher enantioselectivity and comparable diastereoselectivity to ^{1}**TA** in the aldol reaction of the same carboxylic acid substrate with 4-methoxybenzylaldehyde, affording **3-38** (34% yield, 56% ee, 6:1 dr). Remarkably, even readily enolizable aldehydes proved to be feasible substrates. The reaction using cyclohexanecarboxaldehyde as electrophile afforded 50% yield of the aldol adduct (**3-39**) in 63% ee and 8:1 dr when ^{2}**TA** was the chiral auxiliary. A 3:2 mixture of diastereomers (**3-40**) was generated from 3-phenylpropanal with enantiomeric excess of 9 and 80% ee using ^{1}**TA**. The alternative chiral amine ^{2}**TA** occurred with the comparable enantioselectivities of both diastereomers (51 and 71% ee). Besides the aldehydes, ketones were also tested in this asymmetric methodology study. Cyclohexanone afforded the aldol addition product (**3-41**) in good yields (68-88%) and enantioselectivity (77-80% ee) with three related lithium amide reagents, while **3-42** was obtained from the reaction of cyclopentanone in 69% yield and 60% ee.

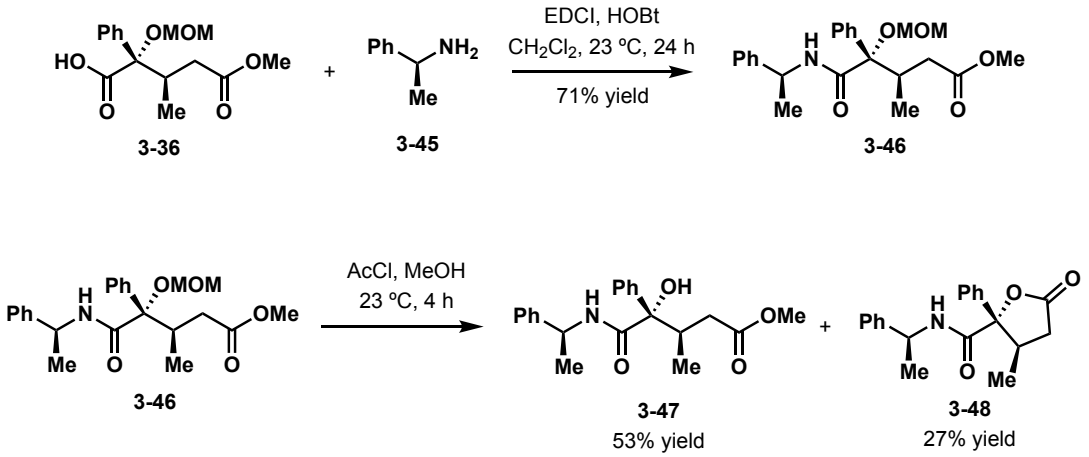
3.6 Determination of Absolute Configuration

The alkylated product 2-methoxy-2-methyl-4-phenylbutanoic acid (**3-15**) was represented in the derivatization to confirm the absolute configuration (Scheme 3-2). Followed by Oku's procedure[10], the α-methoxy group was selectively cleaved by sodium iodide-acyl chloride in acetonitrile at room temperature. The resultant α-acetyl carboxylic acid **3-43** maintained the original stereochemistry, and then transformed to the corresponding methyl ester **3-44** in 61% yield over 2 steps. The optical rotation of **3-44** was consistent with the literature data of the *S*-isomer[11], confirming the absolute configuration of the ester and the original acid **3-15** is *S*.



Scheme 3-2. Determination of absolute configuration of alkylated product 3-15

The conjugate adduct, 5-methoxy-2-methoxymethoxy-3-methyl-5-oxo-2-phenylpentanoic acid (**3-36**), was carried out as the representative in the determination of the absolute configuration (Scheme 3-3).



Scheme 3-3. Determination of absolute configuration of conjugate adduct 3-36

The carboxylic acid **3-36** was coupled with (*S*)-α-methylbenzylamine (**3-45**) using EDCI·HCl and HOBt·H_2O as condensation reagents, affording the amide in 71% yield as a single diastereomer. The MOM group of the amide was removed by stirring with acetyl chloride in methanol at room temperature for 4 hours and the reaction resulted with 53% yield of α-hydroxyamide **3-47** and 27% yield of lactone **3-48**. The single crystal of **3-47** was obtained by recrystallization in hexane-diethyl ether mixed solvent, and the structure was

unambiguously determined by X-ray crystallography (**Figure 3-1**). Thus, the absolute configuration of **3-36** is (2*S*, 3*R*).

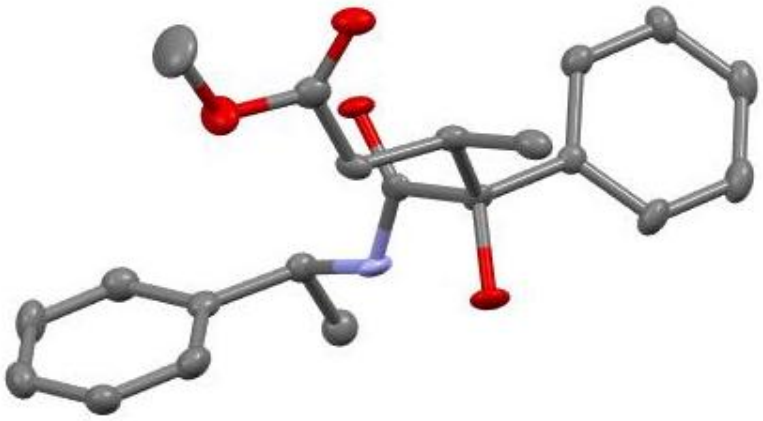
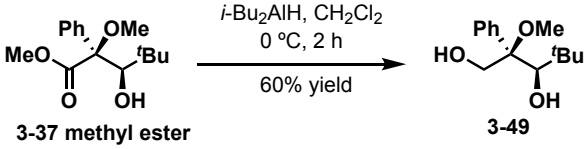


Figure 3-1. Single crystal structure of 3-47

The aldol adducts from pivaldehyde, 3-phenylpropanal, and cyclohexanecarboxaldehyde were respectively applied in the derivatizations to determine the absolute configurations. The aldol adduct **3-37** (89% ee, 13:1 dr, (*S*)-^{2}**TA**) was reduced by diisobutylaluminium hydride (DIBAL) in dichloromethane affording 60% yield of crystalline diol **3-49**, of which the structure was confirmed by X-ray crystallography (Figure 3-2), showing the absolute configuration of **3-37** is (2*S*, 3*R*).



Scheme 3-4. Determination of absolute configuration of aldol adduct 3-37

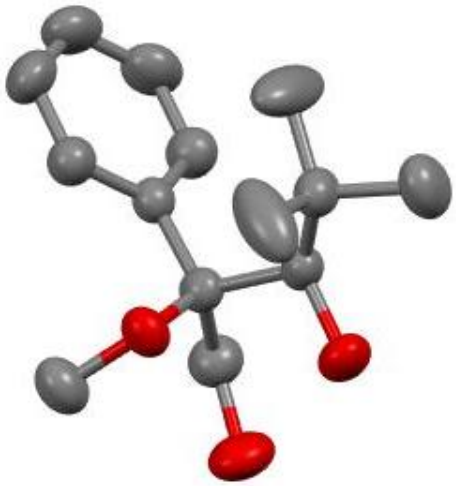
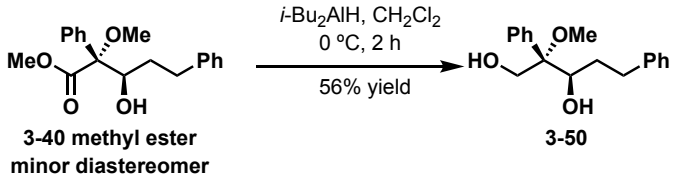


Figure 3-2. Single crystal structure of 3-49

The same reduction (Scheme 3-5) was also applied on the enantiomerically rich, minor diastereomer of **3-40** (9/80% ee, dr 1.5:1, (*R*)-[1]**TA**). The single crystal of the diol **3-50** was obtained by the recrystallization from hexanes, and X-ray crystallography showed the absolute configuration of **3-50** was (2*S*, 3*R*, Figure 3-3). On account of the result, the absolute configurate of the minor diastereomer is (2*R*, 3*R*), and rationally, that of the major diastereomer is (2*R*, 3*S*).



Scheme 3-5. Determination of absolute configuration of aldol adduct 3-40

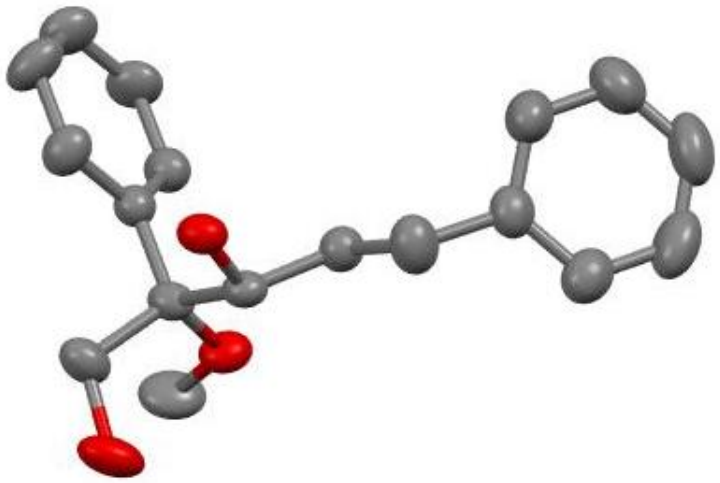
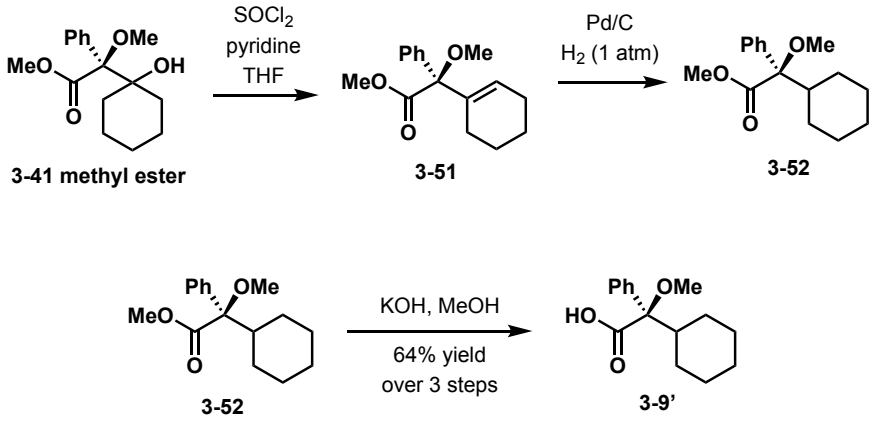


Figure 3-3. Single crystal structure of 3-50

The methyl ester derived from **3-41** (80% ee, (*S*)-^{4}**TA**) was treated with thionyl chloride and pyridine in THF solution, resulting with the dehydrated cyclohexene. Followed by hydrogenation with Pd/C and H_2 at 1 atm and hydrolysis with potassium hydroxide in methanol, 2-cyclohexyl-2-methoxy-2-pheylacetic acid (**3-9'**) was obtained. The optical property of the resulted **3-9'** was consistent with the one in the alkylation substrate scope using (*S*)-^{2}**TA**. Based on the previous study of the alkylated products, the absolute configurations of the acid **3-9'** and the original **3-41** are assigned as *R* and *S*, respectively, as drawn in the Scheme 3-6.

Note that all the results in the previous discussion about substrate scope have been corrected to chiral tetraamine bases with the *R* configuration. Therefore, the absolute configurations of **3-37** and **3-41** in the substrate scope of aldol reactions (Table 3-6) were modified to the opposite, showing as (2*R*, 3*S*), and *R*, respectively. In conclusion, the consistent *R* configuration at 2-position of **3-37, 3-40** and **3-41** showed the preference for *re* face attack,

and the consistent *S* configuration of **3-37** and **3-40** at 3-position supported the diastereoselectivity of aldol reaction.

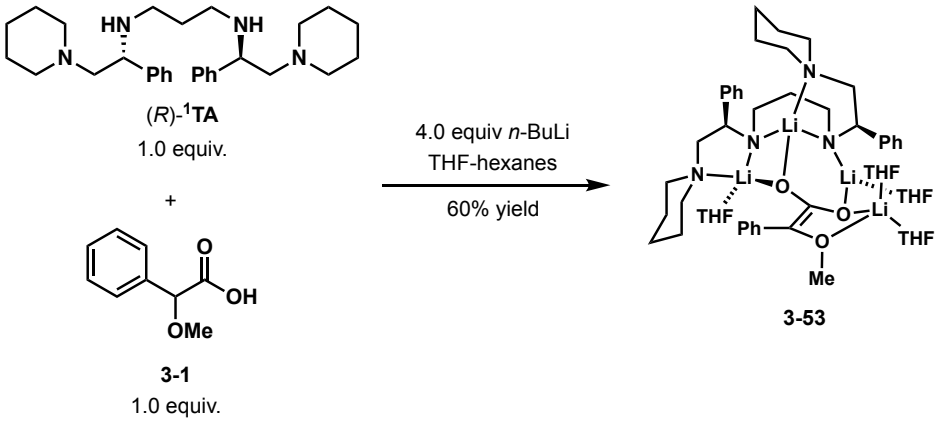


Scheme 3-6. Determination of absolute configuration of aldol adduct 3-41

3.7 Study of the Mixed Aggregate of Lithium Enediolate and Chiral Lithium Amide

The high stereocontrol in the reaction of lithium enediolates directed by chiral lithium amide reagents strongly implicates structurally well-defined mixed aggregates as key reactive species.[12] Thus, the analysis of the mixed aggregates participating in this methodology was carried out based on X-ray crystallography, NMR spectroscopy and density functional theory (DFT) calculation, which are discussed as follow.

We found the evidence of such aggregates in the solid state via X-ray diffraction study. The mixed aggregate **3-53** was prepared from a mixture of 1.0 equiv. each of racemic α-methoxyphenylacetic acid and chiral amine (*R*)-[1]**TA** and 4.0 equiv. of *n*-butyllithium in tetrahydrofuran at a temperature range of –25 to 23 ºC (Scheme 3-7).



Scheme 3-7. Preparation of the mixed aggregate 3-53

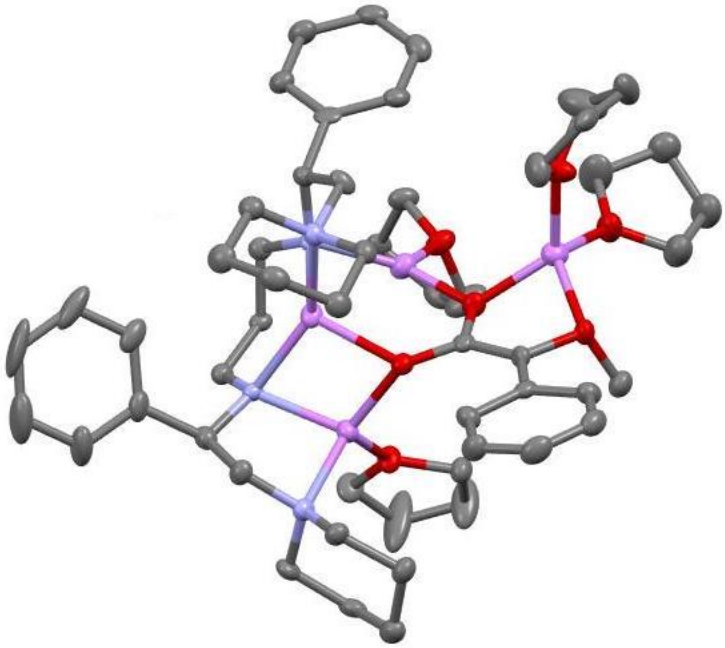


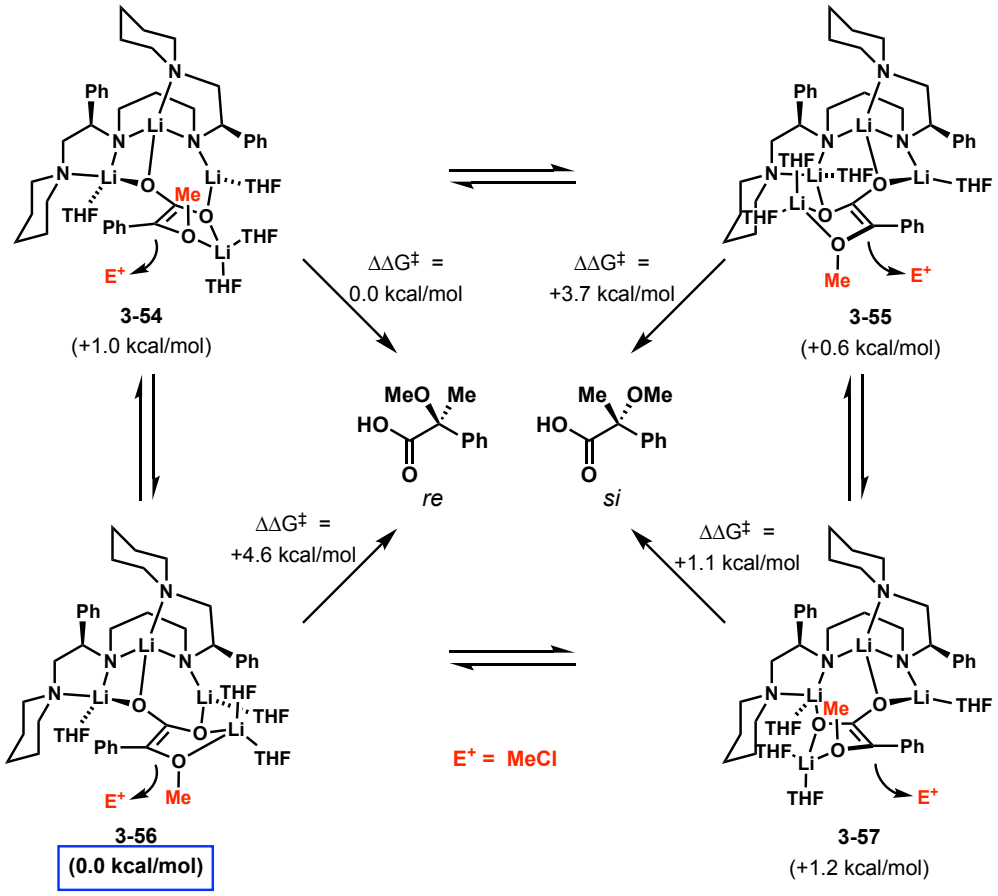
Figure 3-4. Single crystal structure of 3-53

Pale yellow crystalline product was obtained via the crystallization from hexanes at –25 ºC in 60% yield, and a single crystal suitable for X-ray diffraction was grown from a THF solution layered with hexanes. A supramolecular assembly of a doubly deprotonated substrate acid fragment, a doubly deprotonated (*R*)-[1]**TA** fragment, four lithium cations, and four THF

molecules was demonstrated by the single crystallography (Figure 3-4). The chiral lithium amide from (*R*)-[1]**TA** and similar bases continues to display a remarkable capacity to form mixed aggregates with a range of lithium salts.[7]

Given results of previous spectroscopic studies, we anticipated that ^{6}Li NMR spectroscopy would reveal a single mixed aggregate displaying a highly characteristic ensemble of four ^{6}Li resonances in a 1:1:1:1 ratio. Instead, we observed *two* such ensembles in an approximate 3:1 ratio. These ensembles were traced to isomeric species by showing the 3:1 ratio is independent of the absolute concentration of the mixed aggregate as well as the THF concentration (using toluene co-solvent). Variable temperature NMR spectroscopic studies showed the isomers were in slow exchange suggesting that they were not simple conformers. We suspected that the two represented a reversal of the orientation of the enolate relative to the dilithiotetramide fragment.

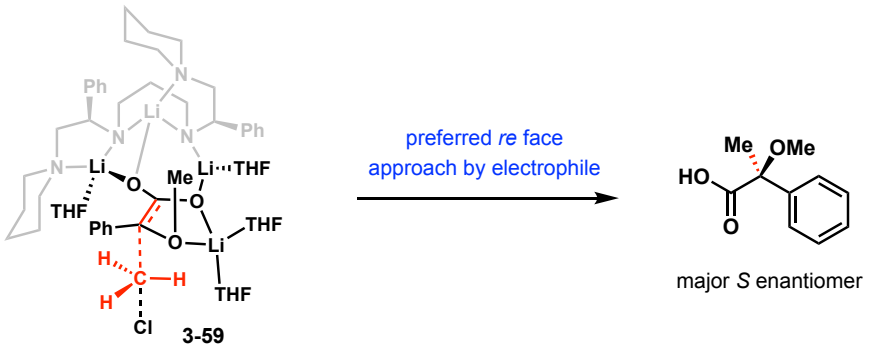
Density functional theory (DFT) calculations at the B3LYP/6–31G(d) level of theory[13] with single-point MP2 corrections revealed the putative isomers **3-54** – **3-57** (Scheme 3-8). The *relative* energies are noted in parentheses. Notable features include: (1) the lowest energy form, **3-56**, corresponds to that found crystallographically; (2) the apparent distortion of the methoxy-derived oxygen from the preferred trigonal geometry[14] seen in all four isomers appears to stem from $A_{1,2}$-strain with the proximate phenyl moiety; (3) although difficult to depict in two dimensions, the uppermost piperidino moiety produces congestion on the upper (β) face of the enolate; (4) in all cases, the preferred approach of the electrophile is from the lower (α) face of the enolate; and (5) the energies predict the **3-54**/**56** structural isomeric pair to be preferred relative to the **3-55**/**57** by approximately 4:1, which would nicely coincide with the ^{6}Li NMR spectroscopy.



Scheme 3-8. Four conformers of aggregates determined by DFT computations

The results of transition state calculations are also summarized in Scheme 3-8. The $\Delta\Delta G^{\ddagger}$ values above the arrows leading to *re* and *si* isomers correspond to the *relative* activation energies referenced to the lowest energy pathway (**3-54**). To obtain relative contributions of the isomers to the overall *re-si* selectivity one adds the relative reactant energies and relative activation energies. In the event that all isomers are fully equilibrating on the timescales of the alkylation, the dominant pathway funnels through **3-54**, and the overall *re–si* selectivity resulting from weighted contributions of all four pathways is predicted to be approximately 60:1. If, however, the structural isomer pairs **3-54/56** and **3-55/57** are *not* equilibrating on the

timescales of the reaction, a loss in selectivity from minor structural isomer **3-55/57** is predicted to reduce the overall selectivity to 4:1. It would appear, therefore, that the computation-driven model predicts *re* selective attack via transition structure depicted as **3-59** (Scheme 3-9).



Scheme 3-9. Transition model for the preferred *re* face approach

3.8 Conclusion

The results of our study showed that chiral lithium amides are effective non-covalently bound chiral auxiliaries for enantioselective alkylations, conjugate additions, and aldol additions of lithium enediolates derived directly from carboxylic acids. The resulting high stereoselectivities, even in the formation of tetrasubstituted and quaternary stereogenic centers, are notable. The chiral tetramine auxiliary can be recovered in high yield via simple acid-base aqueous extraction. Given the ubiquity of organolithium reagents in organic synthesis and the propensity of tetraamines such as **^{1}TA** to form discrete and stable aggregates, we anticipate that other such enantioselective transformations are possible.

3.9 References

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(2) See Chapter 2 for more details about covalent auxiliaries.

(3) For a review on the self-regeneration of stereocenters, see: Seebach, D., Sting, A. R., Hoffmann, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2708-2748.

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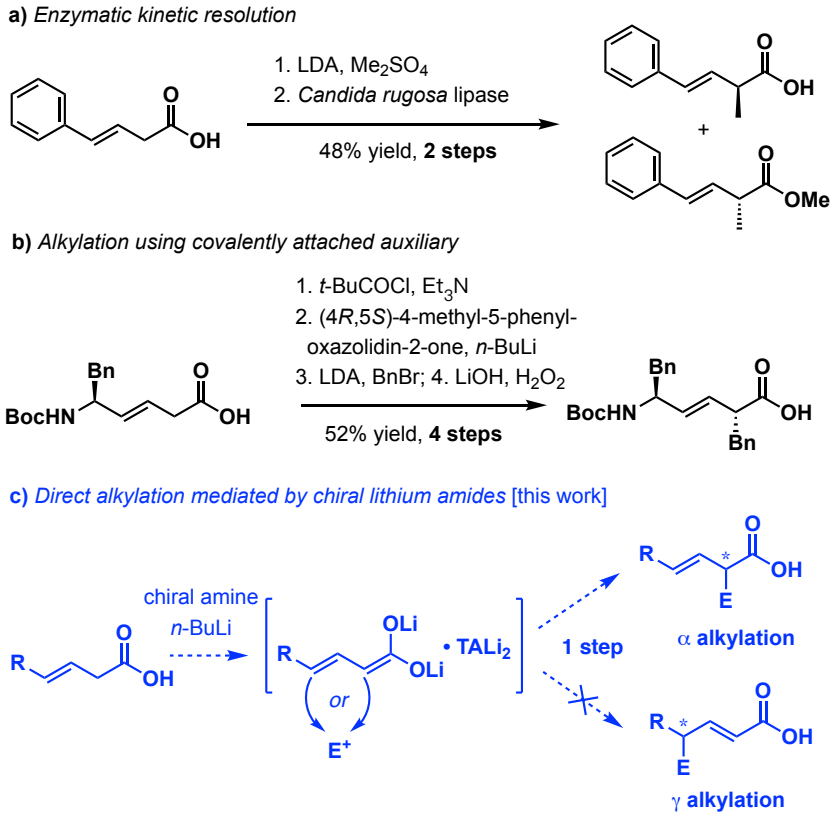
Chapter 4. Direct Enantioselective and Regioselective Alkylation of β,γ-Unsaturated Carboxylic Acids with Chiral Lithium Amides as Traceless Auxiliaries

4.1 Introduction

As discussed previously, the enantioselective alkylation of enolates is a fundamental and broadly utilized transformation in stereoselective organic synthesis. Chiral lithium amides, which form mixed aggregates with organolithium and other organometallic reagents, [1] offer an alternative approach to asymmetric alkylation of enolates.[2,3] Within the context of these complex aggregates, chiral lithium amides in effect function as non-covalent, or traceless, chiral auxiliaries. Formed in situ, they provide a chiral environment enabling asymmetric transformations. Some of the practical advantages of chiral lithium amide-based approach[4,5] are 1) eliminating the need for pre-derivatization of carboxylic acid substrates; 2) simple, high-yielding recovery of the amine reagent by acidic extraction; and 3) high reactivity of enediolates used in direct alkylation of carboxylic acids.

We have demonstrated that C_2-symmetric chiral lithium amides enable highly enantioselective alkylation and conjugate addition of enediolates derived directly mainly from aryl- and heteroarylacetic acids.4 However, other types of carboxylic acids are also highly valuable substrates in organic synthesis. Specifically, we became interested in β,γ-unsaturated aliphatic acids because of their appeal as starting materials and the potential for further elaboration of the double bond. In addition, a new challenge with this class of substrates is the question of α versus γ regioselectivity during the reaction of the electrophile with the enediolate intermediate (Scheme 4-1c).

A few approaches for the stereoselective synthesis of α-substituted 3-alkenoic acids have been reported. In the total synthesis of cryptophycins, Sih *et al.* applied enzymatic kinetic resolution to isolate out the *S*-isomer of 2-methyl 4-phenyl-3-butenoic acid (Scheme 4-1a).[6] Using covalent chiral auxiliary, Kelly *et al.* installed the benzyl group diastereomerically on the α-position of the β,γ-unsaturated acid over four steps — acylating chlorination, attachment of the oxazolidinone, alkylation, and cleavage of oxazolidinone (Scheme 4-1b).[7]



Scheme 4-1. Approaches to the enantio- and regioselective synthesis of α-substituted β,γ-unsaturated carboxylic acids.

However, the direct enantioselective alkylation of β,γ-unsaturated aliphatic acids is still underdeveloped.[8] Also, poor regioselectivities have been observed in the reaction of enolates derived from 3-alkenoic acids with electrophiles: ethylation of 3-butenoic acid with iodoethane

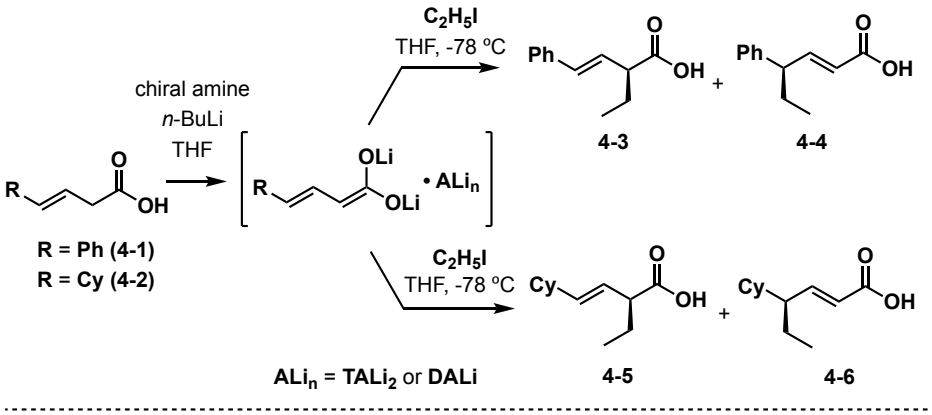
and LDA gave a 5:1 ratio of α and γ alkylation products; similar ethylation of 4-methyl-3-pentenoic acid gave a 3:1 ratio of α and γ alkylation products. Here, we report that chiral lithium amides are effective reagents for highly enantio- and regioselective direct α-alkylation of β,γ-unsaturated carboxylic acids.

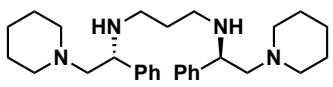
4.2 Optimization of the Alkylation Conditions

Ethylation of (*E*)-4-phenyl-3-butenoic (**4-1**) and (*E*)-4-cyclohexyl-3-butenoic (**4-2**) acids with iodoethane provided a platform to test the feasibility of this approach and to identify the most effective chiral lithium amides from a set of readily available amines, **TA** and **DA** (Table 4-1).

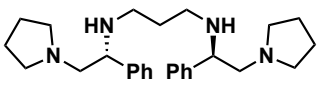
Because aggregation conditions are known to have a profound influence on the outcome of organolithium reactions,4 they were examined first. For **4-1**, optimal aggregation was achieved upon treatment of an equimolar mixture of chiral tetraamine (*R*)-^{1}**TA** and acid **4-1** with 4.0 equiv of *n*-BuLi at 0 °C for 45 min in THF. Addition of iodoethane at –78 °C resulted in 95% yield of (*S*,*E*)-2-ethyl-4-phenyl-3-butenoic acid (**4-3**) with 92% enantiomeric excess (ee)[9] and >20:1 preference for α-alkylation (Table 1, entry 1). High regioselectivity was maintained with other chiral amines tested (entries 2~6). Notably, with LDA there was a reduction of regioselectivity, with a 6:1 ratio of α and γ-alkylation products (entry 7). Enantioselectivity was similar with pyrrolidine derived tetraamine ^{2}**TA**, but generally lower with other chiral amines studied. Interestingly, an inversion in the enantioselectivity was observed with more hindered amine ^{7}**TA**.

Table 4-1. Chiral lithium amides for enantioselective and regioselective ethylation of 4-phenyl-3-butenoic acid and 4-cyclohexyl-3-butenoic acid[a]

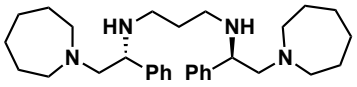




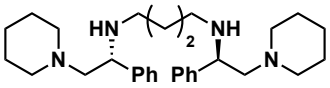
(*R*)-[1]**TA**



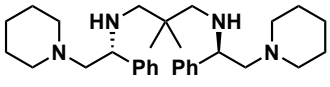
(*R*)-[2]**TA**



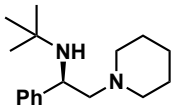
(*R*)-[3]**TA**



(*R*)-[6]**TA**



(*R*)-[7]**TA**



(*R*)-[1]**DA**

entry	acid, (R)	amine	yield (%)	ee (%)	α:γ ratio
1	**4-1** (Ph)[b]	(*R*)-[1]**TA**	95	92	>20:1
2		(*R*)-[2]**TA**	74	63	>20:1
3		(*R*)-[3]**TA**	67	–32	>20:1
4		(*R*)-[6]**TA**	25	8	15:1
5		(*R*)-[7]**TA**	75	–41	>20:1
6		(*R*)-[1]**DA**	30	52	>20:1
7		*i*-Pr_2NH	88	-	6:1

8	**4-2** (Cy)[c,d]	(*R*)-[1]**TA**	71	84	>20:1
9		(*R*)-[2]**TA**	47	51	>20:1
10		(*R*)-[3]**TA**	39	42	>20:1
11		(*R*)-[6]**TA**	16	0	14:1
12		(*R*)-[7]**TA**	37	–70	6:1
13		(*R*)-[1]**DA**	11%	–6	11:1
14		*i*-Pr_2NH	71%	-	6:1

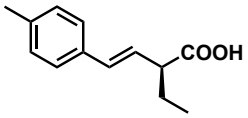
[a] Experiments were performed on a 0.50 mmol scale; all results normalized to bases with the *R* configuration. **TA**/**DA** (1.03 equiv.), *n*-BuLi (4.0 equiv.), C_2H_5I (4.0 equiv.), THF (4.0 mL). [b] Aggregation performed at 0 °C for 45 min with **4-1**. [c] Aggregation performed at 23 °C for 45 min with **4-2**. [d] Cy = cyclohexyl.

Comparable levels of enantio-, regioselectivity, and yields were observed with ethylation of (*E*)-4-cyclohexyl-3-butenoic acid **4-2** (Table 1, entry 8~13). Optimal aggregation now required 45 min at 23 °C with this fully aliphatic substrate. Tetraamine (*R*)-[1]**TA** again proved to be the most effective, giving α-ethylation product **4-4** in 71% yield, 84% ee and >20:1 regioselectivity (entry 8). With LDA, lower regioselectivity of 6:1 was observed, highlighting the impact of the lithium amide structure on regiocontrol (entry 14).

4.3 Scope of β,γ-Unsaturated Carboxylic Acids

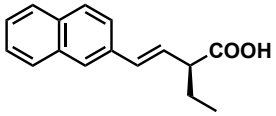
With the optimal reaction parameters for both type of substrate established, we first explored alkylation of various 4-aryl-3-butenoic acids shown in Table 4-2.

Table 4-2. Scope of aryl-substituted β,γ-unsaturated carboxylic acids[a]



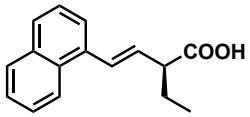
4-7

92% ee, α:γ >20:1
83% yield



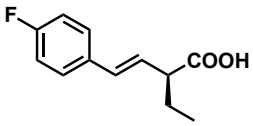
4-8

96% ee, α:γ 16:1, 94% yield
90% ee, α:γ 16:1, 90% yield
(***1 gram scale***)



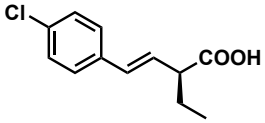
4-9

94% ee, α:γ 12:1
71% yield



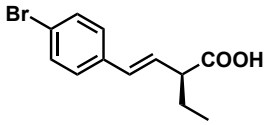
4-10

93% ee, α:γ >20:1
90% yield



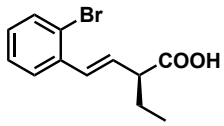
4-11

95% ee, α:γ 12:1
70% yield



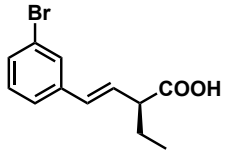
4-12

90% ee, α:γ 16:1
69% yield



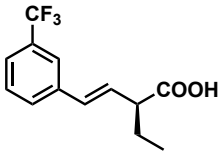
4-13

93% ee, α:γ 8:1
67% yield



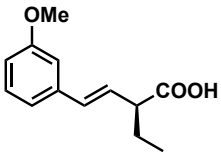
4-14

86% ee α:γ 16:1
67% yield



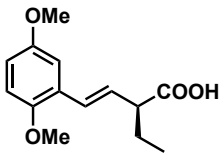
4-15

93% ee, α:γ 13:1
58% yield



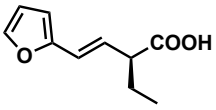
4-16

89% ee, α:γ 20:1
85% yield



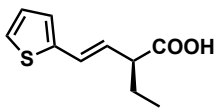
4-17

94% ee, α:γ 8:1
80% yield



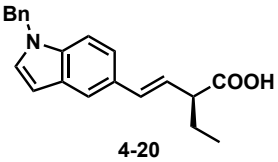
4-18

89% ee, α:γ 20:1
63% yield



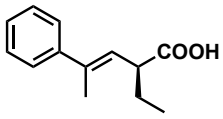
4-19

91% ee, α:γ >20:1
84% yield



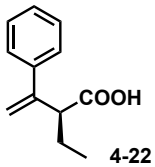
4-20

93% ee, α:γ >20:1
73% yield



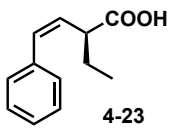
4-21

94% ee, α:γ >20:1
64% yield



4-22

93% ee, α:γ 10:1
77% yield



4-23

13% ee, α:γ >20:1
48% yield

[a] Experiments were performed on a 0.50 mmol scale unless stated otherwise.

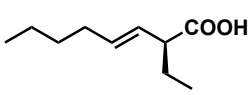
High preference for α-alkylation and enantioselectivity and practical yields were general for most substrates bearing aryl- and heteroaryl substituents. While *para*-substitution in the phenyl group had little impact on reaction outcome (**4-7**, **4-10~12**), *ortho*-substitution resulted in a moderate reduction of α-regioselectivity from >15:1 to 8:1 (**4-13**, **4-14**). Naphthyl and heteroaryl substituents were compatible giving excellent regio- and enantioselectivity and good yields in the alkylation reaction (**4-8, 4-9**, **4-18~20**). Notably, ethylation of 3-phenyl-3-butenoic acid also occurred at the apparently more hindered α-position with good regioselectivity (10:1) and excellent enantioselectivity in 77% yield (**4-22**). Although 4*Z*-methyl substituent had no detrimental effect on the reaction outcome (**4-21**), alkylation of (*Z*)-4-phenyl-3-butenoic acid, while highly regioselective (>20:1), resulted in substantially lower yield and er (**4-23**). A test of the alkylation procedure on 1 gram scale was performed with (*E*)-4-(naphthalen-2-yl)-3-butenoic acid, which afforded **4-8** in excellent yield, enantio-, and regioselectivity. In this case, we demonstrated the simple recovery of tetraamine auxiliary (*R*)-[1]**TA** in 98% yield by aqueous acid-base extraction.

(*E*)-4-Isopropyl-3-pentenoic acid afforded the corresponding alkylation product in 71% yield and 84% ee (**4-26**). More functionalized dienoic acids proved to be particularly suitable substrates affording better enantioselectivities and yields. (**4-27**, **4-28**). Similarly, ethylation of 2-(cyclohexen-1-yl)acetic acid afforded **4-29** in 94% yield and 91% ee. Ethylation of unsubstituted 3-butenoic acid with (*R*)-[1]**TA** , however, afforded **4-30** with low enantio- and regioselectivity (12% ee, α:γ 5:1).

Specifically, the case of the ethylation on unsubstituted 3-butenoic acid to **4-30** encountered several problems. First, the determination of enantiomeric ratio of asymmetric alkylated product were not able to rely on the HPLC measurement. The enantiomers of acid **4-30** or

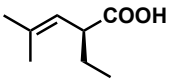
corresponding methyl ester or reduced alcohol could not provide distinguishable separation on the different chiral columns in hand. The problem was solved by measuring the diastereomeric ratio of the amide derivatives of **4-30** with (*R*)-α-methylbenzylamine. The ratio of **4-31**and **4-32** could be easily determined from the ^{1}H NMR of the crude mixture.

Table 3. Scope of Aliphatic β,γ-Unsaturated Carboxylic Acids[a]



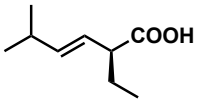
4-24

77% ee, α:γ >20:1
67% yield



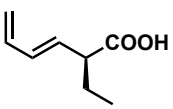
4-25

86% ee, α:γ >20:1
50% yield



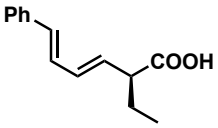
4-26

84% ee α:γ >20:1
71% yield



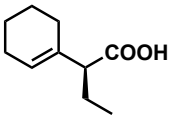
4-27

92% ee, α:γ >20:1
84% yield



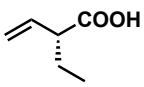
4-28

97% ee α:γ >20:1
60% yield



4-29

91% ee α:γ >20:1
94% yield



4-30

68% ee, α:γ 10:1
81% yield

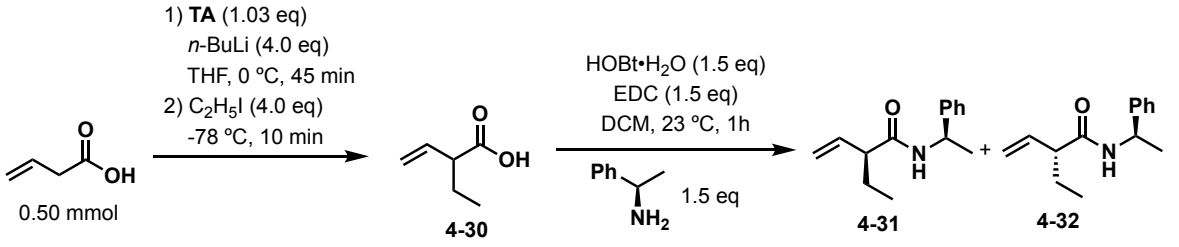
[a] Experiments were performed on a 0.50 mmol scale. [b] With (*S*)-[7]**TA**.

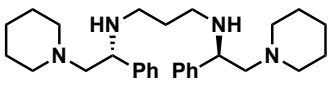
The second problem encountered was the low selectivities on both regio- and stereocontrol under the standard condition. Using (*R*)-[1]**TA** as stereodirecting auxiliary afforded **4-30** in 12% ee and 5:1 α-selectivity. An investigation on chiral amine was taken place.

The partial representatives of screening chiral amines are shown in Table 4-4. No increase on the enantioselectivity was observed by changing the *terminal amine* from piperidine to pyrrolidine ([2]**TA**) or azepane ([3]**TA**). Shortening the *linker* to ethylene ([5]**TA**) dropped the conversion of to only 10%. Replacement of the phenyl group with 2-naphthyl resulted with 60% yield of **4-30** in 22% ee and 10:1 α-selectivity. Later, we found the enantioselectivity

could be enhanced by the bulkiness on the *linker*: the geminal dimethyl groups increased the enantiomeric excess to ~50% (58% ee for ^{7}**TA** and 48% ee for ^{8}**TA**) with a maintenance of the α,γ-regioselectivity over 10:1. Moreover, when the lithiation-aggregation was carried out at 0 ºC for 90 min (45 min for the standard), the bulkier tetraamine (*S*)-^{7}**TA**, as the stereodirecting reagent, afforded **4-30** in 81% yield, 68% ee and 10:1 α-selectivity.

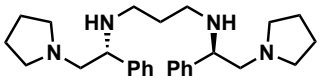
Table 4-4. Determination of enantiomeric excess of 4-30 and chiral amines screening





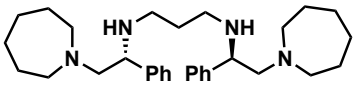
(*R*)-^{1}**TA**

66% yield, 12% ee, a:g 5:1



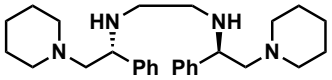
(*R*)-^{2}**TA**

47% yield, 12% ee, a:g 10:1



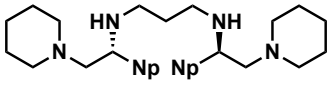
(*R*)-^{3}**TA**

48% yield, 16% ee, a:g 9:1



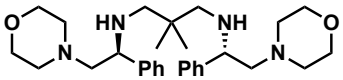
(*R*)-^{5}**TA**

<10% yield, n.d. ee



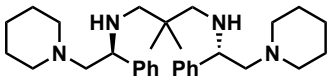
(*R*)-^{11}**TA**

60% yield, 22% ee, a:g 10:1



(*S*)-^{8}**TA**

47% yield, 48% ee, a:g 12:1



(*S*)-^{7}**TA**

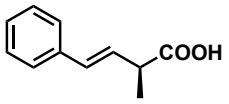
49% yield, 57% ee, a:g 10:1 (aggregation time: 45 min)

65% yield, 68% ee a:g 10:1 (aggregation time: 90 min)

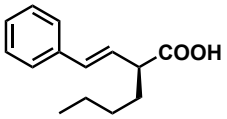
4.4 Scope of Alkylating Agents

Next, we examined various alkyl halides as alkylating reagents with carboxylic acids **4-1** and **4-2** as prototypical substrates (Table 4-5).

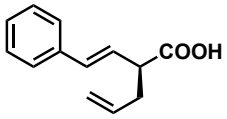
Table 5. Scope of alkylating agents with (*E*)-4-phenyl-3-butenoic acid (4-1) [a]



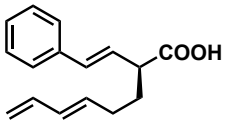
4-33
81% ee, α:γ >20:1
93% yield



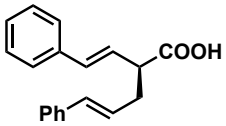
4-34
88% ee, α:γ >20:1
79% yield



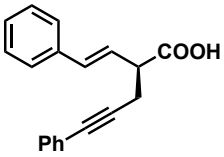
4-35
88% ee, α:γ 14:1
90% yield



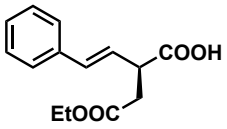
4-36
85% ee, α:γ 7:1
87% yield



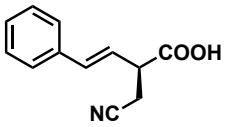
4-37
87% ee, α:γ 10:1
96% yield



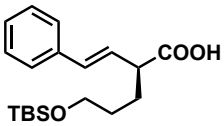
4-38
90% ee α:γ 20:1
87% yield



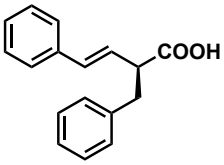
4-39
62% ee, α:γ >20:1
98% yield



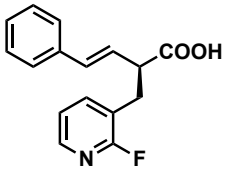
4-40
45% ee[b], α:γ >20:1
90% yield



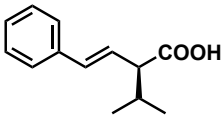
4-41
77% ee[b], α:γ 5:1
63% yield



4-42
90% ee, α:γ 2:1
95% yield



4-43
75% ee[b], α:γ 2:1
66% yield



4-44
0% yield

[a] Experiments were performed on a 0.50 mmol scale. [b] The er values were determined by HPLC analysis of corresponding methyl esters.

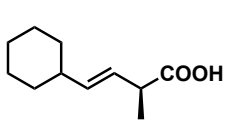
First, iodomethane and 1-iodobutane proved to be suitable alkylating agents for **4-1**, maintaining high regioselectivity and a slight reduction in the er for iodomethane (**4-33**, **4-34**). Allylation with allyl bromide was also effective (**4-35**). Alkylation with sensitive (*E*)-6-iodohexa-1,3-diene[10] prone to competitive elimination was remarkably effective, affording highly functionalized product **4-36** in 87% yield, 85% ee, and 7:1 regioselectivity with the typical preference for α-alkylation. Alkylation with activated halides like cinnamyl and 3-phenylpropargyl bromides was also highly selective and efficient (**4-37**, **4-38**). Surprisingly, alkylation with readily enolizable functionalized halides like ethyl bromoacetate and bromoacetonitrile was high yielding, maintaining high regiocontrol but affording reduced enantioselectivity (**4-39**， **4-40**). These halides also showed much higher reactivity, reducing reaction time from 90 min to less than 15 min. Alkylation with 4-(*tert*-butyldimethylsiloxy)-1-iodobutane[11] gave **4-41** in 63% yield and 77% ee.

An unexpected reduction in regioselectivity to 2:1 was observed during benzylation with benzyl bromide or a more functionalized reagent, 3-bromomethyl-2-fluoropyridine[12] (**4-42**, **4-43**). With BnBr, the α-benzylation product was isolated in 90% ee, while the γ-benzylation product displayed a lower ee (40%). Fluoropyridine product **4-43** was isolated in 66% yield and 75% ee. No reactivity was observed with a more hindered 2-iodopropane (**4-44**).

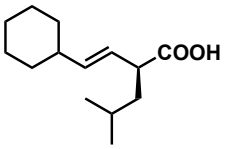
With aliphatic acid **4-2**, the reactivity and selectivity trends were generally similar (Table 4-6). The alkylation with primary alkyl halides like iodomethane and 1-iodo-2-methylpropane resulted **4-45** and **4-46** in excellent α-selectivity and good enantioselectivity, 83% and 76% ee, respectively. There are also some notable differences using aliphatic acid as the substrate. First, secondary alkyl halides like 2-iodopropane now are sufficiently reactive, affording α-alkylation product **4-47** as a single regioisomer in 53% yield and moderate ee (56%). Second,

benzylation is now again highly regioselective (>20:1) with either benzyl bromide (**4-48**, 77% yield, 85% e) or 3-bromomethyl-2-fluoropyridine (**4-49**, 81% yield, 72% ee). For **4-48**, we performed the reaction on >1 g scale and demonstrated the simple extractive recovery of (*R*)-[1]**TA** in 96% yield.

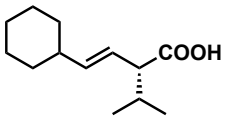
Table 4-6. Scope of alkylating agents with (*E*)-4-cyclohexyl-3-butenoic acid (4-2)[a]



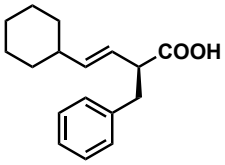
4-45
83% ee, a:g >20:1
77% yield



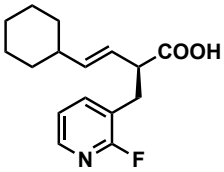
4-46
76% ee, a:g >20:1
64% yield



4-47
56% ee, a:g >20:1
53% yield [b]



4-48
85% ee, a:g >20:1
77% yield
[**>1 g scale**, (*R*)-[1]**TA** recovered in 98% yield]

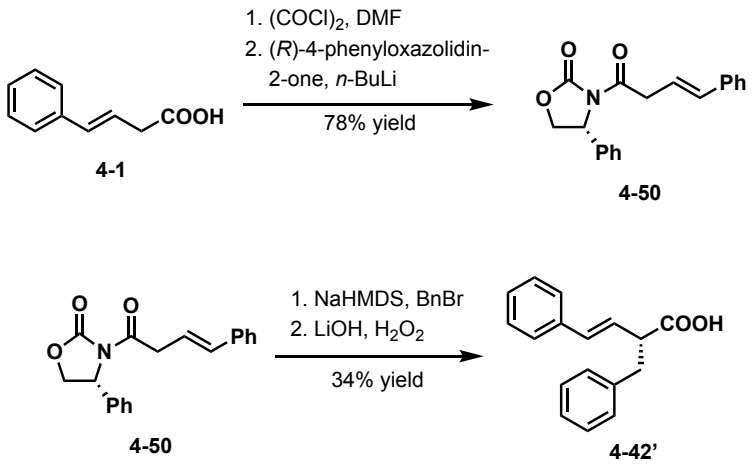


4-49
72% ee, a:g >20:1
81% yield

[a] Experiments were performed on a 0.50 mmol scale. [b] With (*R*)-[2]**TA**.

4.5 Determination of Absolute Configuration

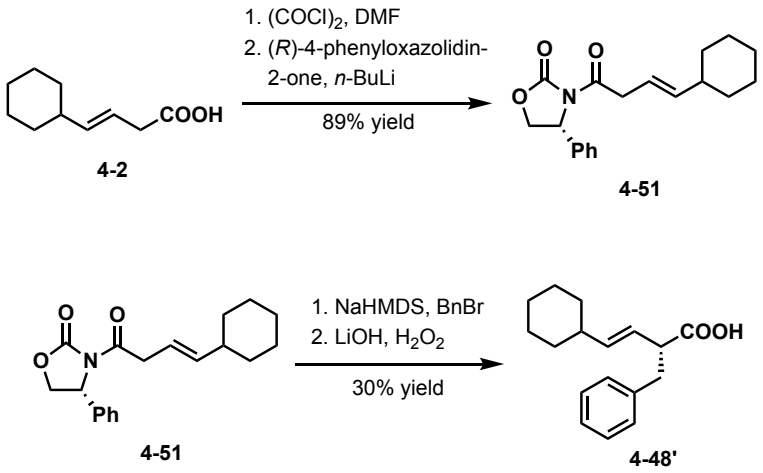
Oxazolidinone as covalent chiral auxiliary was applied in this investigation to construct the premeditated chirality at the α-position of 3-butenoic acids. 2-Benzyl-4-phenyl-3-butenoic acid (**4-42**) and 2-benzyl-4-cyclohexyl-3-butenoic acid (**4-48**) were selected as the synthetic targets to determine the absolute configuration of the products from the above asymmetric methodology, due to the easy access via the covalent chiral auxiliary method.



Scheme 4-2. Determination of absolute configuration of 4-42

(*E*)-4-Phenyl-3-butenoic acid (**4-1**) was firstly converted into the acyl chloride by Vilsmeier reagent generated from oxalyl chloride and dimethylformamide, and coupled with the lithiated (*R*)-4-phenyloxazolidin-2-one, resulting the **4-50** in 78% yield over two steps. **4-50** was then enolized by $NaN(Si(CH_3)_3)_2$ and alkylated with benzyl bromide. The oxazolidinone was then removed by using lithium hydroxide together with hydrogen peroxide, affording **4-42'** in 34% yield and 94% ee. The absolute configuration of **4-42'** can be easily determined as *R* from the chiral oxazolidinone, and its optical rotation, –130.3 (23 ºC, c 0.55, $CHCl_3$), is opposite to that of **4-42**, +92.2 (21 ºC, c 0.56, $CHCl_3$), which was synthesized by direct asymmetric alkylation with lithium chiral amide. Thus, the absolute configuration of **4-42** is *S*.

The same asymmetric benzylation on **4-2** using (*R*)-4-phenyloxazolidin-2-one resulted **4-48'** with *R*-isomer in 27% yield and 98% ee over four steps. The optical rotation of **4-48'**, –50.4 (21 ºC, c 1.08, $CHCl_3$), is opposite to that of **4-48**, +39.9 (20 ºC, c 1.01, $CHCl_3$). Therefore, the absolute configuration of **4-48** is also *S*.



Scheme 4-3. Determination of absolute configuration of 4-48

4.6 Conclusion

In summary, we demonstrated that direct enantioselective alkylation of carboxylic acids with *non-aromatic* substituents is feasible and can provide practical levels of enantiocontrol. Enantio- and regioselective alkylation of 3-alkenoic acids can be accomplished effectively with chiral lithium amides as stereodirecting reagents, providing enantioenriched versatile products primed for further functionalization. The chiral amine is readily recoverable by a simple aqueous extraction simplifying the removal and recycling of the stereodirecting reagent. The preference for alkylation at α-position with chiral lithium amides was notably higher than with simple bases like LDA. This higher selectivity is likely due to yet undetermined structural characteristics of the mixed lithium enolate-chiral lithium amide aggregate involved in the alkylation reaction. Efforts to define the structure of the mixed aggregate and applications of this method in complex molecule synthesis are the subject of our future research.

4.7 References

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Chapter 5. Efforts Towards the Total Synthesis of (–)-Morphine via Chiral Lithium Amides Methodology

5.1 Introduction

Morphine (**5-1**) and other opium alkaloids, codeine (**5-2**), thebaine (**5-3**), and oripavine (**5-4**) are continuously attracting the interest of the chemical community for a number of reasons, including their well-known bioactivities and complex structures.[1]

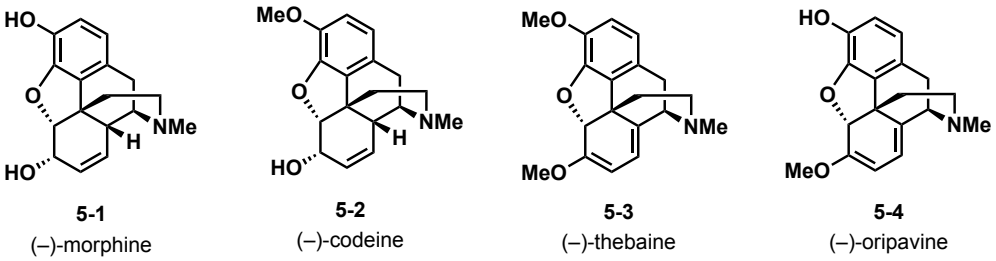


Figure 5-1. Common Morphine Alkaloids

Isolated from the opium poppy *Papaver Somniferum* by Sertürner in early 19th century[1,2], morphine has been popular as a chemical in humankind history for the effectiveness in analgesic and anesthetic properties. During 2013-2018, about 400 tons of morphine globally produced from the cultivation of opium every year, and the majority of them was applied primarily to treat both acute and chronic sever pain in the medical community.[3] Currently, morphine in medicinal (and illicit) use are still produced from natural sources, because no synthetic route can compete on scale and cost with the direct isolation. Biosynthetic study showed morphine (and codeine, thebaine) in the opium poppy is originally from the L-tyrosine.[4]

The correct structure of morphine was first proposed by Robinson in 1925[1,5] as a rigid pentacyclic structure with a fusion of benzene ring (A), two partially unsaturated cyclohexane ring (B and C), a piperidine ring (D) and dihydrofuran ring (E). There are 5 chiral centers (C5, C6, C9, C13 and C14) in the morphine, and only (–)-morphine is active due to the high degree of the stereoselectivity of analgesic action.[6] The absolute stereochemistry was confirmed by Hodgkin's X-ray crystallography in 1955.[7]

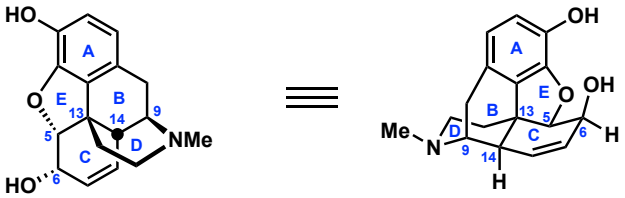
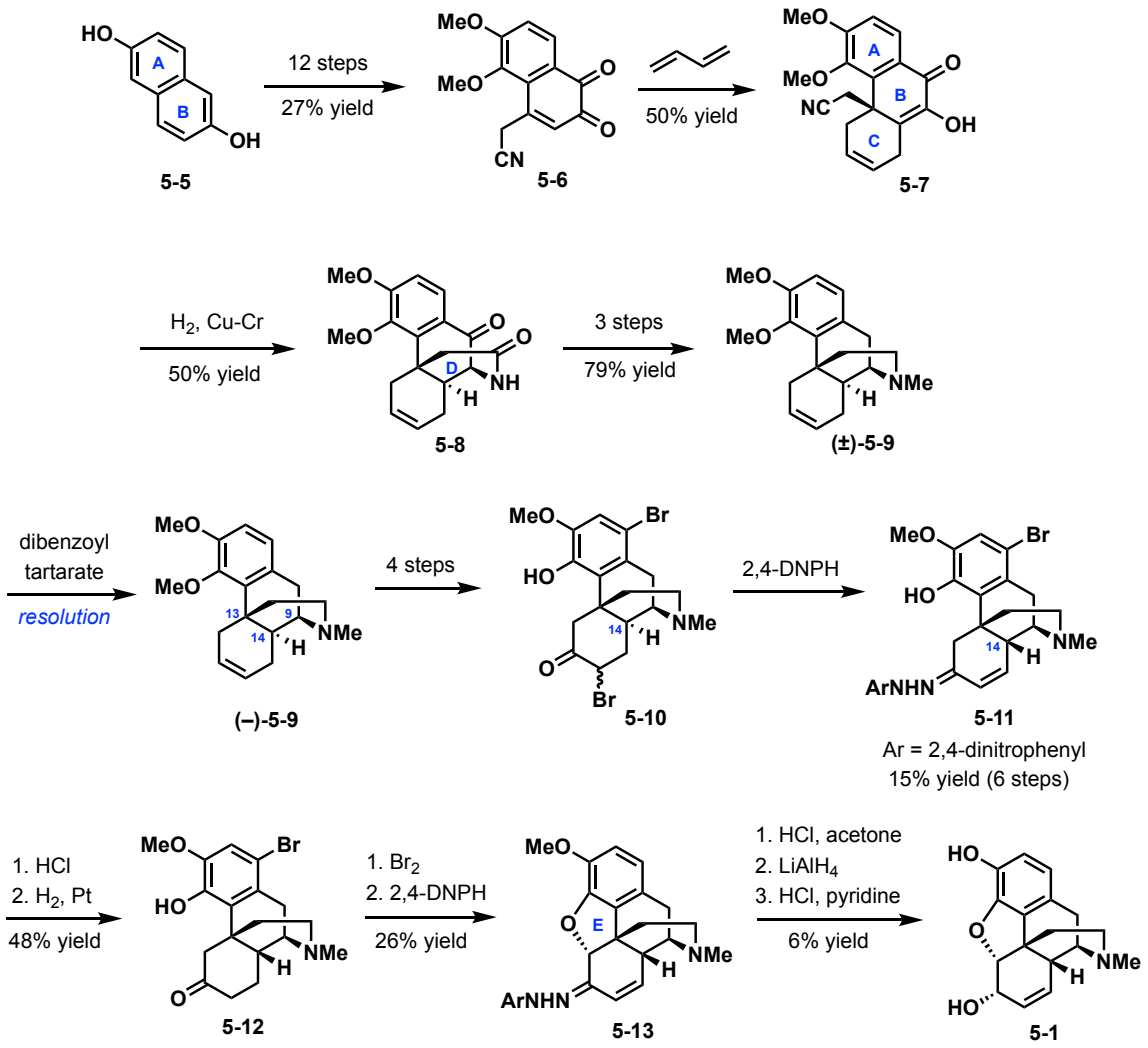


Figure 5-2. Chemical Structure of (–)-Morphine

In 1952, Marshall Gates firstly accomplished the total synthesis of (–)-morphine in 30 steps[8], which was one of the pioneering proofs of morphine's correct structure. 2,6-Dihydroxynaphthalen (**5-5**) was used as starting material and took 12 steps to convert into the nitrile **5-6**, the dienophile in the key [4+2] cycloaddition reaction. The enol **5-7** (or diketone) was afforded in 50% yield by heating **5-6** with butadiene, establishing the A,B,C-ring system of target molecule. The following copper chromite reduction assembled the piperidine ring D and the resultant amide (**5-8**) was then subjected to a series of functional group derivations to the key intermediate, morphinan **5-9**, in 79% yield.

The resolution of racemic morphinan **5-9** was carried out with dibenzoyl tartrate, affording the correct configuration at C9 and C13, however, epimeric at C14. α-Bromo ketone **5-10** was obtained in another four steps, and the epimerization at C14 was induced by the reaction with 2,4-dinitrophenylhydrazine (2,4-DNPH) to the thermodynamically more favored natural

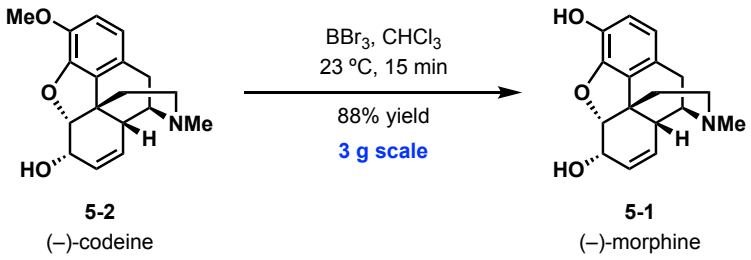
configuration (**5-11**). A sequential hydrolysis and hydrogenation provided **5-12** in 48% yield. After the key formation of dihydrofuran (ring E, **5-13**) with bromination and the following treatment of 2,4-DNPH, three more steps of functional group derivations delivered 6% yield of (–)-morphine as final product.



Scheme 5-1. Gates' Synthesis of (–)-Morphine

After Gates' first accomplishment, more than thirty formal and total syntheses of morphine alkaloids have been carried out. Most attempts are focusing on codeine as the synthetic target,

due to its higher stability as well as an efficient conversion from codeine to morphine released by Rice: *O*-demethylation with BBr_3. [1c,9]



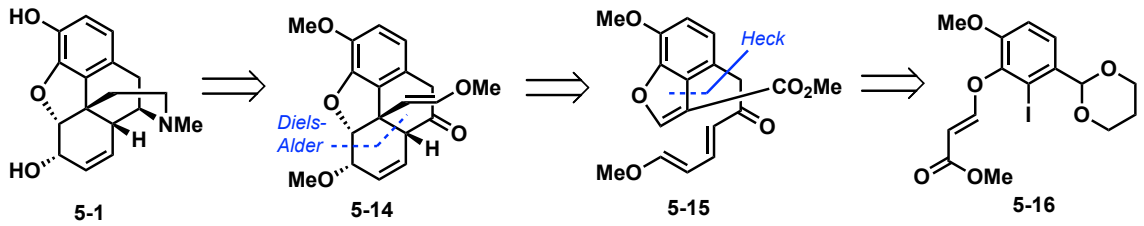
5-2
(–)-codeine

5-1
(–)-morphine

Scheme 5-2. Efficient Conversion from Codeine to Morphine

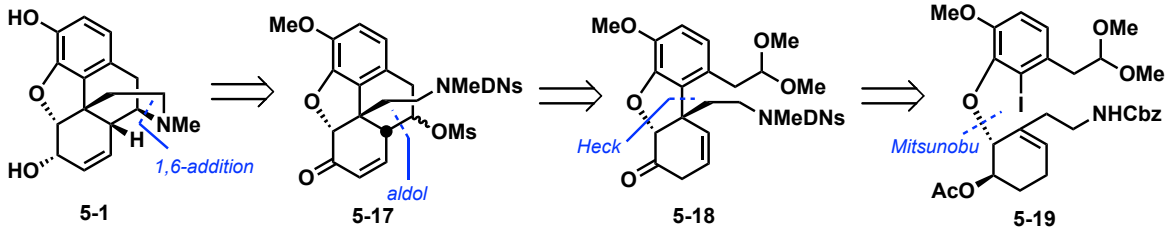
In the past 10 years, although there had been published a tremendous number of synthetic routes towards morphine alkaloids, the enthusiasm on investigating new approaches to this type of molecules did not fade away. Many brilliant synthetic designs towards morphine and its congeners were demonstrated with more conciseness, efficiency and novel methodologies. Several representatives of strategies are discussed below in retrosynthetic analysis.

In 2009, Stork introduced a strategy towards racemic morphine[10] with an intramolecular Diels-Alder cycloaddition between the benzofuran and diene as the key step, establishing the B- and C-ring of morphine (**5-14**) in late game. The benzofuran moiety of **5-15** can be installed via palladium-catalyzed Heck cyclization of **5-16**, which synthesized from the commercially available iodoisovanillin. In this synthetic strategy, the methoxycarbonyl group on the 3-position of benzofuran moiety was acting as the directing group inducing the diastereoselectivity for the intramolecular [4+2] cyclization, with 89% yield of the desired isomer with the correct chirality sequence at C5, C6, C13 and C14.



Scheme 5-3. Stork's Synthesis of (±)-Morphine

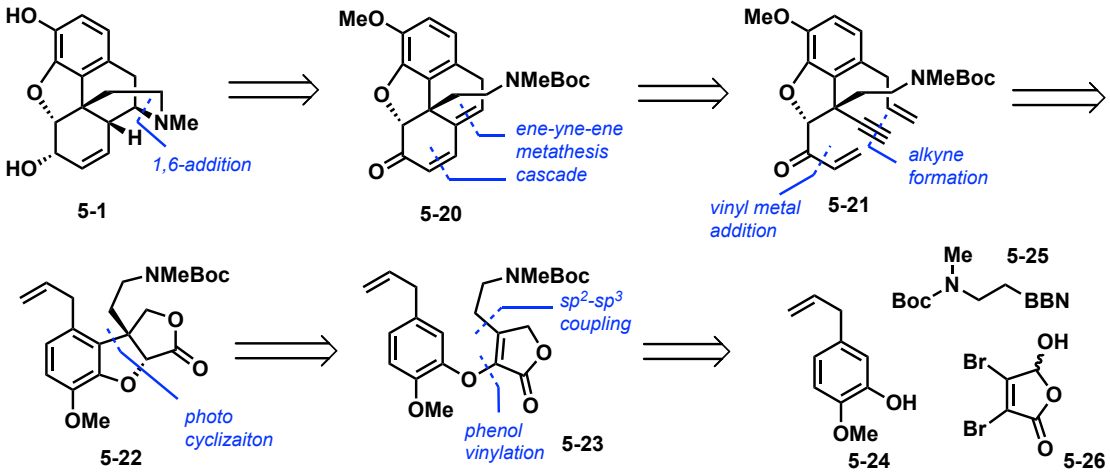
Based on their previous racemic synthesis[11], Fukuyama *et al.* proposed an asymmetric pathway towards (–)-morphine in 2010.[12] The piperidine ring D of morphine was constructed by 1,6-addition of amino group onto the dienone, generated *in situ* from the mesylate **5-17**. Ring B of the alkaloid was formed via intramolecular aldol addition of the acetal unit and β,γ-unsaturated ketone. Heck reaction was applied to establish the dihydrobenzofuran moiety (ring E) in **5-18**. The cross-coupling precursor **5-19** with an essential stereochemistry at C5 was synthesized by the Mitsunobu reaction between the iodoisovanillin derivative and a chiral cyclohexanol, derived from cyclohexenone by enzymatic resolution.



Scheme 5-4. Fukuyama's Synthesis of (–)-Morphine

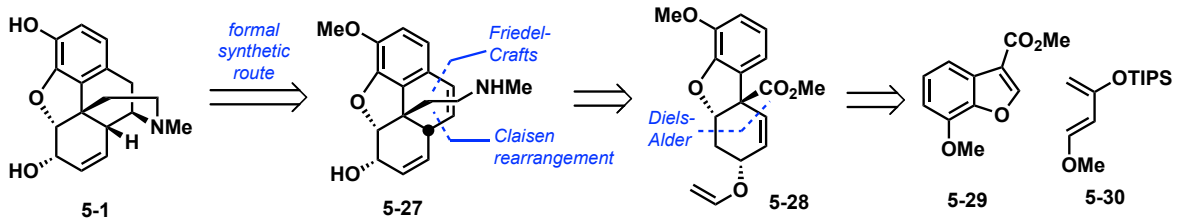
The Smith's synthesis of racemic morphine[13] also applied intramolecular 1,6-addition reaction of an amine analogous (**5-20**). The α,β,γ,δ-unsaturated ketone could be constructed via a cascade ene-yne-ene ring closing metathesis, as the key step to build up the ring B and C simultaneously. The benzofuran **5-21** could be synthesized from the tricyclic lactone **5-22** by

functional group interconversions, including vinyl metal addition and alkyne formation. Photo cyclization was applied to install the benzofuran from the butanolide **5-23**, which could originally from the connection of chavibetol (**5-24**), protected amino-borane (**5-25**) and dibromobutenolide (**5-26**). As they pointed out, using a metathesis cascade cyclization is a novel end-game towards the morphine alkaloids and it can minimize late-stage functional group interconversions.



Scheme 5-5. Smith's Synthesis of (±)-Morphine

In 2019, Barriault demonstrated a concise nice-step formal synthesis of (±)-morphine. The piperidine ring in the target alkaloid could be synthesized via a radical hydroamination of **5-27**. The ring B was established by Claisen rearrangement and Friedel-Crafts alkylation from the derivative of **5-28**, of which the ring C was installed by the [4+2] cycloaddition between the benzofuran (**5-29**) and Danishefsky's diene (**5-30**). **5-29** could be obtained from *o*-vanillin directly. With this strategy, Barriault and his colleagues, using a sequential intermolecular Diels-Alder/Claisen/Friedel-Crafts reaction, efficiently assembled the carbocyclic framework with minimizing the use of protecting group and nonstrategic manipulations.



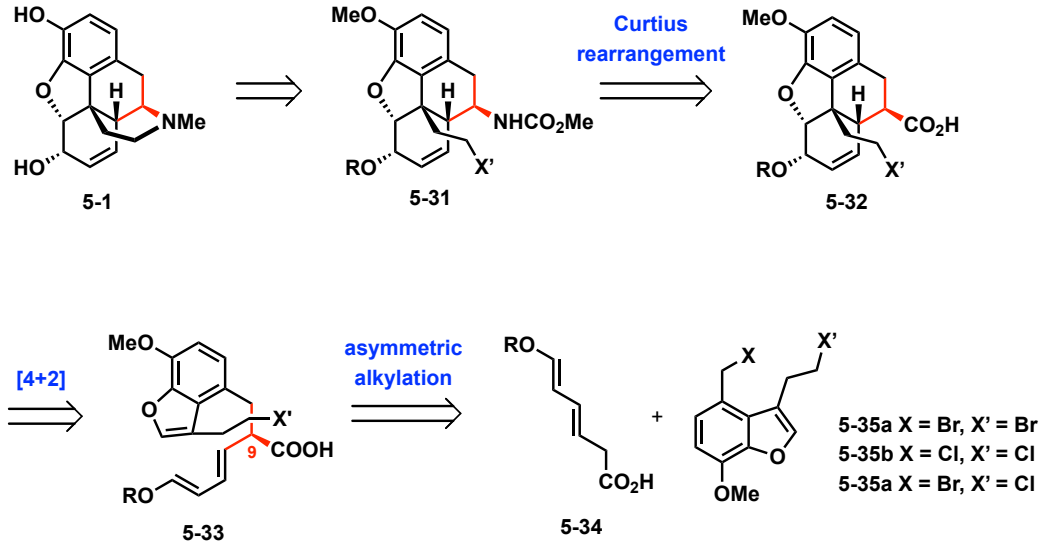
Scheme 5-6. Barriault's Synthesis of (±)-Morphine

5.2 Our Synthetic Plan Towards (–)-Morphine

After disclosing the direct highly selective α-alkylation on β,γ-unsaturated acids[14], we were planning to applied this asymmetric method in the total synthesis of natural product. Morphine, as one of the oldest drugs and unfailing synthetic goal, became our target which can also test the feasibility of our methodology, besides its synthetic attraction.

Enlightened by existing synthetic methods towards morphine[10], a concise enantioselective synthetic route to (–)-morphine was proposed, and the retrosynthetic analysis is shown as follow (**Scheme 5-7**). We decided to choose to build up the piperidine ring of morphine as our end-game, since it has been supported by abundant syntheses previously: the alkaloid will be obtained through the intramolecular ring closure between the primary halide and carbamate of **5-31**, which is derived from the corresponding carboxylic acid (**5-32**) via Curtius rearrangement. Ring B and C can be introduced simultaneously by diastereoselective intramolecular Diels-Alder (IMDA) reaction of **5-33** between the terminal alkoxy diene and benzofuran moiety by using carboxyl group as a stereocontrolling group. In the IMDA reaction, the endo/exo selectivity was designed to be controlled by the side alkyl group at the 3-position of benzofuran, inspired by Stork's work, in which the methoxy carbonyl at the same postion controlled the stereoselectivity (**5-15**). The key stereocenter (C9) in **5-33** will be constructed

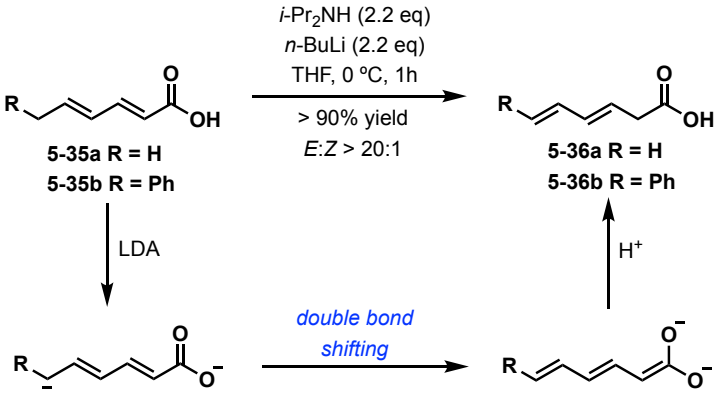
via our asymmetric alkylation on the (3*E*, 5*E*)-6-alkoxydienoic acid (**5-34**) using dihalogenated benzofuran (**5-35**) as electrophile.



Scheme 5-7. Retrosynthetic plan towards (–)-morphine through asymmetric alkylation

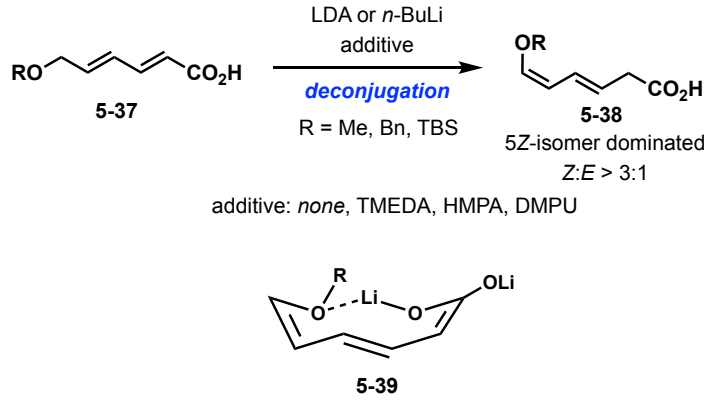
5.3 Synthesis of (3*E*, 5*E*)-6-Alkoxydienoic Acid

Strong base induced deconjugation was applied in the original synthesis of dienoic acids, like (*E*)-hexa-3,5-dienoic acid (**5-36a**) and (3*E*, 5*E*)-6-phenylhexa-3,5-dienoic acid (**5-36b**). With LDA deprotonating the 6-position of the citric acid and its derivative (**5-35**), the resultant dilithiated dienoic species can undergo the isomerization with double bond shifting to lengthen the conjugation, followed by the acidify to afford the deconjugated acids (**5-36**) as product. Generally, over 90% yield of desired products can be obtained with excellent *E*-selectivity on both double bonds after the deconjugation at 0 ºC for 1 hour in 10-gram scale.



Scheme 5-8. Deconjugation of citric acids

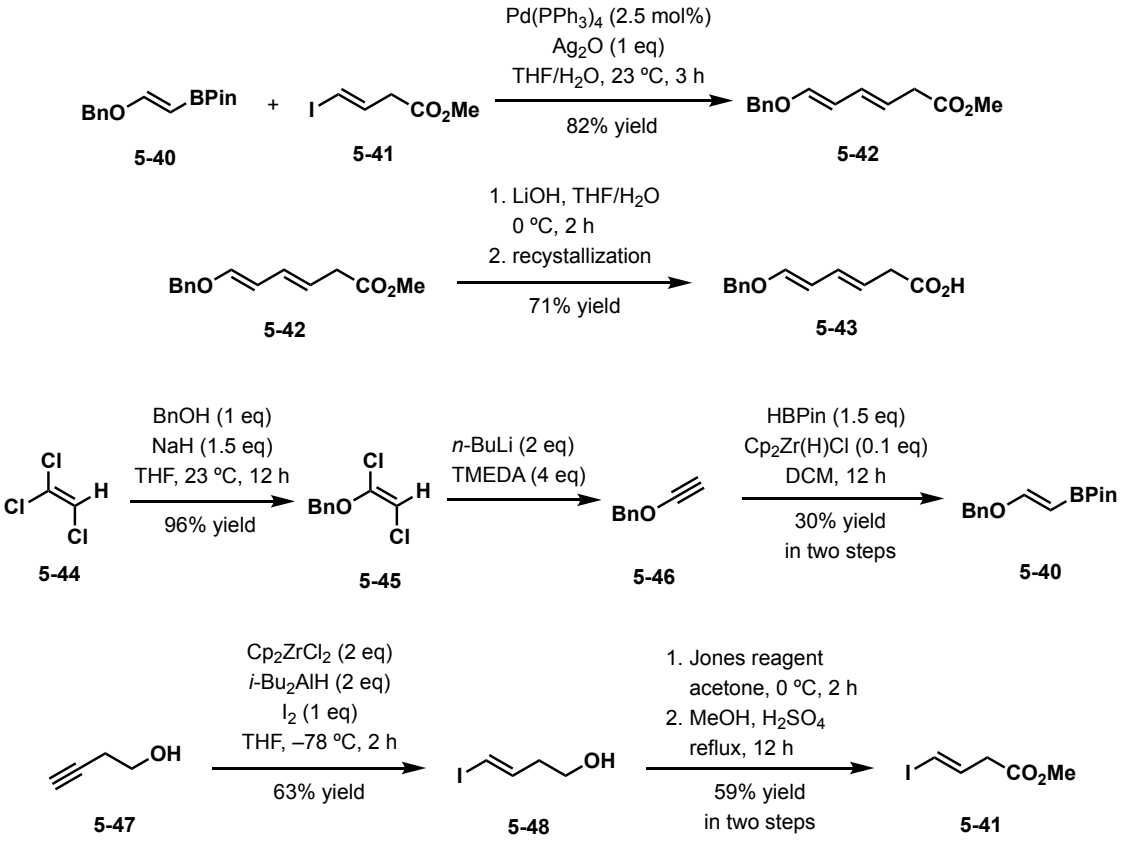
However, when using (2*E*,4*E*)-6-alkoxy citric acid (**5-37**) as the substrate with LDA or *n*-BuLi as lithiating reagent, 5*Z*-isomer dominated in the deconjugation, going through a putative lithiated aggregation (**5-39**). Dearregating additives, like TMEDA, HMPA and DMPU, did not increase the occupation of the 5*E*-isomer in the deconjugated product (**5-38**), maintaining Z/E > 3:1. Other *E* or *Z* isomers of 6-alkoxy-2,4-dienoic acids also provided the 5*Z*-preferred result.



Scheme 5-9. Domination of 5*Z*-isomers in the deconjugation of 6-alkoxy citric acids

To prepare the desired isomer for the later study, palladium-catalyzed Suzuki coupling was successfully applied in the synthesis of (3*E*,5*E*)-6-alkoxydienoic acid (**5-43**). (*E*)-2-Benzyloxyvinyl pinacolborane (**5-40**) and methyl (*E*)-4-iodobut-3-enoate (**5-41**) was coupled

at room temperature in the mixed solvent of THF/H_2O (4:1) catalyzed by tetrakis(triphenylphosphine)palladium with silver(I) oxide as base, affording 82% yield of the dienoic ester (**5-42**) with 3*E*,5*E*-isomer in 2.5-gram scale. The following hydrolysis and recrystallization from hexanes provided the desired acid (**5-43**) in over 70% yield as light yellow crystalline solid.



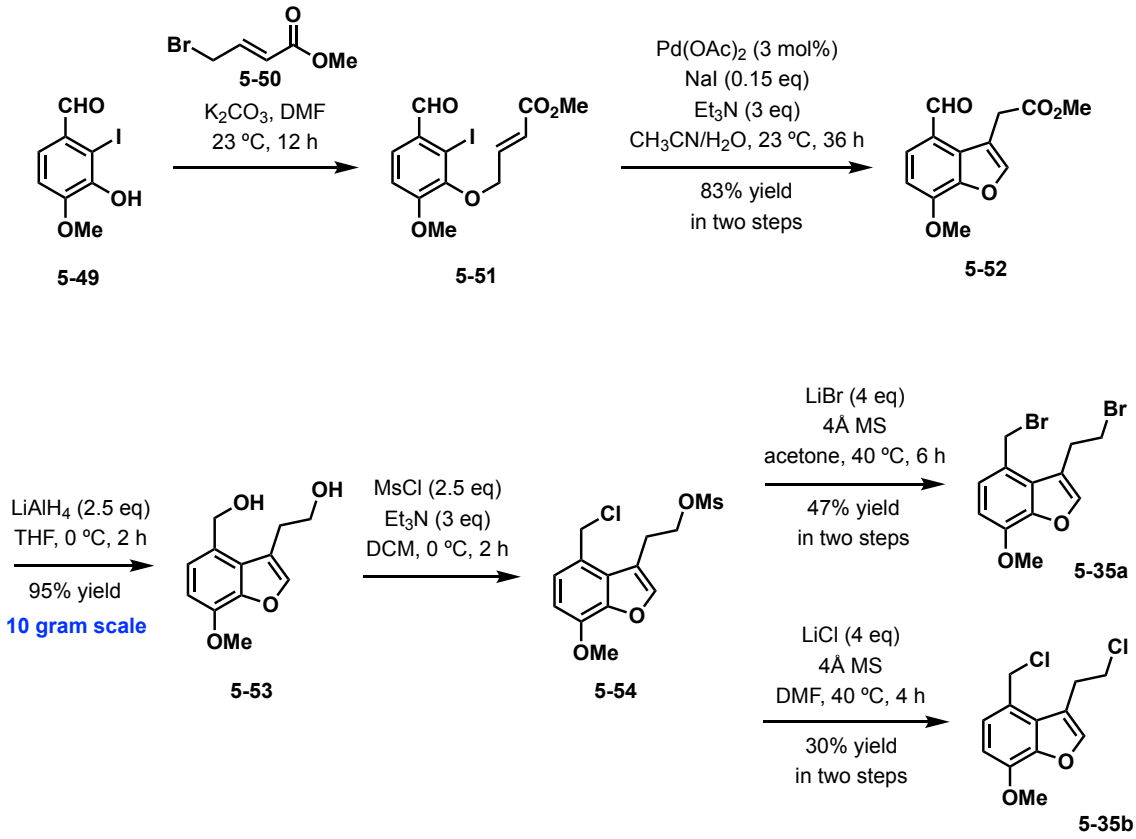
Scheme 5-10. Synthesis of (3*E*,5*E*)-6-alkoxydienoic acid through Suzuki coupling

The borane **5-40** was prepared in multigram scale followed by the literature[15] via hydrozirconation-hydroboration of benzyloxy acetylene (**5-46**), which was synthesized from trichloroethylene (**5-44**) over two steps[16]. From homopropargyl alcohol (**5-47**), a sequence of hydrozirconation-iodination, oxidation and esterification resulted **5-41** in 37% yield over three steps, in multigram scale as well.

5.4 Synthesis of Dihalogenated Benzofuran Electrophile

The dihalogenated benzofurans (**5-35**) were prepared over five steps from isovanillin (**5-49**), which is a common starting material in the total synthesis of opioids[1,10-12].

Isovanillin (**5-49**) condensed with methyl 4-bromocrotonate (**5-50**) with potassium in DMF, and the resultant aryl allyl ether (**5-51**) was then gone through the Heck type cyclization with the optimized condition ($Pd(OAc)_2$ (3 mol%), NaI (0.15 eq), Et_3N (3 eq), CH_3CN/H_2O, 23 ºC, 36h), affording 83% yield of benzofuran (**5-52**) in 83% yield over two steps. The following reduction with lithium aluminum hydride afforded the desired benzofurandiol (**5-53**) in 95% yield. All these reactions could be carried out in 10-gram scale.



Scheme 5-11. Synthesis of dihalogenated benzofuran (5-35) from isovanillin

The diol **5-53** was then attempted in the direct transformation to the dichlorinated and dibrominated benzofuran by using several methods, suck like Appel reaction[17], or treated with phosphine halides (PBr_3, PCl_3, $POCl_3$, etc.). The Appel reactions resulted in excellent conversion, but the isolation of desired products from triphenylphosphine oxide, the byproduct, was troublesome due to the instability of the para-methoxy benzyl halide. Chromatography through either silica gel or alumina provided fully decomposition, no matter the stationary phase was basified forehead or not. A small detour was adopted, in which the diol **5-53** firstly converted into chloromeyslate (**5-54**) by stirring with methanesulfonyl chloride for long enough time (2h), and the resultant **5-54** could convert into the desired dibromide (**5-35a**) and dichloride (**5-35b**) by substituted with LiBr and LiCl respectively. The afterward trituration with cold hexanes offered 30-50% yield of the clean benzofuran electrophiles (**5-35**) from the diol **5-53** in multigram scale.

5.5 Asymmetric Alkylation and the Problems Encountered

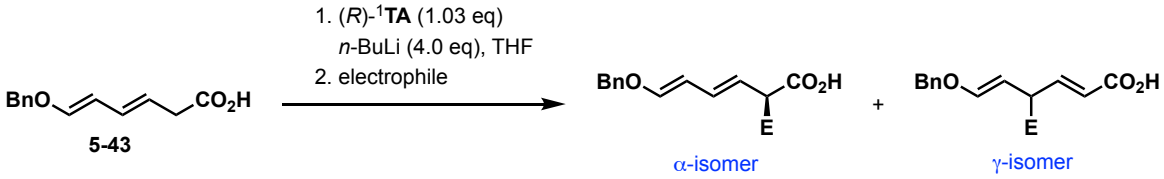
5.5.1 Prior Optimization of the Alkylation on Dienoic Acid 5-43

A prior screening on the simple benzylation on (3*E*,5*E*)-6-benzyloxy 3,5-dienoic acid (**5-43**) was carried out (**Table 5-1**), due to the easier access of the electrophiles.

Benzyl bromide (BnBr) was first examined. Common lithiation-aggregation conditions (0 or 23 ºC, 45 min) followed by the alkylation at –78 ºC for 30 to 90 min resulted 72-82% yield of the benzylated dienoic acid with 65-70% ee and around 4:1 α-selectivity (**entry 1-3**). By rising the aggregation time up to 60 min, the vary on the aggregation temperature form 23 to –20 ºC showed 0 ºC (**entry 4-7**) was the most satisfying temperature for the first step, and the alkylation resulted 73% yield, 80% ee and 5:1 α-selectivity (**entry 5**). Keeping the increase on

the aggregation time to 90 min at 0 ºC provided a slight decrease on both enantio- and regioselectivities (**entry 8-9**), while the lower alkylation temperature (–90 ºC) enhanced the regioselectivity to 7:1, with a maintenance on enantioselectivity (81% ee, **entry 10**).

Table 5-1. Prior Optimization of the Alkylation with Dienoic Acid 5-43



entry	electrophile	Aggregation		Alkylation		yield	ee (α)	α:γ
		temp. (ºC)	time (min)	temp. (ºC)	time (min)			
1	BnBr	0	45	–78	90	82%	65%	4.0:1
2	BnBr	23	45	–78	90	72%	68%	3.6:1
3	BnBr	0	45	–78	30	72%	70%	4.8:1
4	BnBr	23	60	–78	30	61%	70%	2.3:1
5	**BnBr**	**0**	**60**	**–78**	**30**	**73%**	**80%**	**5.0:1**
6	BnBr	-10	60	–78	30	75%	74%	4.8:1
7	BnBr	-20	60	–78	30	73%	70%	4.8:1
8	BnBr	0	75	–78	30	71%	71%	3.3:1
9	BnBr	0	90	–78	30	72%	72%	3.2:1
10	**BnBr**	**0**	**60**	**–90**	**30**	**65%**	**81%**	**7.1:1**
11	BnCl	0	60	–78	90	18%	90%	>20:1
12	BnCl	0	60	–78	300	26%	73%	10:1

13	BnCl	0	60	–40	90	69%	75%	8.0:1
14	PMBCl	0	60	–40	90	67%	70%	8.1:1
15	C_2H_5I	0	60	–78	90	77%	80%	>20:1

Benzyl chloride (BnCl) presented more restricted reactivity. The benzylation carried out at –78 ºC for 90 min only yielded 18% of product, though the stereo- and regioselectivities were excellent (90% ee, α:γ >20:1, **entry 11**). Besides, extending the alkylation time to 5 hours could only increase the yield by 8% and the ee value dropped to 73% (**entry 12**). The balance between yield and enantioselectivity as well as regioselectivity was achieved by raising the alkylation temperature to –40 ºC, 69% yield of benzylated acid was isolated in 75% ee and 8:1 α-selectivity (**entry 13**).

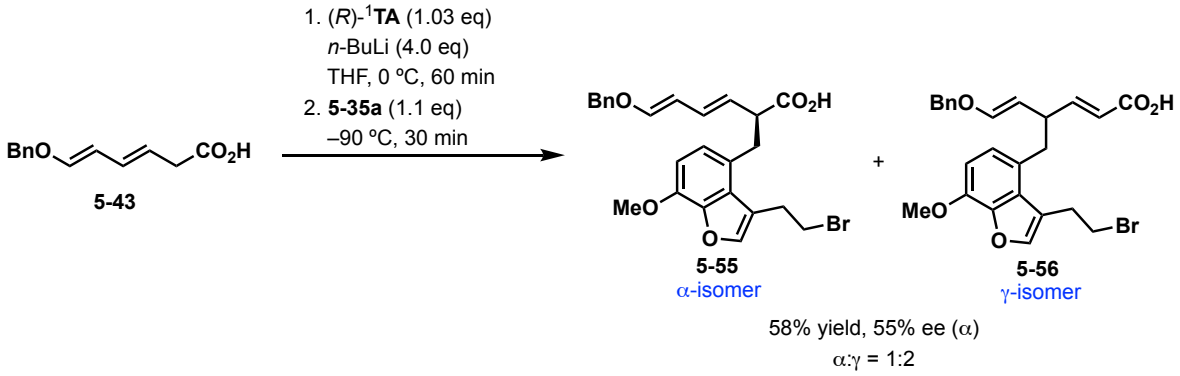
p-Methoxybenzyl chloride (PMBCl) was also tested as an electrophile in the alkylation, showing a slight decrease on enantioselectivity (70% ee, **entry 14**) comparing with the benzyl chloride, which might be due to the higher electron efficiency of the electrophile.

As for the reference, the alkylation with iodoethane afforded the single α-ethylated dienoic acid in 77% yield and 80% ee (**entry 15**).

5.5.2 Asymmetric Alkylation with Dihalogenated Benzofuran as Electrophile

Using the designed benzofuran dibromide (**5-35a**) as electrophile under the above optimized condition, our first attempt obtained 58% yield of the mixture of α- and γ-alkylated product, in which α-isomer (**5-55**) presented 55% ee, while the γ-isomer (**5-56**) was surprisingly more favored in the alkylation (α:γ = 1:2). The γ-preference of this alkylation between the acid **5-43**

and dibromide **5-35a** was consistent in the cases of using other types of chiral amines (up to α:γ 1:4).



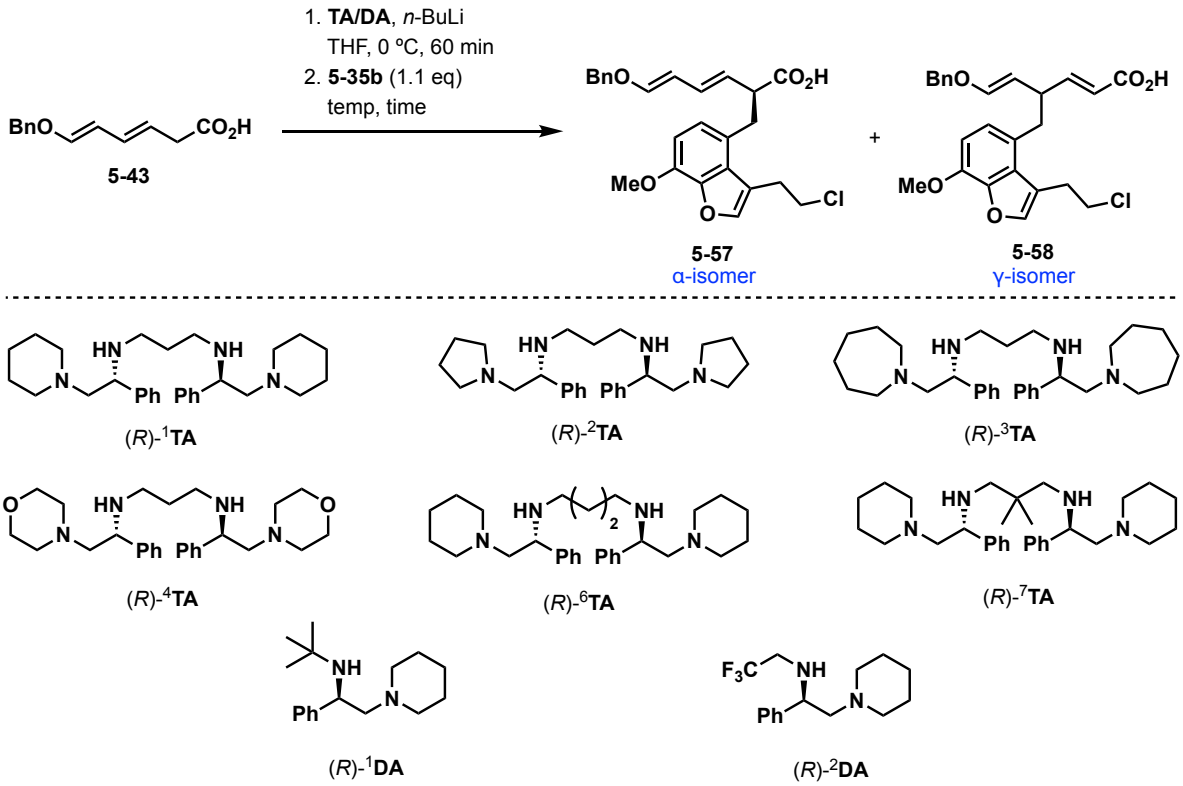
Scheme 5-12. Asymmetric alkylation of acid 5-43 with dibromide 5-35a

A thorough investigation on screening Koga type chiral amine was carried out with benzofuran dichloride **5-35b** shown in **Table 5-2**. With (*R*)-[1]**TA** as the chiral auxiliary, the alkylation at –78 ºC for 90 min only afforded 9% yield of product with 30% ee and 12:1 α-selectivity (**entry 1**). Double of the alkylation time at the same temperature forced the alkylation yield only to 19% and the regioselectivity dropped to around 6:1 (**entry 2**), and increasing the alkylation temperature to –40 ºC pushed the reaction forward to 45% yield, with 22% ee of α-isomer (**5-57**) and 9:1 α-selectivity (**entry 3**). The enantio- and regioselectivity of the product after 3-hour alkylation at –78 ºC decreased significantly with pyrrolidine tetraamine (*R*)-[2]**TA** (**entry 4**, 10% yield, 7% ee (α), α:γ = 1.1:1), and improved mildly with azepane tetraamine (*R*)-[3]**TA** (**entry 5**, 7% yield, 43% ee (α), α:γ = 10:1). Extend the alkylation time to 20 hours at –78 ºC, (*R*)-[3]**TA**, as the stereodirecting auxiliary, afforded 32% yield of alkylated product with 36% ee and 8:1 α-preference (**entry 6**).

Despite the moderate yield and ee with (*R*)-[3]**TA**, no improved result could be obtained by using other chiral tetraamines: barely no regioselectivity with morpholine tetraamine (*R*)-[4]**TA**

could be observed (**entry 7**, α:γ = 1:1.4); with four methylenes as *linker*, (*R*)-^{6}**TA** provided similar stereo- but lower regioselectivity (**entry 8-9**); with geminal dimethyl in *linker*, more bulky tetraamine (*R*)-^{7}**TA** significantly receded the reactivity (**entry 10**, <5% yield). Koga's chiral diamine were also examined in the asymmetric alkylation, after stirring with dichloride **5-35b** at –40 ºC for 3 hours, the ee values were maintained below 40% and α,γ-isomer ratios were around 2:1 to 3:1.

Table 5-2. Screening Chiral Amines with Dichloride 5-35b as Electrophile.



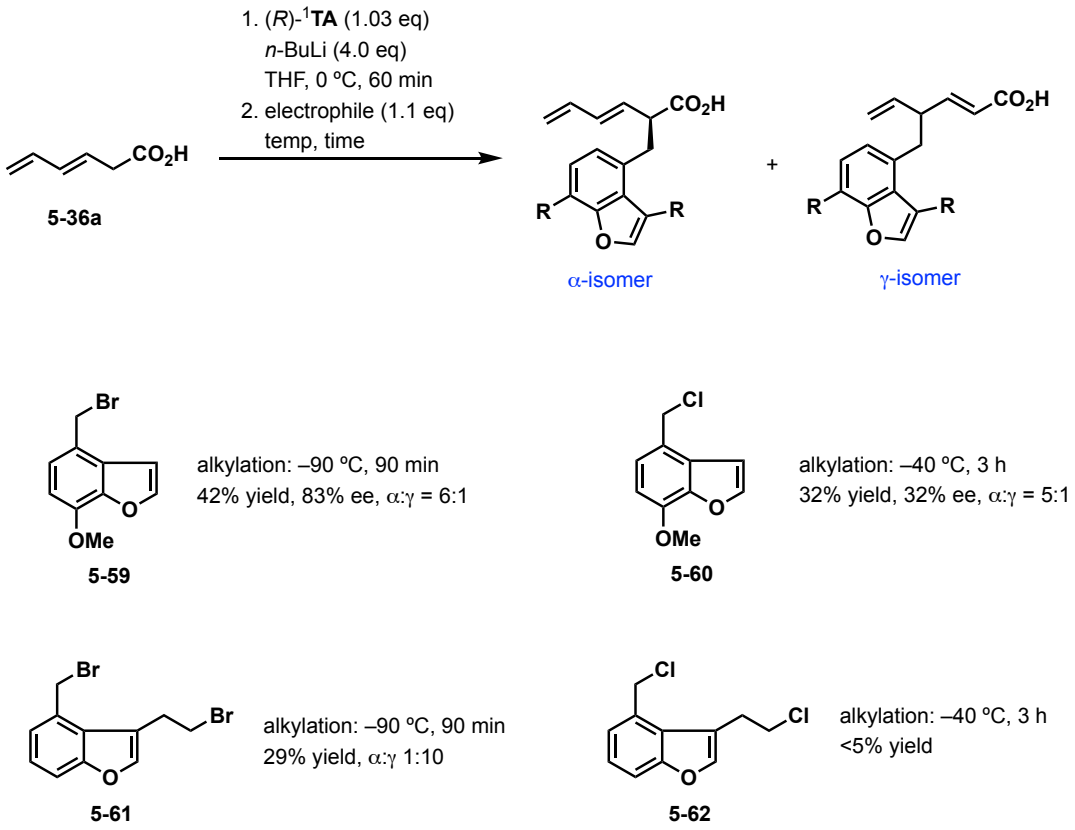
entry	chiral amine	Alkylation		yield	ee (α)	α:γ
		temp. (ºC)	time (h)			
1	(*R*)-^{1}**TA**	–78	1.5	9%	30%	12:1
2	(*R*)-^{1}**TA**	–78	3	19%	32%	6.7:1

3	(*R*)-^{1}**TA**	–40	1.5	45%	22%	9.0:1
4	(*R*)-^{2}**TA**	–78	3	10%	7%	1.1:1
5	(*R*)-^{3}**TA**	–78	3	14%	43%	10:1
6	(*R*)-^{3}**TA**	–78	20	32%	36%	8.0:1
7	(*R*)-^{4}**TA**	–78	3	22%	45%	1:1.4
8	(*R*)-^{6}**TA**	–78	3	5%	37%	10:1
9	(*R*)-^{6}**TA**	–40	3	28%	32%	3.3:1
10	(*R*)-^{7}**TA**	–78	3	<5%	n.d.	n.d.
11	(*R*)-^{1}**DA** (1 eq.)	–78	3	<5%	n.d.	n.d.
12	(*R*)-^{1}**DA** (1 eq.)	–40	3	25%	22%	3.2:1
13	(*R*)-^{1}**DA** (2 eq.)	–40	3	27%	36%	3.2:1
14	(*R*)-^{2}**DA** (1 eq.)	–40	3	36%	37%	2.2:1
15	(*R*)-^{2}**DA** (2 eq.)	–40	3	33%	40%	2.2:1

Thus, a brief conclusion can be made from the above attempts that there is an incompatible contradiction between achieving high stereoselectivity and enforcing high regioselectivity in the direct alkylation of dienoic acid with dihalogenated benzofuran as electrophile.

5.5.3 Investigation on the Side Chained Benzofuran Electrophiles

Other benzofuran electrophiles were examined in the alkylation with dienoic acid, to investigate whether the effects on stereo- and regioselectivities induced from side chain or *para*-methoxy group of **5-35a** and **5-35b**. Due to the easier access, non-substituted (3*E*,5*E*)-hexa-3,5-dienoic acid (**5-36a**) was used as the substrate acid.

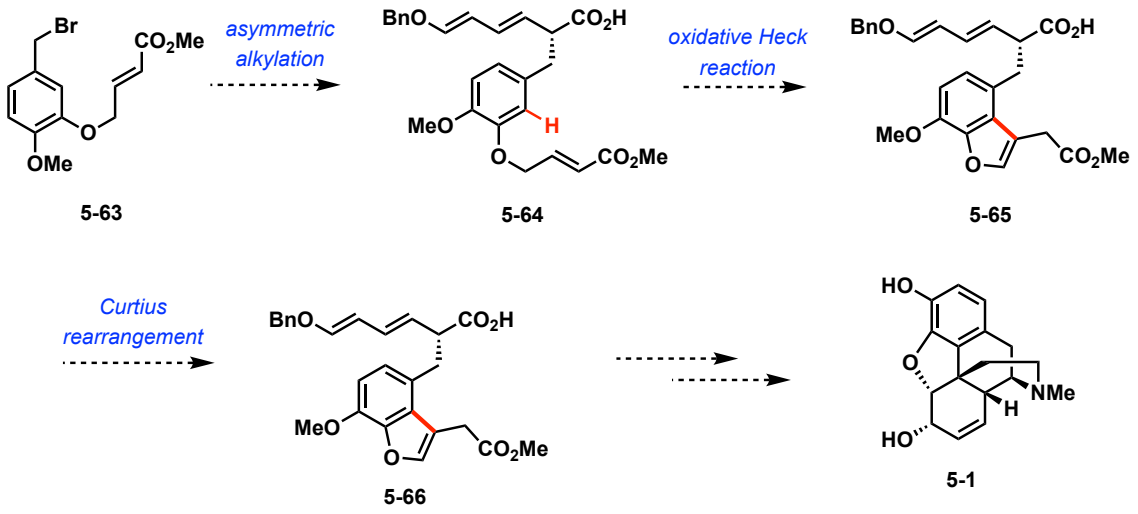


Scheme 5-13. Attempted alkylations with other benzofurans as electrophile

The alkylation with 4-bromomethyl-7-methoxybenzofuran (**5-59**) as electrophile, with no side chain, provided relatively good stereo- and regioselectivities (83% ee, α:γ = 6:1) in 42% yield. The similar 4-chloromethyl **5-60** afforded the result of 32% yield, 32% ee and 5:1 α-selectivity.

The dibromide **5-61** provided 29% yield and the high γ-selectivity (α:γ = 1:10), demonstrating the sterically hindered side chain might block the generally preferred α-position of the acid substrate, and lowered or even overturned the regioselectivity, while the conversion of alkylation with dichloride **5-62** was less than 5% after 90 min at –40 °C.

Thus, we considered that the side chain on the 3-position of the benzofuran electrophiles would build up the sterically hinderance which reduce the α-selectivity and forced to γ-alkylation, and the electrical property derived from the *para*-methoxy group barely encouraged γ-preference of the alkylation. Instead, the *para*-methoxy group is vital to the alkylation forcing with an acceptable reaction rate.



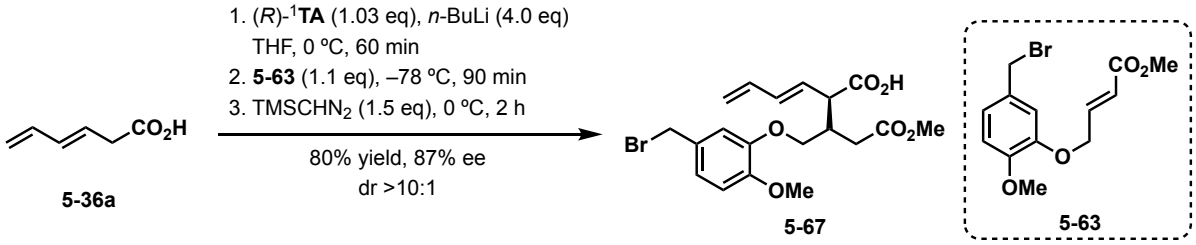
Scheme 5-14. Detour synthetic route with oxidative Heck reaction

5.5.4 Synthetic Detour and Unexpected Disclosure

Applications of oxidative Heck reactions in the synthesis of benzofuran moiety have been introduced by Stolz[18] and Wang[19]. To avoid the bulky side chained benzofuran electrophile in the asymmetric alkylation, we then planned to apply an oxidative Heck precursor (**5-63**) as the electrophile in the asymmetric alkylation shown in Scheme 5-14. If the following intramolecular oxidative Heck reaction[20] favored the crotonate over the diene moiety in **5-64**, we would successfully detour to the similar benzofuran alkylated acid **5-65**.

However, the asymmetric reaction between the dienoic acid **5-36a** and the benzyl bromide **5-63** did not provide any alkylated product, but afforded the Michael adduct. After the

following esterification, the methyl ester **5-67** was yield in 80% with 87% ee and >10:1 diastereomeric ratio.



Scheme 5-15. Unexpected asymmetric Michael reaction with 5-63 as electrophile

Clearly, in this case, the Michael accepting unit in the electrophile **5-63** showed much higher reactivity than the benzylic bromide moiety, which is commonly known as an *active* alkylating agent. We wondered if this tendentiousness would be consistent in the competition between the Michael addition and alkylation at the active spot like benzylic and allylic position.

5.6 Conclusion

We designed a concise synthetic route towards (–)-morphine via our asymmetric methodology using chiral lithium amide as the key step to introduce the pioneering chirality. In the practical proceeding, we developed a method to efficiently synthesize (3*E*,5*E*)-6-alkoxy-3,5-dienoic acid with high *E*-selectivity. The asymmetric alkylation of the dienoic acid with side chained benzofuran electrophile could not provide the designed alkylated product in high stereoselectivity and regioselectivity, exposing a drawback of our previous method on handling sterically large electrophiles. A detour using oxidative Heck reaction was proposed, but the prior asymmetric reaction demonstrated the conjugated addition significantly favored over the benzylic alkylation, leading to a suspension of this project. In the later study, our work will focus on the competition between active alkylations and Michael additions.

5.7 References

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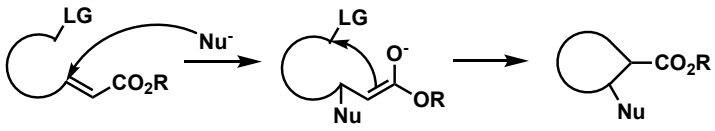
Chapter 6. Construction of Carbocyclic Compounds via Asymmetric MIRC Reaction with Chiral Lithium Amide as Traceless Auxiliaries

6.1 Introduction

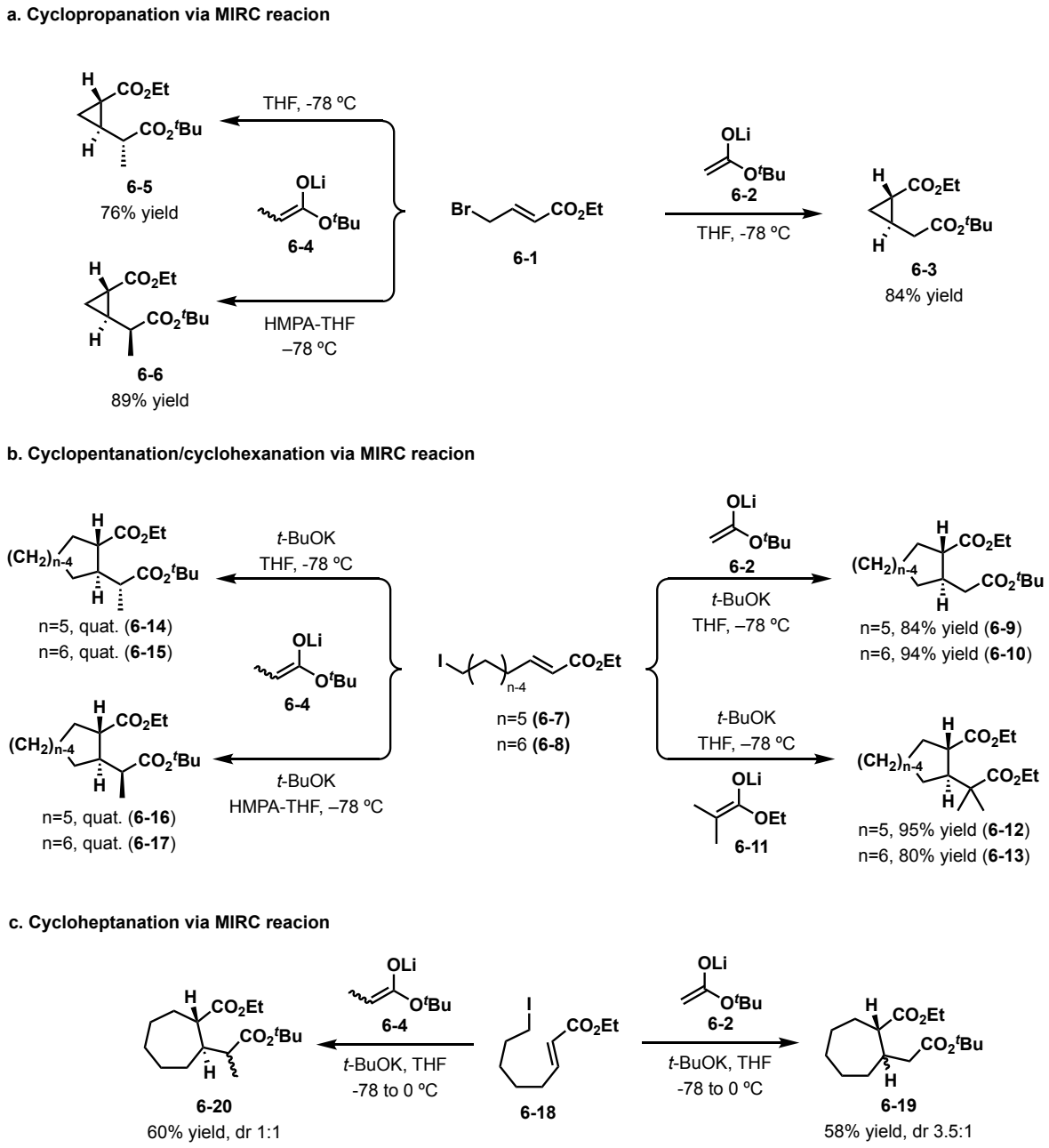
Cyclic compounds are eternal targets in the development of organic synthesis, which are broadly existing in medicines, agrochemicals, dyes, and optical materials. Demand for the development of smart and powerful methods for cyclization is continuing to increase.[1] Besides a tremendous number of cycloadditions[1,2], Michael initiated ring closure (MIRC) reaction[1b,3] is another efficient pathway to construct the ring systems. MIRC reaction, defined by Little *et al.* in 1980,[3b] involves a conjugate addition to an electrophilic olefin to generate an enolate, which then subsequently undergoes an intramolecular ring closure. In this domino process, cyclized product can be obtained directly through multiple bond-forming transformation.



Scheme 6-1. Michael initiated ring closure (MIRC) reaction

In 1985, Yamaguchi and coworkers introduced a highly stereoselective synthesis of carbocyclic compounds, including three, five, six, and seven-membered ring systems, via MIRC reaction.[3d] Ethyl 4-bromocrotonate (**6-1**) was treated with enolate **6-2**, which derived from the lithiation of *tert*-butyl acetate, in THF at −78 ºC, and the cyclopropane **6-3** was obtained in 84% yield as single diastereomer. Lithium enolate of tert-butyl propionate (**6-4**) was also examined in the study, and under the same condition, highly diastereoselective cyclopropanation was achieved with **6-5** as single isomer with an exocyclic chiral center, while

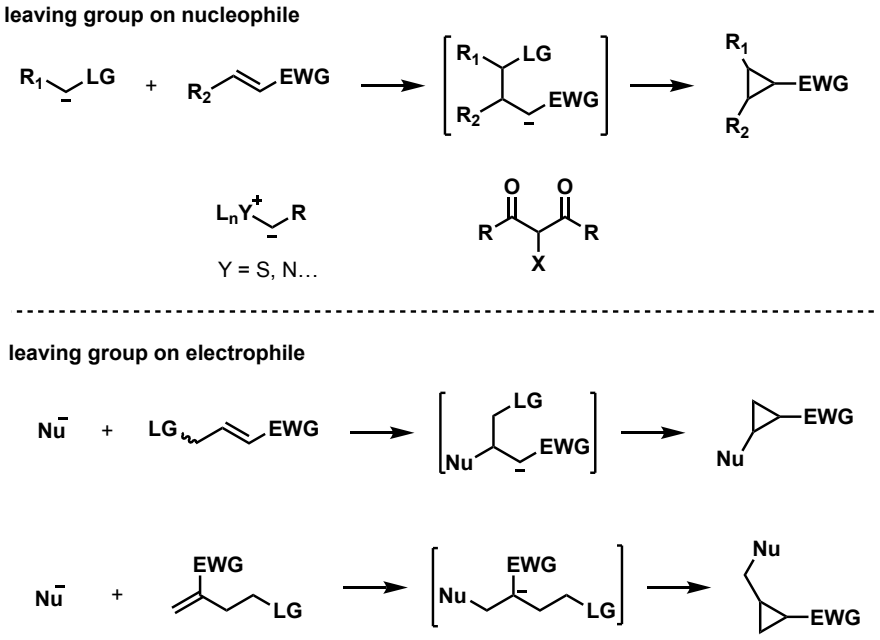
its epimer **6-6** could be obtained in 89% yield when the solvent changed to THF-HMPA (4:1). Notably, *trans*-cyclic products dominated in MIRC reactions, which were confirmed by the ^{1}H-NMR spectroscopy study.



Scheme 6-2. Yamaguchi's MIRC reactions towards carbocyclic compounds

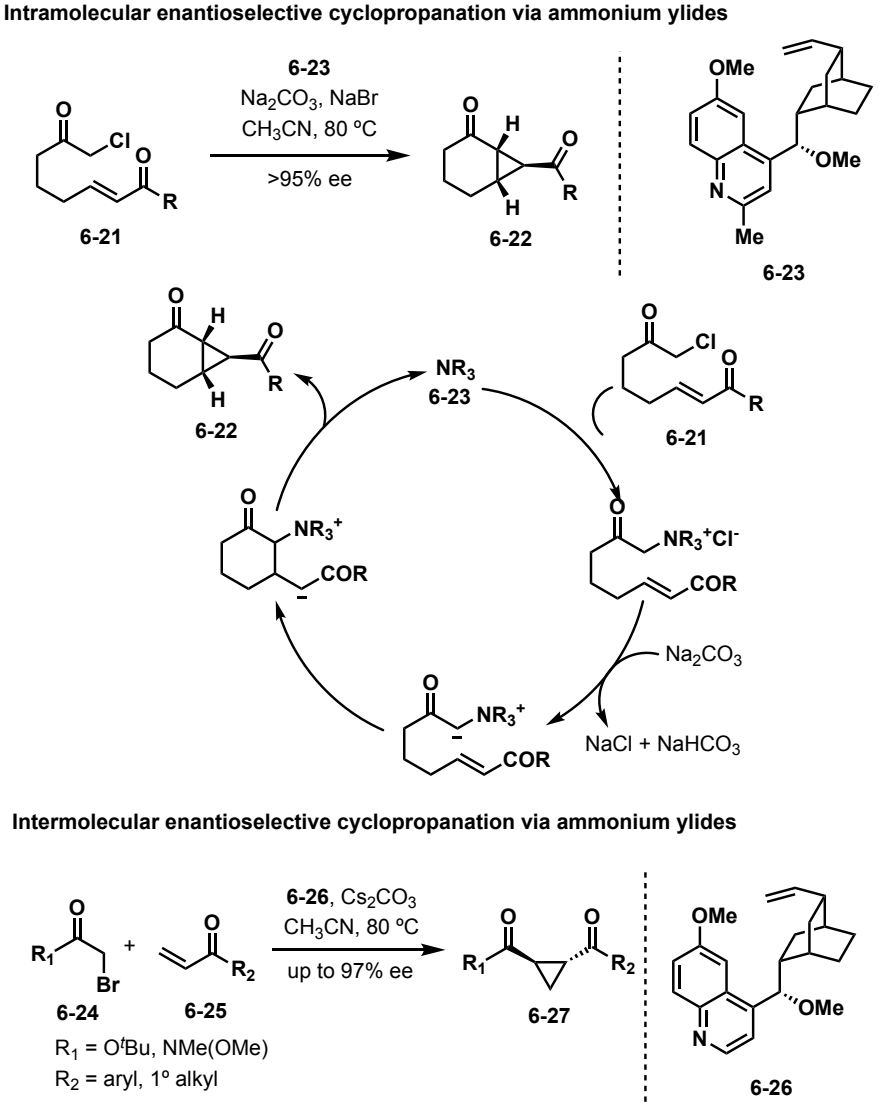
Five and six-membered cyclic compounds **6-9** and **6-10** were obtained in high yields and diastereoselectivities, when ethyl 6-iodo-2-hexenoate and ethyl 7-iodo-2-heptenoate were used as electrophile and treated with enolate **6-2** in the presence of potassium *tert*-butoxide in THF at –78 ºC. Treatment with bulkier enolate of isobutyrate (**6-11**) afforded cyclic proucts in the similar results. Again, using enolate **6-4**, the chirality of the exocyclic carbon could be highly controlled by simply changing the solvent between pure THF and THF/HMPA mixture with quantitative yields of cyclopentane (**6-14**/**6-16**) or cyclohexane (**6-15**/**6-17**).

The generation of cycloheptanes from ethyl 8-iodo-2-octenoate (**6-18**) with enolates had to be carried out at higher temperature (raising up to 0 ºC) due to the much slower intramolecular ring closure. However, epimerizations were noticed due to the high temperature: the reactions with enolate **6-2** and **6-4** provided diastereomer mixture **6-19** (dr 3.5:1) and **6-20** (dr 1:1) respectively.



Scheme 6-3. General MIRC process for cyclopropanations

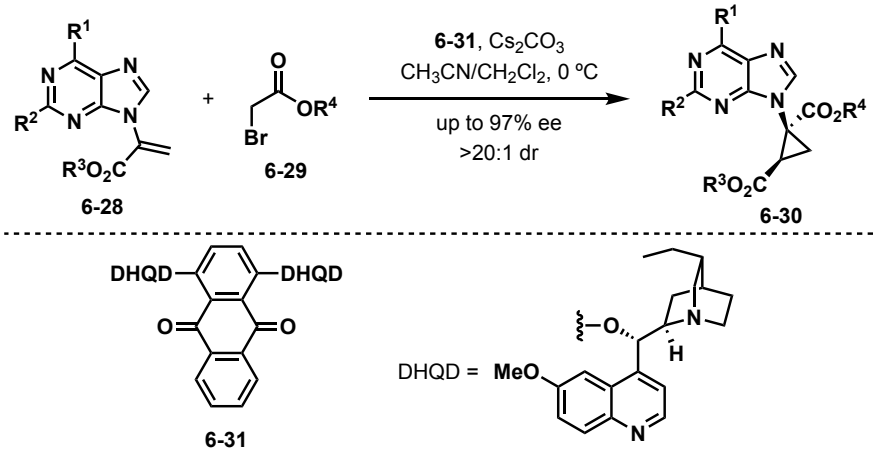
Recently, many efforts have been done on developing MIRC reactions, focusing on the construction of asymmetric cyclopropane units. Not like using electrophiles bearing the leaving group in the Yamaguchi's study, in the most of developed methods, the cyclopropanations were proceeded with nucleophilic substrates bearing the leaving group, such like ammonium or sulfonium ylides, and halogenated dicarbonyl compounds.[4] Several representative methods are introduced as follow.



Scheme 6-4. Enantioselective cyclopropanation via ammonium ylides

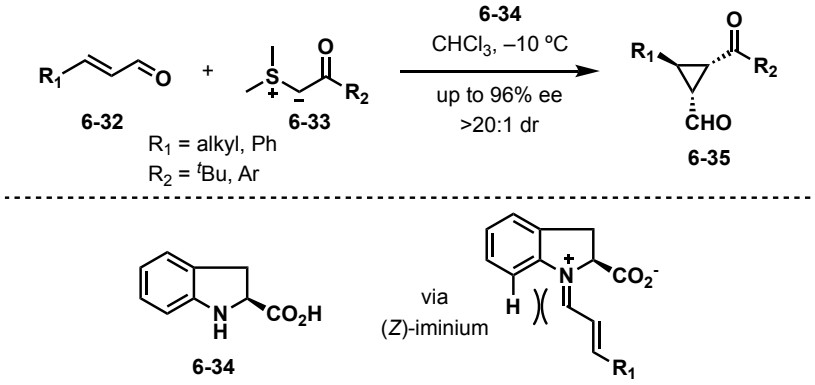
Organocatalysis has become a powerful tool for controlling the MIRC process for highly enantioselective cyclopropanations. An intramolecular organocatalytic cyclopropanation reaction with chiral ammonium ylides was developed by Gaunt and his coworkers in 2004.[5] In this method, the cinchona alkaloid catalyst **6-23** first underwent S_N2 process with α-chloroketone **6-21**, and the following MIRC reaction was finished by deprotonation of α-position, intramolecular conjugate addition and finally displacement of the ammonium group with regeneration of catalyst, affording [4.1.0]-bicyclo compound **6-22**. Intermolecular asymmetric cyclopropanation was also introduced as a similar MIRC reaction between α-bromo ester/amide **6-24** and α,β-unsaturated ketone **6-25**, providing dicarbonyl cyclopropane **6-27** with high stereocontrol.[6]

Using another organocatalyst, C_2-symmetric (bis)cinchona alkaloid derivate (**6-31**), Xie and Guo developed a highly enantioselective synthesis of chiral cyclopropyl nucleosides via asymmetric MIRC reaction between α-purine substituted acrylate **6-28** and bromoacetate **6-29**.[7] Various cyclopropyl purine analogues **6-30** with a chiral quaternary stereocenter were obtained in up to 98% yields, >20:1 dr, and up to 97% ee.



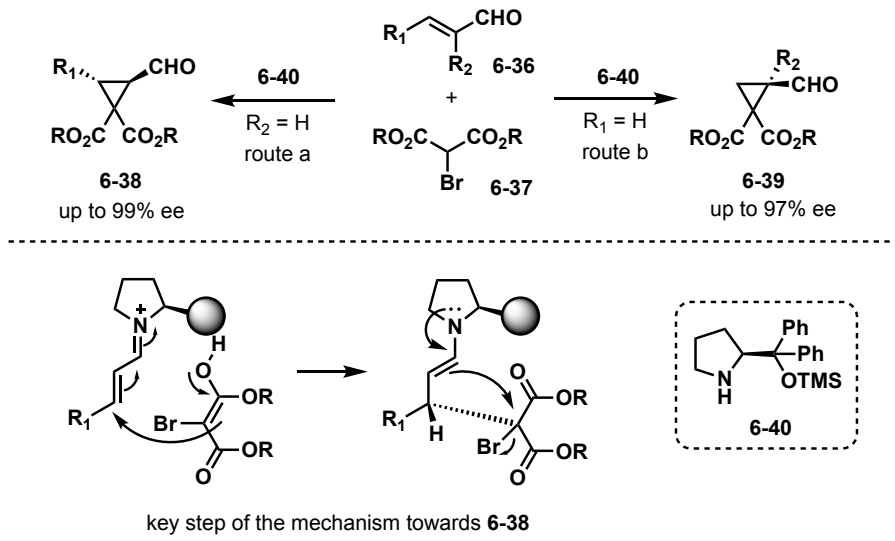
Scheme 6-5. Asymmetric synthesis cyclopropyl purines via MIRC reaction

MacMillan group develop an enantioselective synthesis of 1,2,3-trisubstituted cyclopropanes **6-35**, which was catalyzed in the presence of chiral secondary amine **6-34** by reacting of α,β-unsaturated aldehyde **6-32** with sulfur ylides **6-33**.[8] The catalyst-derived iminium intermediated would hypothetically populate the (*Z*)-isomer to minimize steric interaction between the olefin and aryl hydrogen, which ensured the carboxylate group on the catalyst controlled the approaching of **6-33** with high enantioselectivity. α-Chloroketone could also react with **6-32** to generate the trisubstituted cyclopropanes with similar organocatalyst.[9]

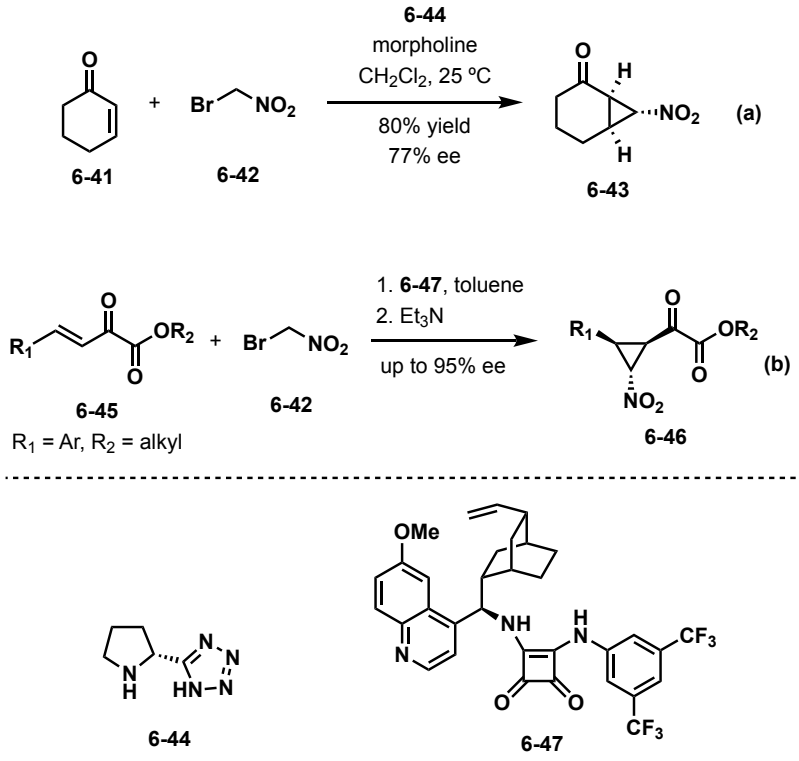


Scheme 6-6. Asymmetric MIRC cyclopropanation from α,β-unsaturated aldehyde

With similar chiral amine as covalent stereodirecting catalyst, the cyclopropanations of α,β-unsaturated aldehyde **6-36** with bromomalonates **6-37** were also achieved in excellent diastereo-and enantioselectivities.[10] Cordova[10a] and Wang[10b] independently introduced the chiral secondary amine catalyzed-cyclization with α-free enal in 2007 (Scheme 6-7, route a): the conjugate addition of bromomalonates to the iminium intermediate sterically controlled by the side group, followed by a intramolecular alkylation, delivering the tetrasubstituted cyclopropane **6-38**. α-Brunched enal could also be applied in this type of cyclization with the formation of cyclopropanes **6-39** bearing a chiral quaternary center (Scheme 6-7, route b).[10f]



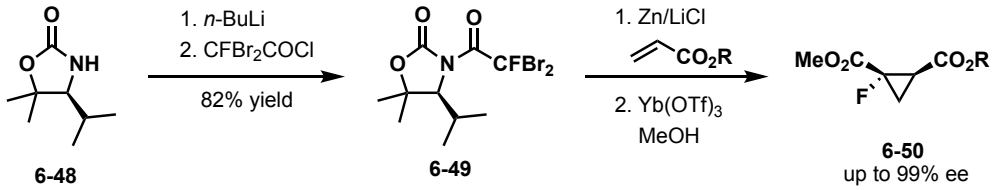
Scheme 6-7. Asymmetric MIRC cyclopropanation with bromomalonates



Scheme 6-8. Asymmetric MIRC cyclopropanation with bromonitromethane

Bromonitromethane (**6-42**) is also an excellent precursor to form the corresponding ammonium ylides, which then participate in cyclopropanation via MIRC domino process.[11] With 5-(pyrrolidine-2-yl)-1*H*-tetrazole (**6-44**) as organocatalyst, the nitrocyclopropanation of 2-cyclohexen-1-one (**6-41**) was achieved in good yield and enantioselective control (Scheme 6-7a)[11a], while using squaramide **6-47**, the cyclization of β,γ-unsaturated α-ketoesters (**6-45**) with **6-36** was also achieved excellent enantioselectivities (up to 95% ee, Scheme 6-7b)[11b].

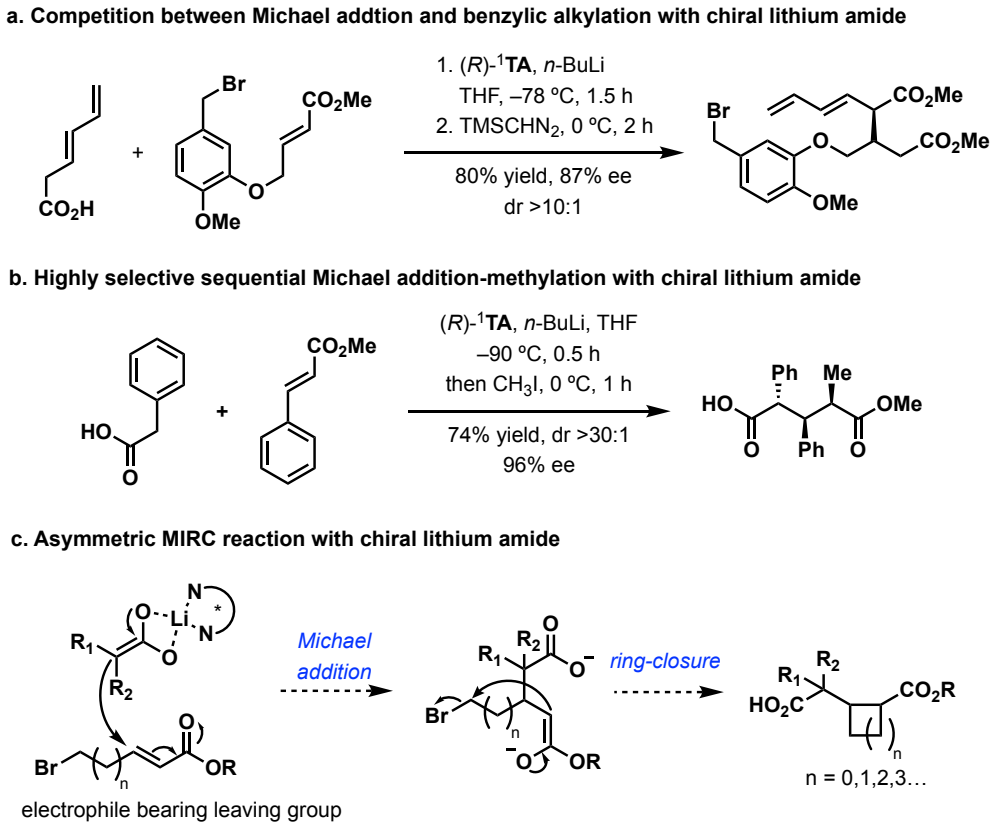
Covalent chiral auxiliary, oxazolidinone, was also applied in the asymmetric MIRC reaction towards cyclopropanes. Jubault *et al.* developed a new chiral fluorinated reagent, *N*-(dibromofluoro)acyloxazolidinone (**6-49**), which was used in the generation of cyclopropanes bearing a fluorinated quaternary stereocenter.[12] The enolate of **6-49** underwent Michael addition onto acrylates and the following ring-closure afford the cyclopropane unit. After removal of the chiral auxiliary with, the fluorocyclopropanes **6-50** could be obtained with moderate cis/trans-selectivities, good yields and up to 99% enantiomeric excess.



Scheme 6-9. Asymmetric MIRC reaction towards fluorocyclopropanes with chiral oxazolidinone

Despite many MIRC methods have been developed for cyclopropanes, however, only a few of studies introduced the constructions of five or six-membered rings with MIRC reaction, most of which are actually targeting heterocycles.[13] Furthermore, there is no detailed study on the synthesis of cyclobutane in this cascade strategy. Like in Yamaguchi's study, all other small

size carbocyclic compounds via MIRC process were introduced, but no discussion about constructing cyclobutane.



Scheme 6-10. Asymmetric MIRC reaction towards carbocyclic compounds with chiral lithium amides

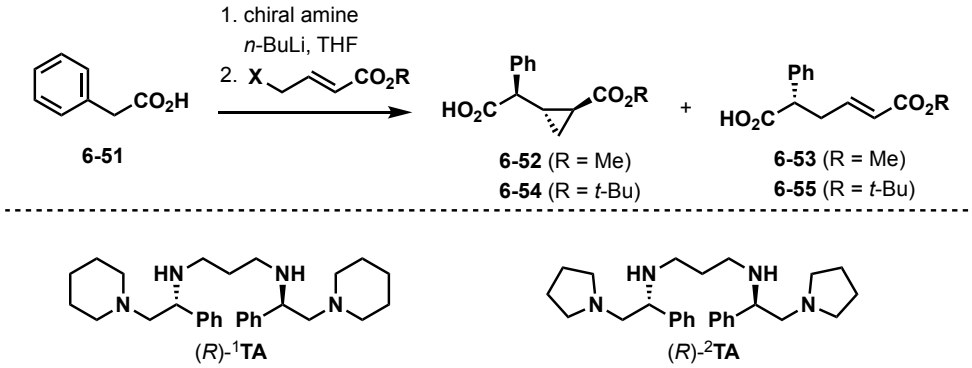
In Chapter 5, we introduced the conjugate addition with compatible benzylic bromide in the presence of chiral lithium amides, resulting 80% yield of the Michael adduct as single product with 87% ee and over 10:1 dr (Scheme 6-10a). Earlier, we also found the maintenance on stereoselectivities in the sequential Michael addition-methylation using the chiral lithium amides (Scheme 6-10b, 96% ee, dr >30:1).[14] Inspired from these works, here, we are introducing a method to construct various membered carbocyclic compounds via MIRC reactions in high enantio- and diastereoselectivities with chiral lithium amides as traceless

auxiliaries. Not like the most recent studies using nucleophiles bearing leaving group, this asymmetric MIRC method will apply the strategy with leaving group on electrophiles, again, recalling the 1980s' study from Little and Yamaguchi.

6.2 Cyclopropanation Between Phenylacetic Acid and 4-Bromocrotonate Derivatives

Due to a thorough study on the chiral amine, aggregation time and temperature for Michael addition has been achieved[14], the optimized aggregation condition with chiral tetraamine (**[1]TA** or **[2]TA**) was directly applied in the study of the Michael initiated ring-closure reactions.

Table 6-1. Pioneering study on MIRC cyclopropanation with phenylacetic acid[a]



entry	electrophile X	electrophile R	chiral amine	yield	ee	dr	cyclo : alkyl
1	Br	Me	(*R*)-**[1]TA**	82%	40%	20:1	20:1
2	Br	*t*-Bu	(*R*)-**[1]TA**	61%	17%	>20:1	1:1
3	Br	Me	(*R*)-**[2]TA**	68%	7%	6:1	10:1
4	Cl	Me	(*R*)-**[1]TA**	69%	4%	18:1	18:1
5	Cl	*t*-Bu	(*R*)-**[1]TA**	69%	13%	7:1	8:1

6	Cl	Me	(*R*)-^{2}**TA**	75%	15%	15:1	>20:1
7[b]	Br	Me	(*R*)-^{1}**TA**	49%	10%	1.4:1	2.3:1
8	OTs	Me	(*R*)-^{1}**TA**	71%	37%	15:1	>20:1
9	OMs	Me	(*R*)-^{1}**TA**	73%	36%	20:1	>20:1

[a] Experiments were performed on a 0.50 mmol scale. (*R*)-**TA** (1.03 equiv.), *n*-BuLi (4.0 equiv.), electrophile (1.1 equiv.), and THF (4.0 mL). [b] LiCl (2.0 equiv.) was added right after the addition of the electrophile at –78 ºC.

Phenylacetic acid (**6-51**) was the target substrate in the pioneering study of the asymmetric MIRC reaction (Table 6-1). With the aggregation of chiral tetraamine (*R*)-^{1}**TA** and *n*-BuLi at 0 ºC, the cyclopropanation with 4-bromocrotonate at –78 ºC afforded 82% yield of a 20:1 mixture of cyclized product (**6-52**) and alkylated product (**6-53**). The cyclized product, (*R*)-2-((1*S*,2*S*)-2-(methoxycarbonyl)cyclopropyl)-2-phenylacetic acid[15], was afforded in 40% ee and 20:1 dr (entry 1). By switching the electrophile with *tert*-butyl 4-bromocrotonate, we surprisingly found that barely no chemoselectivity between the cyclization and allylic alkylation was achieved (**6-54**:**6-55** = 1:1), and the ee value of the cyclized product **6-54** was only 17% (entry 2). Enantio- and diastereoselectivities also decreased dramatically with pyrrolidine-derived tetraamine (*R*)-^{2}**TA** in the cyclopropanation with methyl 4-bromocrotonate (entry 3, 7% ee, dr 6:1).

With different leaving group, 4-chlorocrotonate generally provided lower enantiocontrol. The cyclized acids were obtained only in 4% and 13% ee respectively with (*R*)-^{1}**TA** and corresponding methyl or *tert*-butyl ester (entry 4, 5), while switching to (*R*)-^{2}**TA** kept the ee value at the similar level (entry 6, 15% ee). The relatively low enantiocontrol made from 4-

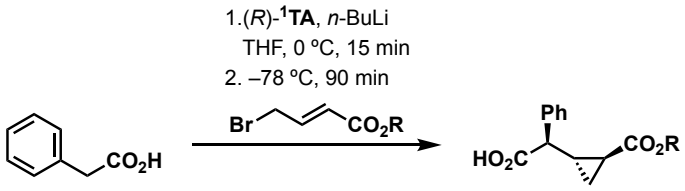
chlorocrotonate is possibly due to the *in situ* generated lithium chloride which jeopardized the chiral lithium aggregates. The test with the addition of LiCl during the cyclization with methyl 4-bromocrotonate preliminarily confirmed this hypothesis (entry 7, 10% ee, dr 1.4:1, cyclo:alkyl = 2.3:1). With no formation of counter ion interfering the aggregates, methyl 4-tosyloxycrotonate provided 71% yield of **6-52** as single product with 37% ee, while methyl 4-metylsulfonylcrotonate afforded **6-52** in 73% yield, 36% ee and 20:1 dr. Based on the brief screening on the leaving group, we decided to use 4-bromocrotonate as electrophile for our later study on MIRC cyclopropanation.

Also, from the pioneering study, it is not hard to notice that the difference on the alcoholic parts of esters would affect enantiocontrol and chemoselectivities.

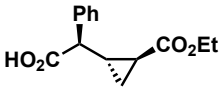
Thus, we explored a series of 4-bromocrotonates in the cyclopropanation of phenylacetic acid with (*R*)-^{1}**TA** (Table 6-2). With ethyl or isopropyl ester, the enantio- and diastereoselectivities of cyclization maintained at 33~36% ee and 20:1 dr. Comparing the synthesis of **6-52**, **6-55**, **6-56** and **6-54**, a decreasing tendency of the chemoselectivity between cyclization and alkylation would be noticed with increasing the bulkiness of alkyl group in the ester. Benzyl ester provided the cyclopropane **6-58** in 42% ee and 20:1 ratio of cyclization to alkylation, while 2-methoxyethyl ester, with an extra possible coordinating atom, afforded **6-59** in similar enantio- and chemoselectivities. We also tested the unsaturated amide, (*E*)-4-bromo-*N*,*N*-dimethyl-2-butenamide, which delivered **6-60** in the same level of selectivities.

The enantiocontrol increases to 68% ee when the phenyl 4-bromocrotonate was used instead of alkyl esters (**6-61**), and the cyclization dominated in the most of cases using aryl esters with at least 10:1 chemoselectivity.

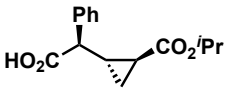
Table 6-2. Screening of derivatives of 4-bromocrotonates[a]



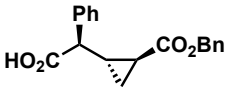
6-51



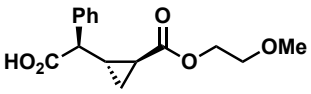
6-56
72% yield, 33% ee
dr >20:1, cyclo : alkyl = 14:1



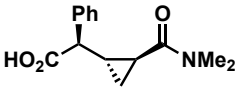
6-57
56% yield, 36% ee
dr 20:1, cyclo : alkyl = 7:1



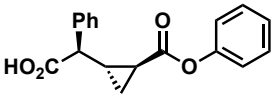
6-58
79% yield, 42% ee
dr >20:1, cyclo : alkyl = 20:1



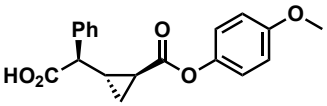
6-59
70% yield, 36% ee
dr >20:1, cyclo : alkyl = 16:1



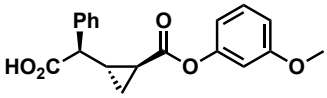
6-60
72% yield, 44% ee
dr >20:1, cyclo : alkyl >20:1



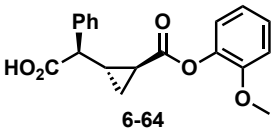
6-61
78% yield, 68% ee
dr >20:1, cyclo : alkyl = 16:1



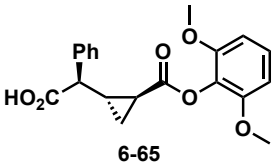
6-62
83% yield, 77% ee
dr >20:1, cyclo : alkyl >20:1
80% ee[b]



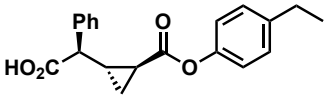
6-63
72% yield, 68% ee
dr 8:1, cyclo : alkyl >20:1



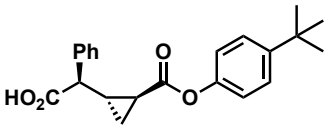
6-64
79% yield, 54% ee
dr >20:1, cyclo : alkyl 13:1



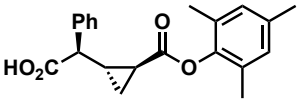
6-65
69% yield, 60% ee
dr >20:1, cyclo : alkyl 10:1



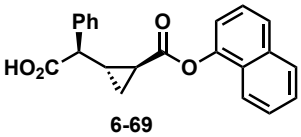
6-66
60% yield, 70% ee
dr >20:1, cyclo : alkyl >20:1



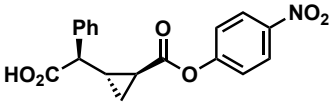
6-67
61% yield, 76% ee
dr >20:1, cyclo : alkyl >20:1



6-68
66% yield, 57% ee
dr >20:1, cyclo : alkyl >20:1



6-69
76% yield, 65% ee
dr >20:1, cyclo : alkyl = 3:1



6-70
decomposed

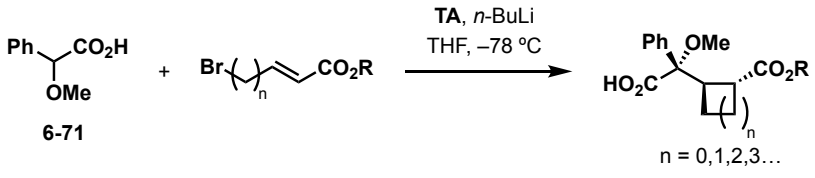
[a] Experiments were performed on a 0.50 mmol scale. (*R*)-[1]**TA** (1.03 equiv.), *n*-BuLi (4.0 equiv.), electrophile (1.1 equiv.), and THF (4.0 mL). [b] Cyclopropanation at –90 ºC.

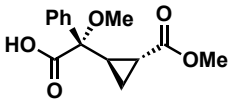
With *para*-methoxy group, the aryl ester delivered 83% yield of **6-62** in 71% ee after 90-min reaction at –78 ºC, while the ee value increased to 80% when the MIRC reaction was carried out at –90 ºC. The *ortho*-substitution receded the enantiocontrol to ~60% ee possibly due to its sterically hinderance (**6-64**, **6-65**). With other electron donating groups, the cyclopropanation of phenylacetic acid with 4-ethylphenyl and 4-(*tert*-butyl)phenyl esters afforded **6-66** and **6-67** in 70% and 76% ee, respectively. With electron withdrawing property, the reaction with 4-nitrophenyl 4-bromocrotonate was only found as decomposition (**6-70**).

6.3 Highly Enantioselective MIRC Reactions of α-Methoxy Phenylacetic Acid

We then examined the MIRC reactions with α-methoxy phenylacetic acid (**6-71**) as substrate acid (Table 6-3).

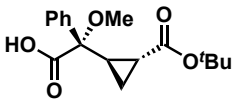
Table 6-3. Asymmetric MIRC reaction towards 3/4/5/6-membered carbocyclic acid[a]





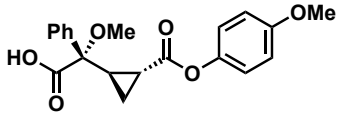
6-72

[1]TA: 90% yield, 85% ee, dr >20:1
[2]TA: 63% yield, 84% ee, dr >20:1



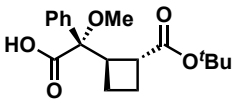
6-73

[1]TA: 61% yield, 93% ee[b], dr >20:1
[2]TA: 61% yield, 96% ee[b], dr >20:1



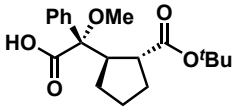
6-74

[1]TA: 61% yield, 80% ee, dr >20:1
[2]TA: 62% yield, 82% ee, dr >20:1



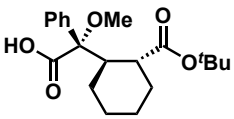
6-75

[1]TA: 67% yield, 99% ee[b], dr 11:1



6-76

[1]TA: 75% yield, 94% ee[b], dr >20:1

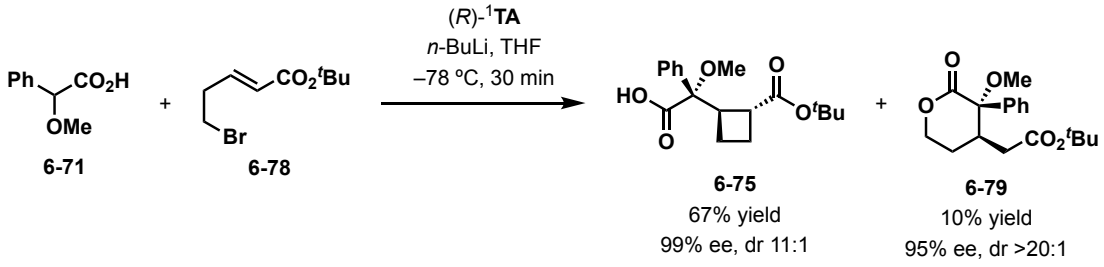


6-77

[1]TA: 46% yield, 99% ee[b], dr >20:1

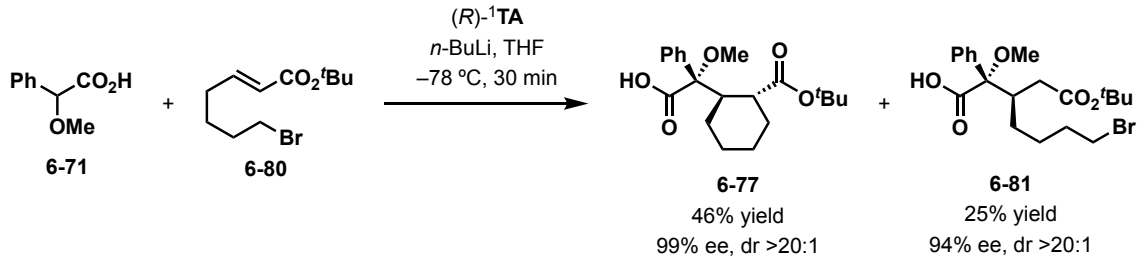
[a] Experiments were performed on a 0.50 mmol scale. (*R*)-**TA** (1.03 equiv.), *n*-BuLi (4.0 equiv.), electrophile (1.1 equiv.), and THF (4.0 mL). [b] The ee values were determined by HPLC analysis of corresponding methyl esters.

Besides cyclopropanation, the asymmetric MIRC reactions for cyclobutanes, cyclopentanes and cyclohexanes were also investigated with **6-71** as substrate acid. The MIRC cyclobutanation with *tert*-butyl (*E*)-5-bromo-2-pentenoate[15c] and (*R*)-[1]**TA** was carried out at –78 ºC for 30 min, affording 67% yield of cyclobutyl acid **6-75** (99% ee, dr 11:1) and 10% yield of lactone **6-79** (95% ee, dr >20:1) as byproduct (Scheme 6-11). The formation of **6-79** and the consistency on ee's also supported the Michael-initiated mechanism.



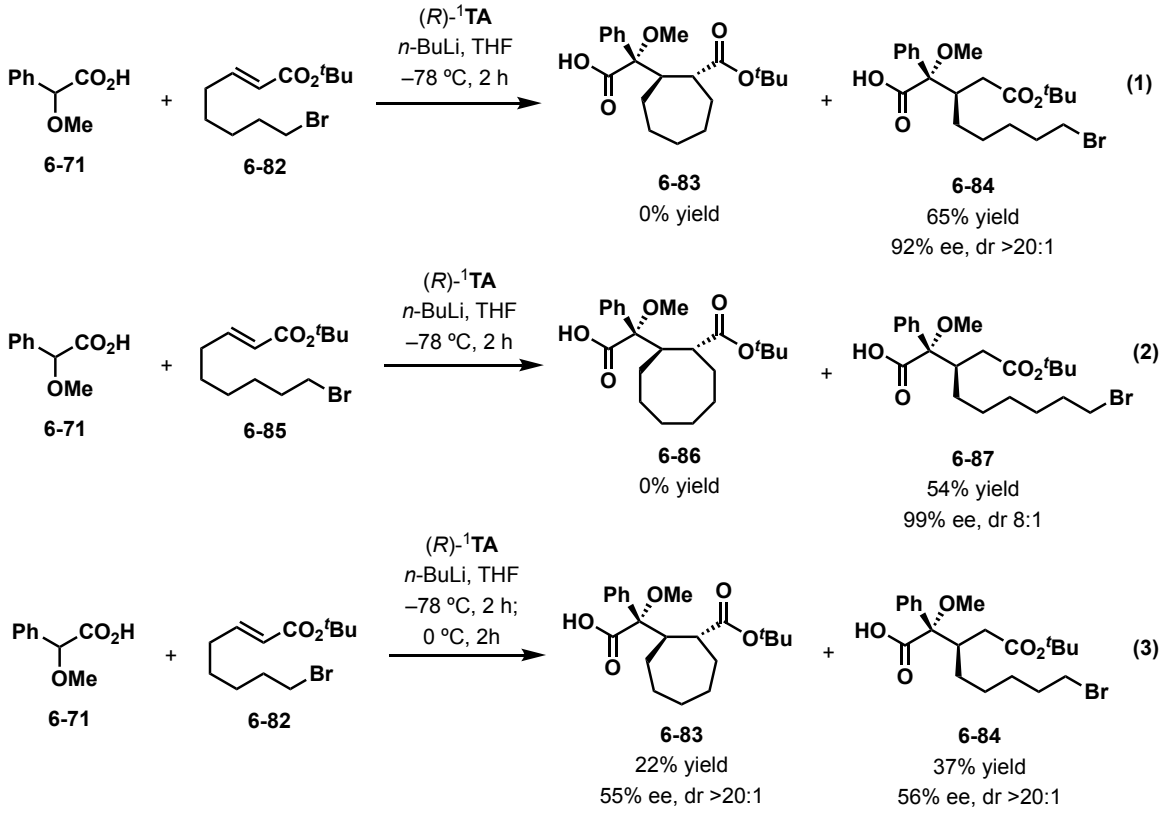
Scheme 6-11. Enantioselective cyclobutanation of 6-71 and 6-78

High stereoselectivities are maintained very well in the cyclopentanation and cyclohexanation with *tert*-butyl (*E*)-6-bromo-2-hexenoate [16] and *tert*-butyl (*E*)-7-bromo-2-heptenoate[17] respectively. After 30-min reaction at –78 ºC, cyclopentyl acid **6-76** was obtained as only product in 75% yield, 94% ee and >20:1 dr. However, the intramolecular S_N2 substitution proceeded more slowly in the MIRC cyclohexanation (Scheme 6-12). The 30-min reaction afforded 46% yield of cyclohexyl acid **6-77** (99% ee, dr >20:1) and 25% yield of Michael adduct **6-81** (94% ee, dr >20:1).



Scheme 6-12. Enantioselective cyclohexanation of 6-71 and 6-80

We also attempt our asymmetric MIRC method on the construction of middle size ring, cycloheptane and cyclooctane (Scheme 6-13).



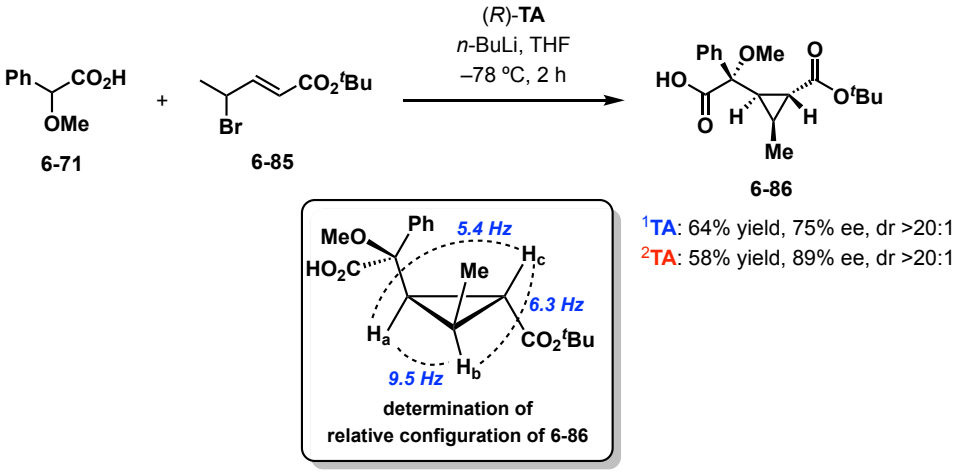
Scheme 6-13. Attempt on enantioselective cycloheptanation and cyclooctanation

Not surprisingly, like shown in Yamaguchi's study[3d], the reaction between α-methoxy phenylacetic acid and corresponding electrophiles at –78 ºC only afforded the Michael adducts

6-84 and **6-86**, despite with uniformly high enantioselectivity (eq 1 and eq 2). By raising the reaction temperature up to 0 ºC for another 2 hours, the ring-closure was proceeded in around 40% and yielded 22% of cycloheptyl acid **6-83** with a sharply decreased enantioselectivity (55% ee).

6.4 More Study on Asymmetric MIRC Cyclopropanation

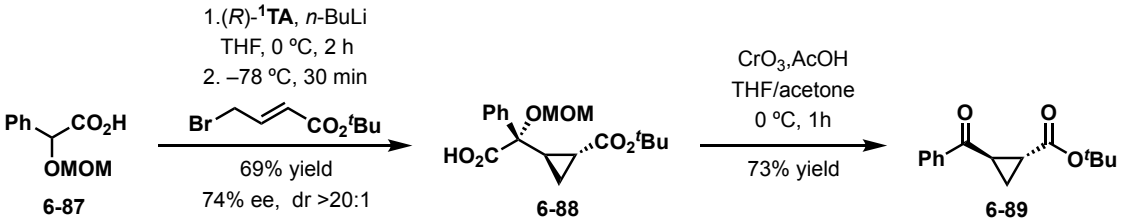
Brunched bromo ester was also examined in the asymmetric MIRC cyclopropanation. Racemic *tert*-butyl (*E*)-4-bromo-2-pentenoate (**6-85**) was tested as electrophile (Scheme 6-14). Interestingly, cyclopropyl acid **6-86** was obtained as single diastereomer with a *S*-methyl configuration. The cyclopropanation using piperidine tetraamine (*R*)-^{2}**TA** afforded **6-86** in 58% yield, 89% ee and >20:1 dr. The relative configuration of the cyclopropane moiety in **6-86** was determined by the ^{1}H-NMR spectroscopy study.



Scheme 6-14. Asymmetric cyclopropanation with brunched bromo ester 6-85

Dicarbonyl cyclopropanes are difficult to be derived from Simmon-Smith cyclopropanation of carbene moiety and the electron deficient olefin.[18] Usually they can be accessed from MIRC

process (see introduction for more information). We disclosed a short pathway from the product of our method to chiral dicarbonyl cyclopropanes shown as follow. Cyclopropyl acid **6-88** was obtained via the enantioselective cyclopropanation between α-methoxymethyl phenylacetic acid (**6-87**) and *tert*-butyl 4-bromocrotonate in 69% yield and 74% ee. The treatment of **6-88** with CrO_3 in acidic condition would carry out a sequential removal of MOM group and oxidative decarboxylation in one pot, quickly affording 73% yield of *tert*-butyl (1*R*,2*R*)-2-benzoylcyclopropane-1-carboxylate (**6-89**) of which the spectra was matched with the literature data.[19]



Scheme 6-15. Synthesis of dicarbonyl cyclopropanes

6.5 Conclusion

A method to asymmetrically construct carbocyclic compounds has been demonstrated, which underwent an asymmetric MIRC process with electrophile bearing leaving group. With chiral lithium amides as stereodirecting reagents, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl compounds were synthesized with high enantio- and diastereoselectivities. A thorough screening on the electrophiles for cyclopropanation showed the importance of the leaving group, and the alcoholic moiety of ester is also vital to the stereo- and chemoselectivities. We also provided a method to convert the products of our method to the dicarbonyl cyclic compounds.

Our future work will be focused on three points: 1) Although we determined the absolute configuration of carbocyclic product based on our previous study on the corresponding Michael addition, a solid support is still required, from X-ray crystallography or optical property of derivatives from known chiral compounds; 2) So far, the possibility of highly selective synthesis of small size carbocyclic compounds has been demonstrated. Substrate scopes on the carboxylic acids and more electrophiles are waiting to be completed. Also, improvement on the intramolecular reactivities for the construction of middle size rings (typically, cycloheptanes and cyclooctanes) needs to be solved; 3) We also will focus on the application of this methodology in complex molecule synthesis.

6.6 References

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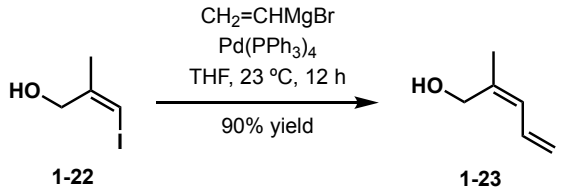
Chapter 7. Experimental Details

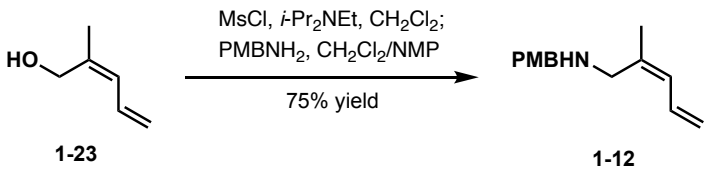
7.1 General Information

All reactions were carried out under an atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether (diethyl ether) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, diisopropylamine and triethylamine were distilled from calcium hydride in a continuous still under and atmosphere of argon. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F254 (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova spectrometers. Carbon nuclear magnetic resonance spectra were recorded at 100, 125, and 150 MHz on Varian Unity Inova spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical rotations were measured on a Rudolph Autopol III polarimeter. Mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.

7.2 Large-Scale Total Synthesis Towards (–)-Muironolide A

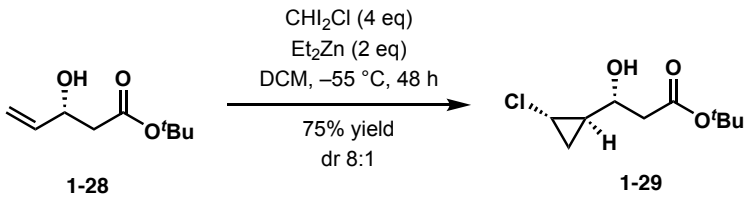


(Z)-2-Methylpenta-2,4-dien-1-ol (1-23). Vinyl magnesium bromide (1.5 M in THF, 150 mL, 0.226 mol, 2.5 equiv) was added dropwise to a solution of vinyl iodide **1-22** (17.9 g, 90.5 mmol) in dry, degassed THF (150 mL) at 0 ºC. The resultant solution was stirred at 23 ºC for 6 h, and cooled back to 0 ºC. Tetrakis(triphenylphosphine)palladium (1.04 g, 0.905 mmol) was then added to the reaction mixture, and the reaction was raised up 23 ºC for additional 12-hour stirring. The reaction was quenched by adding saturated aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether (3×200 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure at 0 °C, and the residue was purified by column chromatography on silica gel (30% diethyl ether in pentane) to afford **1-23** (8.02 g, 81.6 mmol, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.63 (dt, J = 16.7, 10.6 Hz, 1H), 5.96 (d, J = 11.1 Hz, 1H), 5.17 (d, J = 16.7 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 4.27 (d, J = 5.9 Hz, 2H), 1.88 (s, 3H), 1.26 (s, 1H).



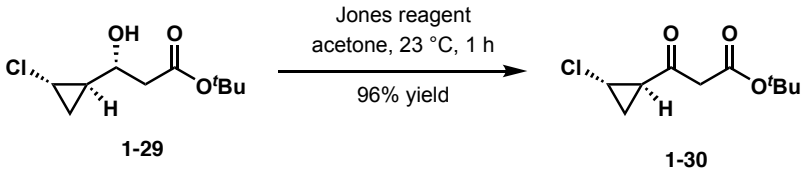
(*Z*)-*N*-(4-Methoxybenzyl)-2-methylpenta-2,4-dien-1-amine (1-12). Methanesulfonyl chloride (9.81 g, 85.6 mmol, 1.2 equiv) was added dropwise to a solution of alcohol **1-23** (7.00 g, 71.3 mmol) and *i*-Pr_2NEt (27.7 g, 0.214 mol, 3.0 equiv) in CH_2Cl_2 (200 mL) at 0 ºC under argon. The resultant solution was then raised up 23 ºC and kept stirring for 30 min, showing the fully conversion of **1-23** on TLC. NMP (50 mL) was then added to the reaction mixture,

followed by the dropwise addition of 4-methoxybenzylamine (29.3 g, 0.214 mol, 3.0 equiv). The reaction mixture was then stirred at 23 ºC for 12 h, before quenched by 1M NaOH aqueous solution and extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with water and brine, dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in hexanes with 2% triethylamine) to afford amine **1-12** (11.6 g, 53.4 mmol, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.54 (dt, *J* = 16.7, 10.6 Hz, 1H), 5.99 (d, *J* = 11.1 Hz, 1H), 5.12 (d, *J* = 16.7 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 2H), 3.34 (s, 2H), 1.86 (s, 3H).



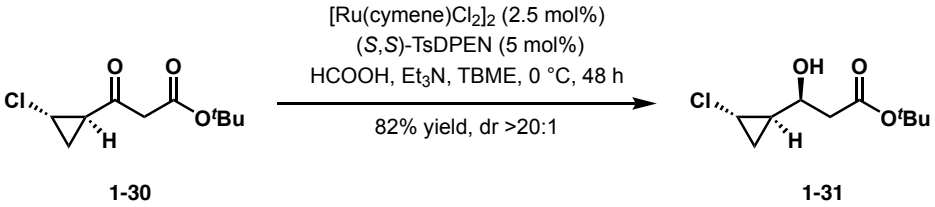
***tert*-Butyl (*R*)-3-((1*R*,2*S*)-2-chlorocyclopropyl)-3-hydroxypropanoate (1-29).** Diethylzinc (9.0 mL, 87.6 mmol, 2.0 equiv) was added dropwise to a stirring solution of **1-28** (7.55 g, 43.8 mmol) in CH_2Cl_2 (120 mL) at –78 °C and the reaction mixture was stirred for 10 min. Diiodochloromethane [1] (16.6 mL, 0.175 mol, 4.0 equiv) was added dropwise and resulting mixture was protected from light and stirred at –55 °C for 48 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and allowed to warm to 23 °C and stirred for an additional 1 h. The aqueous layer was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were sequentially washed with saturated Na_2SO_3 aqueous solution, water and brine, then dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (2% ethyl acetate in dichloromethane) to deliver product **1-29** (7.25 g, 32.8

mmol, 75% yield, dr 8:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.61 (ddt, *J*=8.5, 6.4, 3.7 Hz, 1H), 3.11 (d, *J*=3.9 Hz, 1H), 3.06 (ddd, *J*=6.8, 4.9, 3.2 Hz, 1H), 2.61 – 2.44 (m, 2H), 1.37 (s, 9H), 1.47 (s, 9H), 1.38 – 1.28 (m, 1H), 1.03 – 0.91 (m, 2H).



1-29 1-30

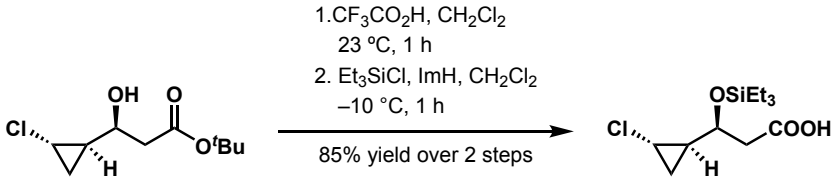
***tert*-Butyl 3-((1*R*,2*S*)-2-chlorocyclopropyl)-3-oxopropanoate (1-30).** Jones reagent (2.18 M, 20 mL, 43.2 mmol, 1.5 equiv) was added dropwise to a solution of alcohol **1-29** (6.35 g, 28.8 mmol) in acetone (72 mL). The mixture was stirred at 23 °C for 1 h. Methanol (40 mL) was added and stirring was continued for 30 min. After addition of water (40 mL), the mixture was extracted with diethyl ether (3×200 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, concentrated and residue was purified by column chromatography on silica gel (30% diethyl ether in pentanes) to deliver keto ester **1-30** (6.06 g, 27.7 mmol, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.51 (s, 2H), 3.31 (ddd, *J*=7.6, 4.9, 2.8 Hz, 1H), 2.42 (ddd, *J*=8.9, 5.9, 2.7 Hz, 1H), 1.66 (dt, *J*=7.4, 5.8 Hz, 1H), 1.48 (s, 9H), 1.45 – 1.38 (m, 1H).



1-30 1-31

***tert*-Butyl (*S*)-3-((1*R*,2*S*)-2-chlorocyclopropyl)-3-hydroxypropanoate (1-31).** Dichloro(*p*-cymene)ruthenium(II) dimer (0.424 g, 0.693 mmol) and Et_3N (0.20 mL, 1.38 mmol)

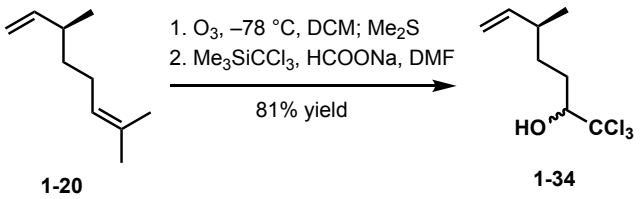
were added to a solution of (1*S*,2*S*)-(–)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (0.508 g, 1.38 mmol) in DMF (5.0 mL) at 23 °C. The mixture was stirred for 1 h. In parallel, a mixture of HCO_2H (10.5 mL, 0.277 mol) and Et_3N (15.3 mL, 0.110 mol) was prepared at 23 °C for 10 min. A solution of **1-30** (6.06 g, 27.7 mmol) in *tert*-butyl methyl ether (277 mL) was added to the formic acid-triethylamine mixture followed by the solution of the preformed catalyst. The mixture was stirred at 0 °C for 48 h. Water (100 mL) was added, layers separated, and the aqueous layer extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the alcohol **1-31** (5.02 g, 22.7 mmol, 82% yield, dr >20:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.74 (ddd, J = 9.2, 6.3, 3.2 Hz, 1H), 3.07 (s, 1H), 2.98 (dt, J = 7.2, 3.4 Hz, 1H), 2.57 (dd, J = 16.4, 3.1 Hz, 1H), 2.47 (dd, J = 16.4, 8.7 Hz, 1H), 1.31 (dtd, J = 9.6, 6.4, 3.2 Hz, 1H), 1.09 (q, J = 6.7 Hz, 1H), 0.99 (ddd, J = 9.8, 6.1, 3.9 Hz, 2H).



1-31 **1-33**

(*S*)-3-((1*R*,2*S*)-2-chlorocyclopropyl)-3-((triethylsilyl)oxy)propanoic acid (1-33). Ester **1-31** (5.02 g, 22.7 mmol) was stirred in a solution of trifluoroacetic acid and CH_2Cl_2 (1:1, v/v, 50 mL) at 0 °C. After 10 min, the reaction mixture was warmed to 23 °C and stirred for another hour. The mixture was concentrated, toluene was added (50 mL), and the solution was concentrated again. The dilution-concentration protocol was repeated twice. To the solution of resultant acid in CH_2Cl_2 (110 mL), imidazole (3.40 g, 50.0 mmol) and chlorotriethylsilane (7.6

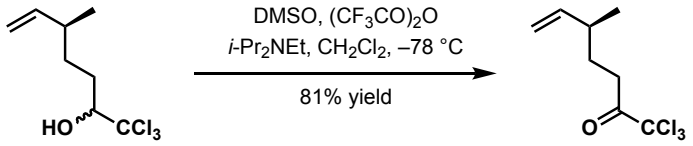
mL, 45.0 mmol) were successively added at –10 °C. After 1-hour stirring at this temperature, the reaction mixture was poured into acetate buffer (pH=4, 80 mL) and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (17% ethyl acetate in hexanes) to afford the acid **1-33** (5.38 g, 19.3 mmol, 85% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.99 (q, *J*=6.0 Hz, 1H), 2.91 (dt, *J*=7.3, 3.6 Hz, 1H), 2.74 – 2.51 (m, 2H), 1.50 – 1.39 (m, 1H), 1.06 – 0.86 (m, 9H), 0.68 – 0.55 (m, 6H).



(5*S*)-1,1,1-Trichloro-5-methylhept-6-en-2-ol (1-34). Ozone was bubbled through a solution of citronellene **1-20** (31.9 g, 0.231 mol) in CH_2Cl_2 (600 mL) at –78 °C. Once the reaction mixture turned to light purple, dimethylsulfide (40 mL, 0.542 mol) was added at –30 ºC and the mixture was stirred at 0 °C for overnight. The solvent was then removed via distillation, and the resultant crude mixture (~98.6 g) was directly used in the next step.

Sodium formate (1.57 g, 23.1 mmol) and Me_3SiCCl_3 (66.4 g, 0.347 mol) were added to the above crude mixture in dry DMF (400 mL) at 23 °C and the mixture was stirred for 1 h. A mixture of methanol and 1 M aqueous HCl (300 mL, 1:5, v/v) was added and the reaction mixture was stirred at 23 °C for 1 h. Water (200 mL) was added, the aqueous layer was separated and extracted with diethyl ether (3×500 mL). The combined organic phase was washed with brine and dried over Na_2SO_4, concentrated and the crude product was purified by

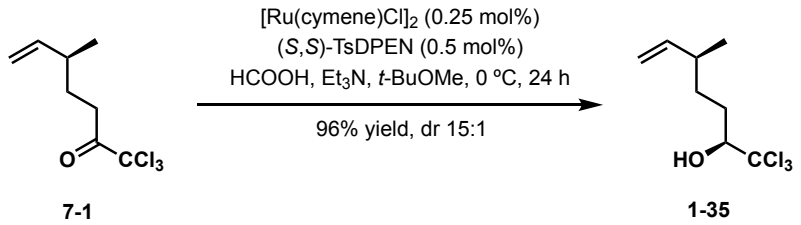
column chromatography on silica gel (10% diethyl ether in pentanes) to afford the alcohol **1-34** (43.3 g, 0.187 mol, 81% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.70 (dddd, J=17.4, 13.8, 10.3, 7.7 Hz, 1H), 5.08 – 4.89 (m, 2H), 4.06 – 3.94 (m, 1H), 2.64 (ddd, J=14.6, 5.7, 1.5 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.14 – 2.01 (m, 1H), 1.74 – 1.55 (m, 2H), 1.52 – 1.41 (m, 1H), 1.05 – 1.03 (m, 3H).



1-34 **7-1**

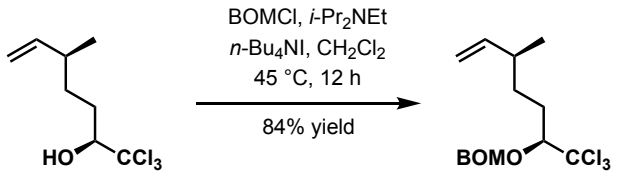
(*S*)-1,1,1-Trichloro-5-methylhept-6-en-2-one (7-1). Trifluoroacetic anhydride (53 mL, 0.373 mol) in CH_2Cl_2 (100 mL) was added to a solution of dimethyl sulfoxide (32 mL, 0.447 mol) in CH_2Cl_2 (300 mL) dropwise at –78 °C over 1.5 h. The mixture was stirred at –78 °C for 30 min. A solution of **1-34** (34.5 g, 0.149 mol) in CH_2Cl_2 (100 mL) was added dropwise over 1.5 h at –78 °C and stirred for an additional 10 min. The reaction mixture was warmed to 23 °C and stirred for another 2 h. The solution was cooled to 0 °C and *i*-Pr_2NEt (130 mL, 0.745 mol) was added dropwise. The mixture was warmed to 23 °C for overnight. The solution was diluted with diethyl ether (400 mL) and washed with 1 M HCl, and saturated aqueous $NaHCO_3$. The aqueous layers were extracted with diethyl ether (3×400 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under atmospheric conditions and purified by column chromatography on silica gel (10% diethyl ether in hexanes) to deliver trichloromethyl ketone **7-1** (27.7 g, 0.121 mol, 81% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 5.65 (ddd, J=17.2, 10.3, 7.9 Hz, 1H), 5.06 – 4.94 (m, 2H), 3.04 – 2.87 (m, 2H), 2.24 –

2.17 (m, 1H), 1.79 (dddd, J = 13.8, 8.6, 6.8, 5.3 Hz, 1H), 1.69 (dtd, J = 13.8, 8.6, 6.2 Hz, 1H), 1.06 (d, J=6.7 Hz, 3H).



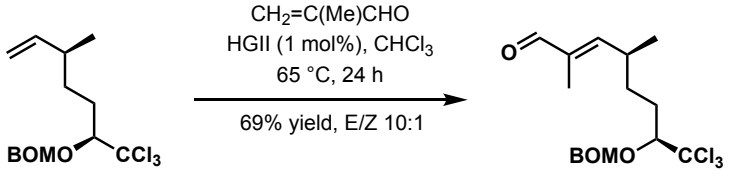
7-1 **1-35**

(2*S*,5*S*)-1,1,1-Trichloro-5-methylhept-6-en-2-ol (1-35). Dichloro(*p*-cymene)ruthenium(II) dimer (0.144 g, 0.235 mmol) and Et_3N (66 μL, 0.470 mmol) were added to a solution of (1*S*,2*S*)-(–)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (0.172 g, 0.470 mmol) in DMF (2.0 mL) at 23 °C and the mixture was stirred for 1 h. In parallel, formic acid (13.9 mL, 0.471 mol) and Et_3N (26.3 mL, 0.189 mol) were stirred at 23 °C for 10 min. A solution of substrate **7-1** (21.6 g, 94.2 mmol) in *tert*-butyl methyl ether (180 mL) was added to the formic acid-triethylamine mixture, followed by the solution of the catalyst. After stirring at 0 °C for 24 h, water (200 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the alcohol **1-35** (20.9 g, 90.4 mmol, 96% yield, dr 15:1). $[\alpha]_D^{25}$ –23.4 (c 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 5.71 (ddd, *J* = 17.5, 10.3, 7.6 Hz, 1H), 5.05 – 4.86 (m, 2H), 3.99 (dd, *J* = 9.7, 1.9 Hz, 1H), 2.68 (s, 1H), 2.19 (p, *J* = 7.0 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.68 (dddd, *J* = 13.0, 10.9, 6.1, 4.8 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.44 (dddd, *J* = 13.0, 10.5, 7.6, 5.6 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H).



1-35 7-2

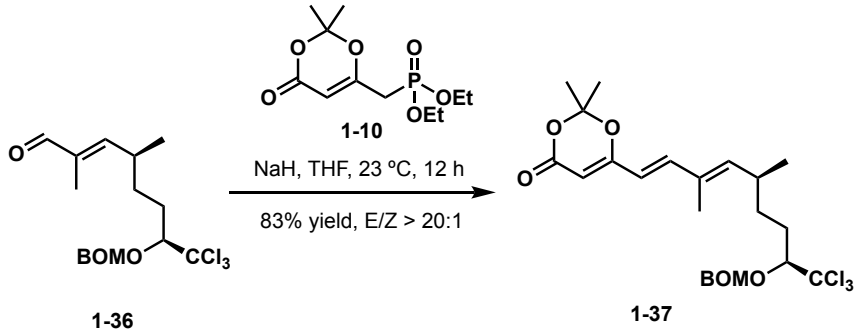
(((((2*S*,5*S*)-1,1,1-Trichloro-5-methylhept-6-en-2-yl)oxy)methoxy)methyl)benzene (7-2). Diisopropylethylamine (90 mL, 0.518 mol) was added to a solution of **1-35** (20.0 g, 86.4 mmol), benzyloxymethyl chloride (48 mL, 0.385 mol), and tetrabutylammonium iodide (3.20 g, 8.64 mmol) in CH_2Cl_2 (170 mL) at 0 °C and the mixture was stirred for 15 min. The solution was then heated at 45 °C for 12 h. The crude mixture was cooled to 23 °C, water (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (3% ethyl acetate in hexanes) to afford **7-2** (25.5 g, 72.6 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.27 (m, 5H), 5.66 (ddd, J = 17.5, 10.3, 7.6 Hz, 1H), 5.11 (d, J = 7.2 Hz, 1H), 5.02 (d, J = 7.3 Hz, 1H), 5.00 – 4.90 (m, 2H), 4.82 (d, J = 11.8 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 3.99 (dd, J = 8.5, 2.3 Hz, 1H), 2.21 – 2.06 (m, 1H), 1.83 – 1.61 (m, 2H), 1.46 (dddd, J = 13.2, 11.4, 7.4, 5.2 Hz, 1H), 0.99 (d, J = 6.7 Hz, 3H).



7-2 1-36

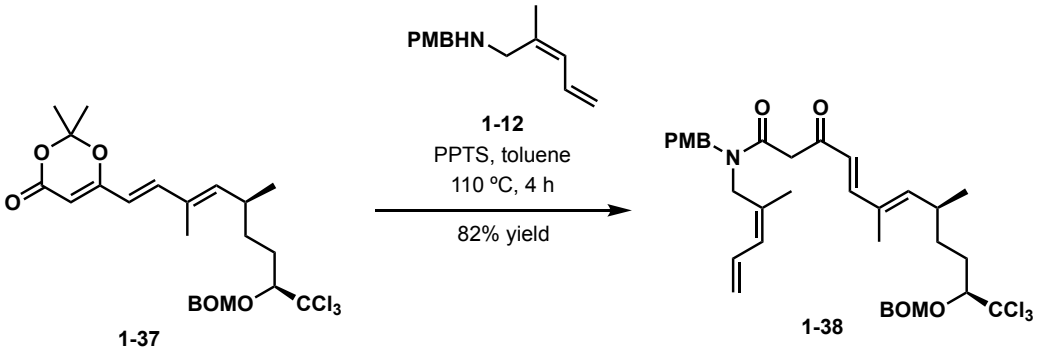
(4*S*,7*S*,*E*)-7-((Benzyloxy)methoxy)-8,8,8-trichloro-2,4-dimethyloct-2-enal (1-36). Hoveyda- Grubbs II catalyst (1,3-bis-(2,4,6,-trimethylphenyl)-2-

imidazolidinylidene)dichloro(*o*- isopropoxyphenylmethylene)ruthenium (336 mg, 0.537 mmol) was added to a degassed solution of **7-2** (18.9 g, 53.7 mmol) and metacrolein (44 mL, 0.537 mol) in CH_2Cl_2 (190 mL). The solution was heated at 65 °C for 24 h. The crude mixture was concentrated and immediately purified by column chromatography on silica gel (7% ethyl acetate in hexanes) to afford aldehyde **1-36** (14.6 g, 37.1 mmol, 69% yield, *E*:*Z* 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.34 (s, 1H), 7.39 – 7.27 (m, 5H), 6.16 (dq, *J* = 9.9, 1.4 Hz, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 7.3 Hz, 1H), 4.82 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 3.97 (dd, *J* = 8.5, 2.4 Hz, 1H), 2.75 – 2.62 (m, 1H), 2.07 – 1.99 (m, 1H), 1.85 – 1.76 (m, 2H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.58 – 1.47 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H).



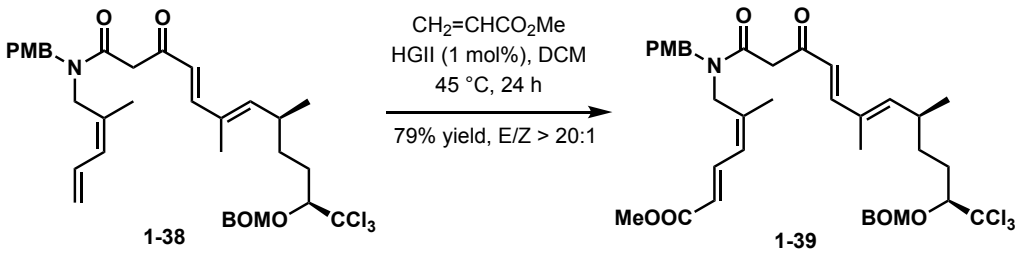
6-((1*E*,3*E*,5*S*,8*S*)-8-((Benzyloxy)methoxy)-9,9,9-trichloro-3,5-dimethylnona-1,3-dien-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one (1-37). A solution of diethyl ((2,2-dimethyl-4-oxo-4*H*-1,3- dioxin-6-yl)methyl)phosphonate **1-10** (13.0 g, 46.6 mmol) in THF (50 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 1.86 g, 46.6 mmol) in THF (200 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to 23 °C and stirred for an additional 1 h. This mixture was added via cannula into a solution of aldehyde **1-36** (12.2 g, 31.0 mmol) in THF (200 mL) at –78 °C over 30 min. This solution was stirred at –78 °C for 1 h and then warmed to 23 °C and stirred for an additional 12 h. Brine (300 mL) was

added, layers separated, and the aqueous layer was extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (17% ethyl acetate in hexanes) to afford dioxinone **1-37** (13.3g, 25.7 mmol, 83% yield) as the only isomer. $[\alpha]_D^{24}$ – 40.6 (c 0.93, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.28 (m, 5H), 6.92 (d, *J* = 15.6 Hz, 1H), 5.88 (d, *J* = 15.6 Hz, 1H), 5.59 (d, *J* = 9.7 Hz, 1H), 5.32 (s, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 5.02 (d, *J* = 7.3 Hz, 1H), 4.81 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 3.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 2.56 (dt, *J* = 15.0, 6.8 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.94 – 1.63 (m, 2H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.73 (d, *J* = 4.4 Hz, 6H), 1.46 (tdd, *J* = 11.9, 8.1, 5.5 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 3H).



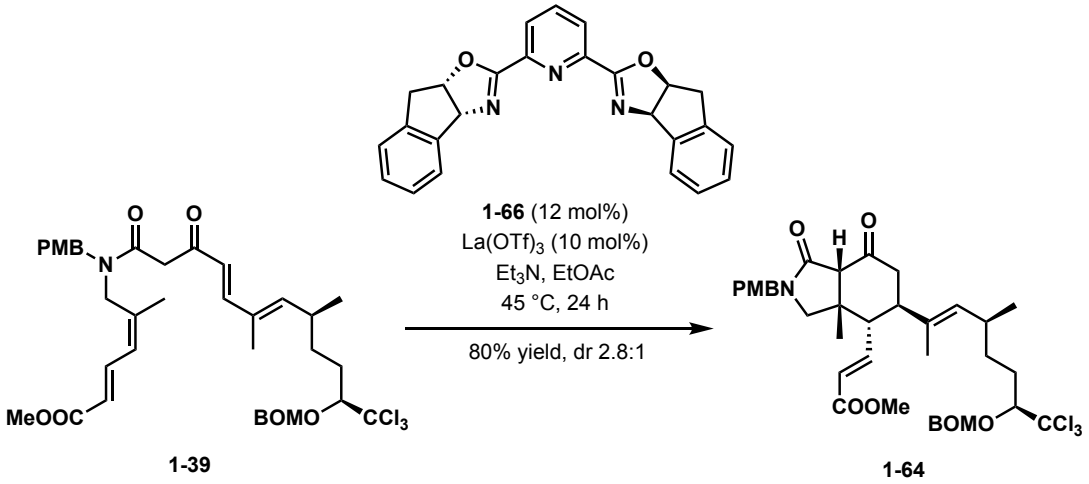
(4*E*,6*E*,8*S*,11*S*)-11-((Benzyloxy)methoxy)-12,12,12-trichloro-*N*-(4-methoxybenzyl)-6,8-dimethyl-*N*-((*Z*)-2-methylpenta-2,4-dien-1-yl)-3-oxododeca-4,6-dienamide (1-38). Pyridinium *p*-toluenesulfonate (0.251 g, 1.00 mmol) was added to a stirring solution of amine **1-12** (2.36 g, 10.0 mmol) and dioxinone **1-37** (5.17 g, 10.0 mmol) in toluene (200 mL) in a sealed flask and heated at 110 °C for 4 h. The crude mixture was allowed to cool to room temperature and concentrated. The residue was purified by column chromatography on silica gel (14% ethyl acetate in hexanes) to afford the amide **1-38** (5.58 g, 8.24 mmol, 82% yield),

which exists as a mixture of rotamers and tautomers as observed by NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.28 (m, 5H), 7.19 (d, J = 7.9 Hz, 1H), 7.15 – 7.01 (m, 2H), 6.87 (dd, J = 14.2, 8.5 Hz, 2H), 6.52 – 6.10 (m, 1H), 6.07 (d, J = 15.9 Hz, 1H), 5.88 – 5.47 (m, 2H), 5.10 (dd, J = 7.3, 3.6 Hz, 1H), 5.01 (dd, J = 7.0, 3.8 Hz, 1H), 4.81 (dd, J = 11.7, 3.1 Hz, 1H), 4.65 – 4.60 (m, 1H), 4.37 – 4.15 (m, 2H), 3.97 (d, J = 7.6 Hz, 3H), 3.89 – 3.75 (m, 3H), 2.62 – 2.46 (m, 1H), 2.11 – 1.98 (m, 1H), 1.82 – 1.70 (m, 6H), 1.50 – 1.37 (m, 1H), 1.00 – 0.93 (m, 3H).



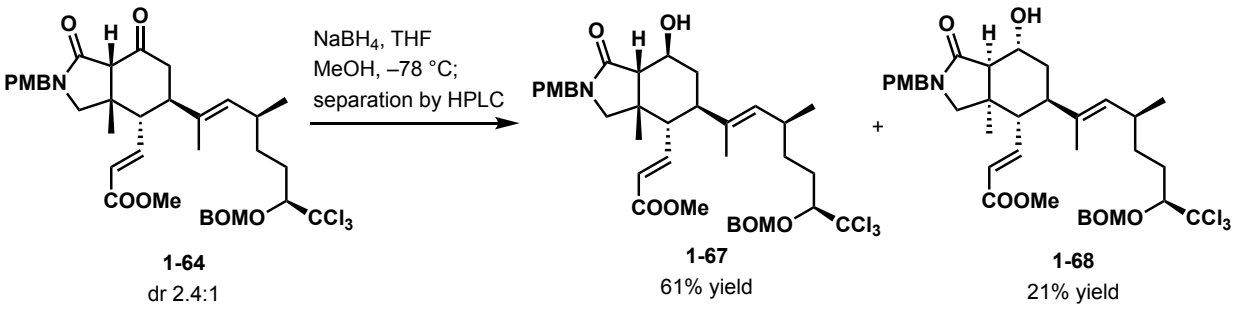
Methyl (2*E*,4*Z*)-6-((4*E*,6*E*,8*S*,11*S*)-11-((benzyloxy)methoxy)-12,12,12-trichloro-*N*-(4-methoxybenzyl)-6,8-dimethyl-3-oxododeca-4,6-dienamido)-5-methylhexa-2,4-dienoate (1-39). Hoveyda Grubbs II catalyst (93.9 mg, 0.150 mmol) was added to a stirring degassed solution of methyl acrylate (1.8 mL, 20 mmol) and substrate **1-38** (3.39 g, 5.01 mmol) in CH_2Cl_2 (150 mL). The resulting solution was heated at 45 °C for 24 h. The crude mixture was cooled to room temperature and immediately concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the amide **1-39** as a mixture of rotamers and tautomers (2.91 g, 3.96 mmol, 79% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.28 (m, 5H), 7.21 – 7.14 (m, 1H), 7.13 – 7.05 (m, 2H), 6.92 – 6.82 (m, 2H), 6.21 – 6.14 (m, 1H), 5.83 (dt, *J* = 29.8, 15.1 Hz, 2H), 5.53 (d, *J* = 9.7 Hz, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 5.01 (d, *J* = 7.2 Hz, 1H), 4.81 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.32 (d, *J* = 16.4 Hz, 2H), 4.08 – 4.03 (m, 1H), 3.97 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.84 – 3.77

(m, 3H), 3.76 – 3.67 (m, 3H), 2.61 – 2.46 (m, 1H), 2.09 – 1.98 (m, 1H), 1.88 – 1.79 (m, 3H), 1.80 – 1.68 (m, 6H), 1.44 (dq, *J* = 18.9, 11.9, 8.9 Hz, 1H), 1.01 – 0.92 (m, 31H).



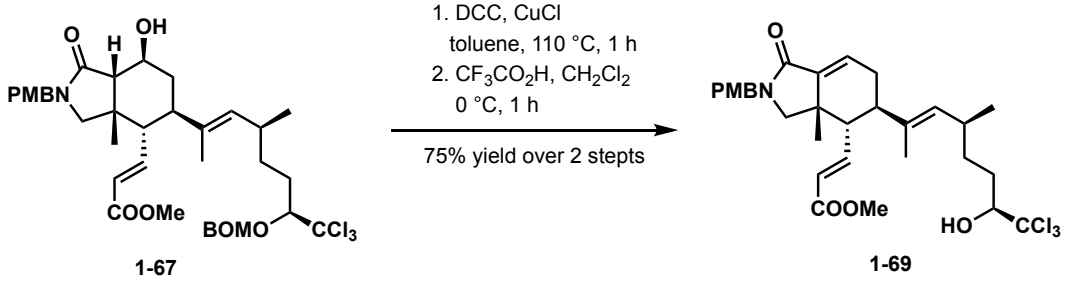
Methyl (*E*)-3-((3a*S*,4*S*,5*R*,7a*S*)-5-((4*S*,7*S*,*E*)-7-((benzyloxy)methoxy)-8,8,8-trichloro-4-methyloct-2-en-2-yl)-2-(4-methoxybenzyl)-3a-methyl-1,7-dioxooctahydro-1*H*-isoindol-4-yl)acrylate (1-64). Lanthanum(III) triflate (17.5 mg, 30 μmol) was added to a solution of ligand **1-66** (14.2 mg, 36 μmol) in ethyl acetate (2 mL). After stirring at 23 °C for 1 h, the catalyst was added to **1-39** (0.220 g, 0.299 mmol) in ethyl acetate (13 mL). The resulting solution was heated at 45 ºC for 24 h. The reaction mixture was cooled, concentrated, and the residue was purified by chromatography on silica gel (70% ethyl acetate in hexanes) to afford product **1-64** (0.176 g, 0.240 mmol, 80% yield, dr 2.8:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.23 (m, 5H), 7.16 (dd, *J* = 8.7, 2.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.41 – 6.31 (m, 1H), 5.80 (dd, *J* = 15.5, 1.8 Hz, 1H), 5.08 (d, *J* = 7.2 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 4.86 (dd, *J* = 9.6, 1.4 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 4.35 (d, *J* = 14.6 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.34 – 3.24 (m, 1H), 3.00 – 2.91 (m, 1H), 2.67 – 2.60 (m, 0H), 2.52 – 2.31 (m, 4H), 2.30 – 2.17 (m, 1H),

2.02 – 1.88 (m, 1H), 1.77 – 1.52 (m, 3H), 1.49 – 1.40 (m, 3H), 1.34 – 1.22 (m, 1H), 1.16 (s, 3H), 0.75 (d, J = 6.7 Hz, 3H).



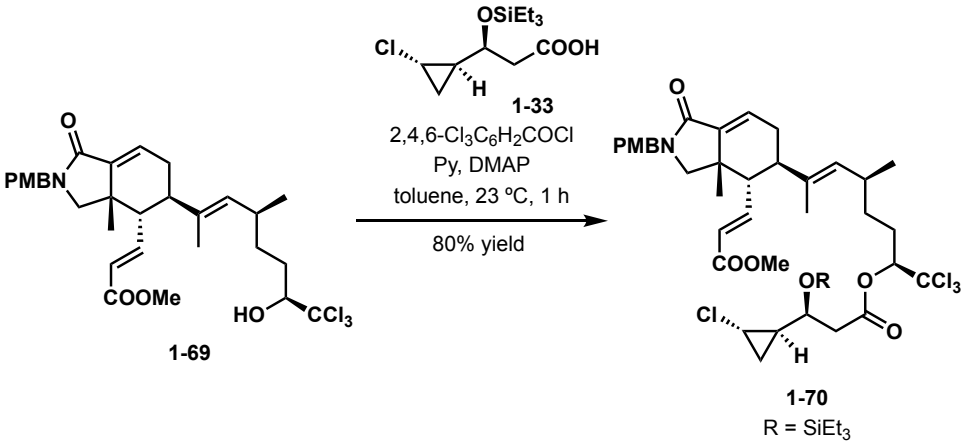
Methyl (*E*)-3-((3a*S*,4*S*,5*R*,7*S*,7a*S*)-5-((4*S*,7*S*,*E*)-7-((benzyloxy)methoxy)-8,8,8-trichloro-4-methyloct-2-en-2-yl)-7-hydroxy-2-(4-methoxybenzyl)-3a-methyl-1-oxooctahydro-1*H*-isoindol-4-yl)acrylate (1-67). Sodium borohydride (30.4 mg, 0.804 mmol) was added to a solution of **1-64** (0.394 g, 0.536 mmol) in MeOH and THF (1:1, 27 mL) at –78 °C. After stirring at –78 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and warmed to 23 °C, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (70% ethyl acetate in hexanes) to deliver products **1-67** and **1-68** as a mixture (0.375 g, 0.509 mmol, 95% yield). The mixture was separated by preparative HPLC (YMC Pak-Sil; 2% *i*-PrOH in toluene; flow rate = 50.0 mL/min; detection at 290 nm; t_1=27.8 min (**1-67**); t_2= 37.0 min (**1-68**)) to provide **1-67** as a white crystalline solid (0.240 g, 0.326 mmol, 61% yield). $[\alpha]_D^{21}$ –7.9 (c 0.73, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.31 (m, 4H), 7.29 – 7.23 (m, 1H), 7.15 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.34 (dd, J = 15.5, 10.5 Hz, 1H), 5.73 (d, J = 15.4 Hz, 1H), 5.07 (d, J = 7.2 Hz, 1H), 4.99 (d, J = 7.1 Hz, 1H), 4.85 (dd, J = 9.5, 1.5 Hz, 1H), 4.78 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 14.5 Hz, 1H), 4.32 (d, J = 14.4 Hz, 1H), 3.93 (dd, J = 8.5, 2.3 Hz, 1H),

3.80 (s, 3H), 3.67 (s, 3H), 3.57 (ddd, J = 11.5, 9.5, 4.2 Hz, 1H), 3.24 (d, J = 9.8 Hz, 1H), 2.59 (d, J = 9.8 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.10 (t, J = 11.0 Hz, 1H), 2.04 – 1.93 (m, 3H), 1.81 (ddd, J = 12.4, 4.2, 2.5 Hz, 1H), 1.73 – 1.57 (m, 2H), 1.48 – 1.36 (m, 4H), 1.27 (dddd, J = 18.0, 9.7, 6.4, 4.7 Hz, 1H), 1.05 (s, 3H), 0.74 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 175.4, 166.0, 159.2, 146.95, 137.30, 133.8, 133.7, 129.5, 128.4, 128.0, 127.8, 127.6, 123.8, 114.2, 102.6, 97.0, 89.7, 70.5, 70.0, 58.0, 55.2, 52.3, 51.4, 49.3, 46.3, 45.9, 39.7, 36.0, 33.6, 32.1, 30.2, 28.2, 20.7, 12.4.



Methyl (*E*)-3-((3a*S*,4*S*,5*R*)-2-(4-methoxybenzyl)-3a-methyl-1-oxo-5-((4*S*,7*S*,*E*)-8,8,8-trichloro-7-hydroxy-4-methyloct-2-en-2-yl)-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-4-yl)acrylate (1-69). *N,N'*-Dicyclohexylcarbodiimide (0.260 g, 1.26 mmol) and CuCl (0.250 g, 2.53 mmol) were sequentially added to a stirring solution of substrate **1-67** (0.186 g, 0.253 mmol) in dry toluene (13 mL). The reaction mixture was stirred at 110 °C for 1 h. The resulting mixture was cooled and quenched with saturated aqueous NH_4Cl. The mixture was stirred at 23 °C for 2 h. The aqueous layer was extracted with ethyl acetate (3×15 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (50% ethyl acetate in hexanes) to deliver the product which was submitted to the next step directly.

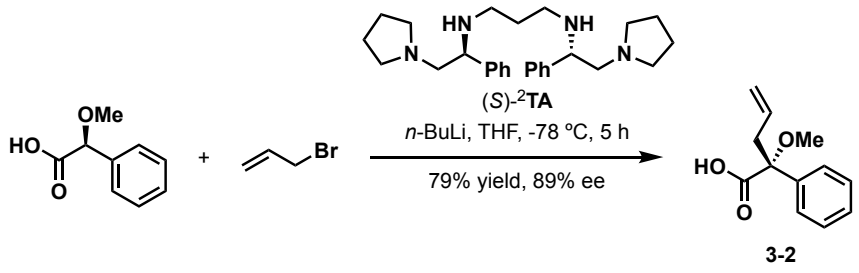
The crude product from the previous step was stirred in a solution of trifluoroacetic acid and CH_2Cl_2 (1:1, v/v, 15 mL) at 0 °C for 1 h. The crude mixture was then concentrated. The dilution-concentration using toluene was repeated three times. The residue was purified by column chromatography (50% ethyl acetate in hexanes) to deliver alcohol **1-69** (0.114 g, 0.190 mmol, 75% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.13 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.74 (dd, *J* = 7.3, 3.2 Hz, 1H), 6.56 (dd, *J* = 15.5, 10.3 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 4.98 (dd, *J* = 9.4, 1.5 Hz, 1H), 4.60 (d, *J* = 14.6 Hz, 1H), 4.18 (d, *J* = 14.6 Hz, 1H), 3.94 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.09 (d, *J* = 9.2 Hz, 1H), 2.55 (d, *J* = 9.2 Hz, 1H), 2.40 (t, *J* = 10.6 Hz, 1H), 2.37 – 2.28 (m, 1H), 2.22 – 2.08 (m, 2H), 2.05 – 1.93 (m, 2H), 1.73 – 1.51 (m, 3H), 1.49 (d, *J* = 1.3 Hz, 3H), 1.40 – 1.28 (m, 1H), 1.14 (s, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).



Methyl (*E*)-3-((3a*S*,4*S*,5*R*)-2-(4-methoxybenzyl)-3a-methyl-1-oxo-5-((4*S*,7*S*,*E*)-8,8,8-trichloro-7-(((*S*)-3-((1*R*,2*S*)-2-chlorocyclopropyl)-3-((triethylsilyl)oxy)propanoyl)oxy)-4-methyloct-2-en-2-yl)-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-4-yl)acrylate (1-70). 2,4,6-Trichlorobenzoyl chloride (36 μL, 0.229 mmol) was added to a solution of acid **1-33** (30.7 mg, 0.110 mmol) and pyridine (44 μL, 0.550 mmol) in toluene (4.0 mL) at 0 °C. After 45 min, a

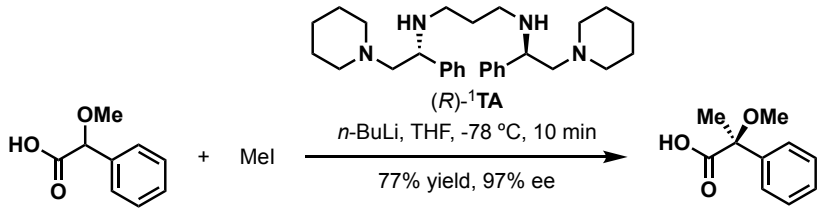
solution of alcohol **1-69** (54.9 mg, 91.7 μmol) and 4-(dimethylamino)pyridine (28.0 mg, 0.229 mmol) in toluene (2.0 mL) was added at 0 °C. After 10 min, the reaction mixture was warmed to 23 °C and stirred for an additional 1 h. Brine was added, and the aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (50% ethyl acetate in hexanes) to deliver **1-70** (63.1 g, 73.4 μmol, 80% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.14 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.74 (dd, *J* = 7.5, 2.9 Hz, 1H), 6.56 (dd, *J* = 15.5, 10.3 Hz, 1H), 5.78 (d, *J* = 15.5 Hz, 1H), 5.45 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.96 (d, *J* = 9.4 Hz, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.04 (q, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.09 (d, *J* = 9.2 Hz, 1H), 2.93 (dt, *J* = 7.3, 3.5 Hz, 1H), 2.74 – 2.60 (m, 2H), 2.55 (d, *J* = 9.2 Hz, 1H), 2.40 (t, *J* = 10.7 Hz, 1H), 2.29 (tt, *J* = 8.5, 5.9 Hz, 1H), 2.23 – 1.98 (m, 4H), 1.71 (dddd, *J* = 22.9, 13.1, 9.3, 4.4 Hz, 2H), 1.49 (s, 3H), 1.48 – 1.40 (m, 1H), 1.39 – 1.29 (m, 2H), 1.20 (ddd, *J* = 13.7, 11.0, 5.3 Hz, 1H), 1.15 (s, 3H), 1.03 (q, *J* = 6.7 Hz, 1H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 167.1, 166.2, 159.1, 147.9, 140.3, 134.3, 133.6, 129.5, 129.2, 128.4, 122.6, 114.1, 99.8, 81.3, 67.4, 55.2, 53.8, 51.5, 49.9, 49.4, 46.1, 41.6, 41.1, 33.9, 32.8, 31.9, 30.0, 29.4, 28.45, 28.37, 27.4, 25.6, 24.9, 20.6, 13.2, 13.0.

7.3 Enantioselective Construction of Tetrasubstituted Carbon Centers



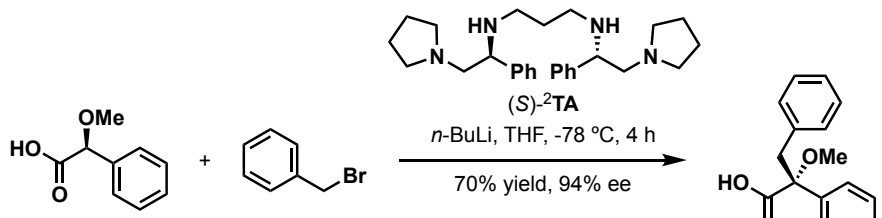
"General Procedure I"

(*R*)-2-Methoxy-2-phenylpent-4-enoic acid (3-2). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol) and (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 ºC and the resulting mixture was stirred at this temperature for 15 min. The reaction mixture was then cooled to –78 ºC and stirred for an additional 5 min. Allyl bromide (0.17 mL, 0.238 g, 1.96 mmol, 3.9 equiv) was added to the above reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 5 h before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 ºC. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **3-2** (81.9 mg, 0.397 mmol, 79% yield). Ee 89% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=30.1 min (major); t_2=38.1 min). $[\alpha]_D^{27}$ –10.8 (c 1.67, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.50–7.45 (m, 2H), 7.40-7.35 (m, 2H), 7.34–7.30 (m, 1H), 7.18 (brs, 1H), 5.77-5.67 (m, 1H), 5.23–5.12 (m, 2H), 3.25 (s, 3H), 3.18 (ddt, J = 14.9, 7.3, 1.3 Hz, 1H), 2.96 (ddt, J = 14.9, 6.6, 1.4 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 175.1, 137.8, 131.2, 128.5, 128.4, 126.4, 119.3, 83.7, 51.4, 37.3. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.0841; found, 229.0831.



3-3

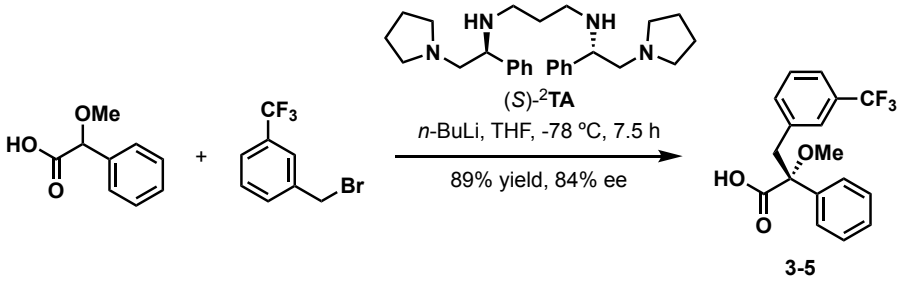
(*S*)-2-Methoxy-2-phenylpropanoic acid (3-3). The title compound was prepared according to **general procedure I** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of iodomethane (0.12 mL, 0.274 g, 1.93 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched immediately, and product **3-3** (69.2 mg, 0.384 mmol, 77% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 97% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_2=47.0 min (major); t_1=40.7 min). $[\alpha]_D^{25}$ +32.1 (c 2.61, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.50–7.46 (m, 2H), 7.40–7.36 (m, 2H), 7.35–7.31 (m, 1H), 3.27 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 175.8, 138.9, 128.6, 128.4, 126.2, 81.3, 51.7, 20.7. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{10}H_{12}O_3Na$, 203.0684; found, 203.0664.



3-4

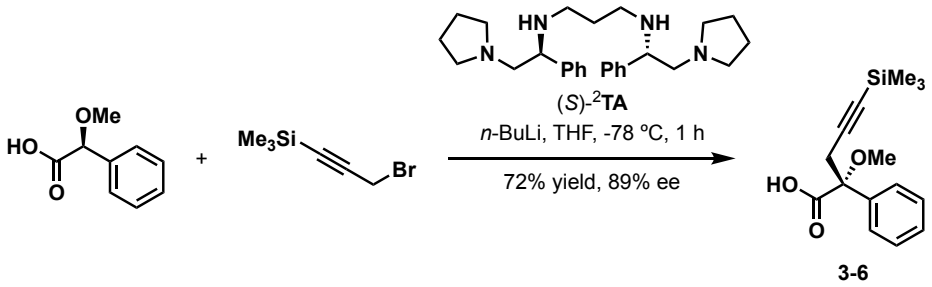
(*R*)-2-Methoxy-2,3-diphenylpropanoic acid (3-4). The title compound was prepared according to **general procedure I** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500

mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of benzyl bromide (0.23 mL, 0.331 g, 1.93 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched after 4 h, and product **3-4** (89.2 mg, 0.348 mmol, 70% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=43.9 min (major); t_2=53.0 min). $[\alpha]_D^{22}$ –12.7 (c 1.75, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.10 (brs, 1H), 7.52–7.47 (m, 2H), 7.43–7.34 (m, 3H), 7.27–7.23 (m, 3H), 7.22-7.17 (m, 2H), 3.71 (d, J = 14.4 Hz, 1H), 3.50 (d, J = 14.4 Hz, 1H), 3.32 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 175.0, 137.8, 135.0, 130.1, 128.6, 128.5, 128.1, 126.8, 126.7, 84.9, 52.0, 38.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{16}O_3Na$, 279.0997; found, 279.0984.



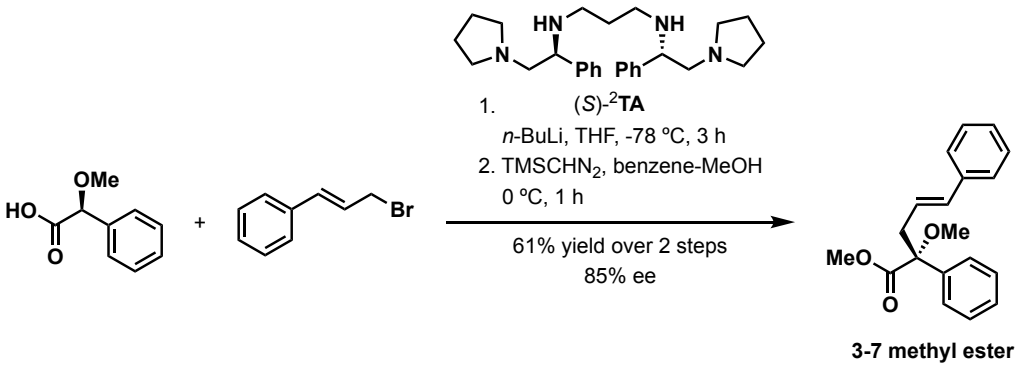
(*R*)-2-Methoxy-2-phenyl-3-(3'-(trifluoromethyl)phenyl)propanoic acid (3-5). The title compound was prepared according to **general procedure I** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of 3-(trifluoromethyl)benzyl bromide (0.30 mL, 0.470 g, 1.96 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched after 7.5 h, and product **3-5** (0.145 g, 0.447 mmol, 89% yield) was obtained after purification by column chromatography on silica gel (2% methanol

in dichloromethane). Ee 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=30.3 min (major); t_2=40.6 min). $[\alpha]_D^{22}$ +6.53 (c 1.99, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.43 (brs, 1 H), 7.51-7.46 (m, 1H), 7.45–7.42 (m, 2H), 7.42–7.34 (m, 4H), 7.34–7.31 (m, 2H), 3.70 (d, J = 14.4 Hz, 1H), 3.52 (d, J = 14.4 Hz, 1H), 3.34 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 175.3, 137.3, 136.1, 133.6 (q, J = 1.4 Hz), 130.3 (q, J = 32.1 Hz), 128.69, 128.65, 128.5, 126.98 (q, J = 3.9 Hz), 126.5, 124.1 (q, J = 272 Hz), 123.7 (q, J = 3.9 Hz), 84.9, 52.4, 39.4. ^{19}F NMR (376 MHz, CDCl3) δ (ppm) –62.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{15}O_3F_3Na$, 347.0871; found, 347.0854.



(*R*)-2-Methoxy-2-phenyl-5-(trimethylsilyl)pent-4-ynoic acid (3-6). The title compound was prepared according to **general procedure I** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of 3-bromo-1-(trimethylsilyl)-1-propyne (0.191 g, 1.00 mmol, 2.0 equiv) at –78 °C over 10 min. The reaction was quenched after 50 min, and product **3-6** (99.5 mg, 0.360 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 89% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 0.5 mL/min; detection at 215 nm; t_1=23.2 min (major); t_2=26.8 min). $[\alpha]_D^{24}$ +5.6 (c 0.77, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.53 (brs, 1H), 7.47–7.43 (m, 2H), 7.39–7.31 (m, 3H), 3.37 (s,3H),

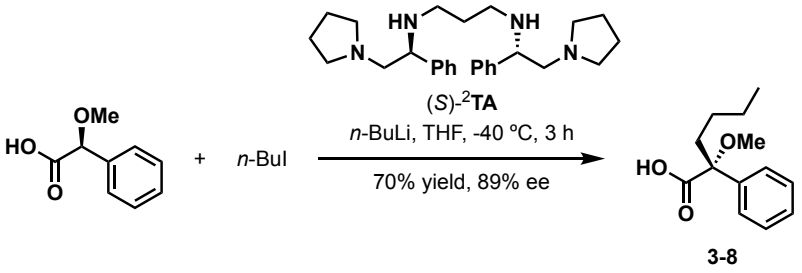
3.33 (d, J = 17.2 Hz, 1H), 3.07 (d, J = 17.2 Hz, 1H), 0.10 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 174.6, 137.1, 128.6, 128.5, 126.2, 100.0, 88.9, 83.1, 52.2, 26.2, -0.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{20}O_3NaSi$, 299.1079; found, 299.1090.



(2*R*,4*E*)-2-Methoxy-2,5-diphenylpent-4-enoic acid (3-7). The alkylation product was prepared according to **general procedure I** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of 3-bromo-1-phenyl-1-propene (0.191 g, 1.00 mmol, 2.0 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 3 h, and product **3-7** (0.117 g) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane) contaminated with inseparable mixture.

(2*S*,4*E*)-Methyl 2-methoxy-2,5-diphenylpent-4-enoate (3-7 methyl ester). A solution of $TMSCHN_2$ in hexanes (1.2 mL, 0.65 M, 0.780 mmol) was added dropwise to a solution of above product **3-7** (0.117 g) in a mixture of benzene-MeOH (4:1, 5.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (9% ethyl

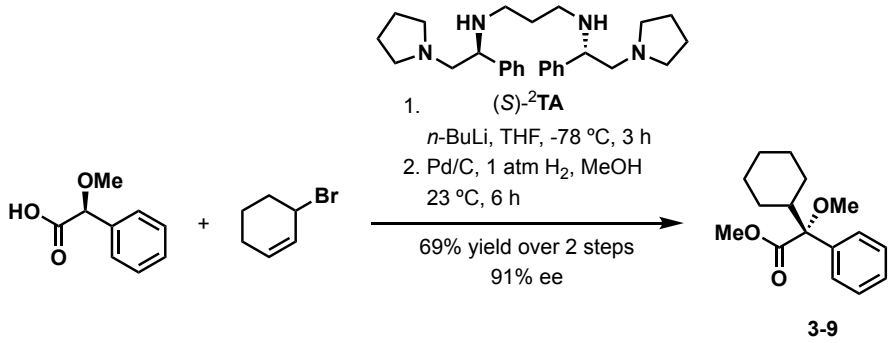
acetate in hexanes) to afford the product **3-7 methyl ester** (90.9 mg, 0.307 mmol, 61% yield over 2 steps). Ee 85% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=12.6 min (major); t_2=14.2 min). $[\alpha]_D^{19}$ +37.1 (c 2.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.52–7.48 (m, 2H), 7.40–7.36 (m, 2H), 7.34–7.24 (m, 5H), 7.21–7.17 (m, 1H), 6.45 (virt. dt, J = 15.9, 1.4 Hz, 1H), 6.06 (ddd, J = 15.9, 7.8, 6.3 Hz, 1H), 3.73 (s, 3H), 3.31 (s, 3H), 3.24 (ddd, J = 15.1, 7.9, 1.3 Hz, 1H), 3.11 (ddd, J = 15.1, 6.3, 1.7 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 172.7, 139.0, 137.3, 133.5, 128.4, 128.0, 127.2, 126.24, 126.15, 123.6, 84.4, 52.4, 52.0, 38.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{20}O_3Na$, 319.1310; found, 319.1309.



3-8

(*R*)-2-Methoxy-2-phenylhexanoic acid (3-8). The title compound was prepared according to **general procedure I** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.79 mL, 2.52 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of iodobutane (0.23 mL, 0.317 g, 2.00 mmol, 4.0 equiv) at –78 °C. The reaction was quenched after stirring at –40 °C for 3 h, and product **3-8** (77.6 mg, 0.349 mmol, 70% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 89% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=22.1 min (major); t_2=29.9 min). $[\alpha]_D^{20}$ –42.3 (c 1.89, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.22 (brs, 1H),

7.50–7.46 (m, 2H), 7.40–7.35 (m, 2H), 7.34–7.29 (m, 1H), 3.20 (s, 3H), 2.41 (ddd, J = 14.1, 11.4, 4.6 Hz, 1H), 2.13 (ddd, J = 14.1, 11.9, 4.2 Hz, 1H), 1.44–1.18 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 175.7, 138.2, 128.5, 128.3, 126.4, 83.9, 51.1, 32.1, 25.1, 22.7, 13.9. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{13}H_{17}O_3$, 221.1178; found, 221.1181.

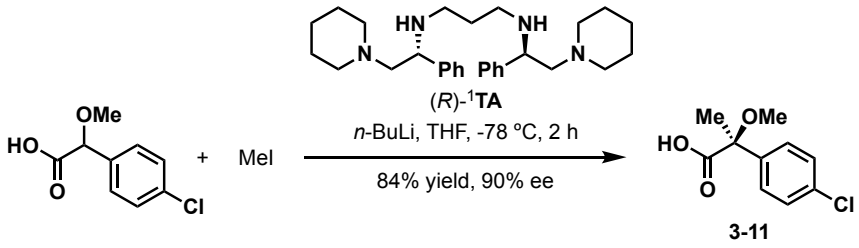


3-9

(*R*)-2-Cyclohexyl-2-methoxy-2-phenylacetic acid (3-9). A solution of n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*S*)-2-methoxy-2- phenylacetic acid (83.1 mg, 0.500 mmol) and (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. 3-bromocyclohexene (0.17 mL, 0.238 g, 1.48 mmol, 3.0 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 3 h before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford the diastereomeric product (0.106 g, 0.430 mmol,

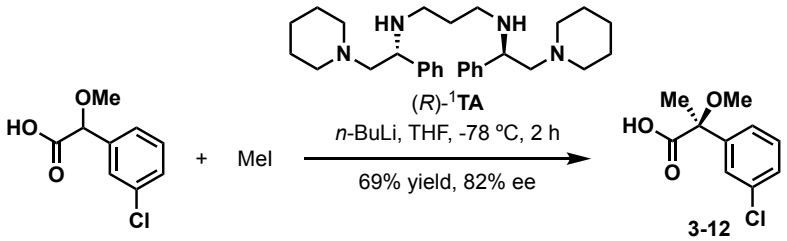
86% yield). The product was directly submitted to the next step without further characterization.

A solution of above compound (0.106 g, 0.430 mmol) and 10% Pd/C (27.2 mg, 25,7 μmol) in methanol (5 mL) was stirred at 23 °C under 1 atm of hydrogen atmosphere for 6 h. The mixture was then filtered through a pad of celite and rinsed with ethyl acetate. The combined filtrate was concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford the product **3-9** (85.7 mg, 0.345 mmol, 69% yield over two steps). Ee: 91% (Chiralcel® OD-H; 1% i-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=16.5 min (major); t_2=20.2 min). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 7.47 (d, J = 7.1 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 3.17 (s, 3H), 2.09 (virt. tt, J = 12.0, 2.9 Hz, 1H), 1.93 (d, J = 12.5 Hz, 1H), 1.73 (d, J = 13.2 Hz, 1H), 1.70–1.57 (m, 2H), 1.54 (d, J = 12.9 Hz, 1H), 1.30–1.14 (m, 2H), 1.07–0.88 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ (ppm) 174.8, 138.5, 129.3, 128.6, 128.6, 89.6, 53.9, 48.3, 29.3, 28.7, 27.73, 27.70, 27.6. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{15}H_{19}O_3$, 247.1334; found, 247.1328.



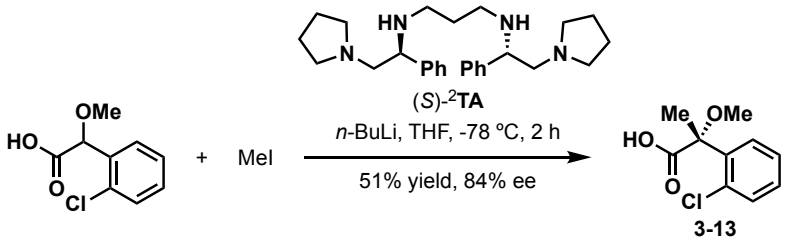
(*S*)-2-(4-Chlorophenyl)-2-methoxypropanoic acid (3-11). The title compound was prepared according to **general procedure I** using (±)-2-(4-chloropheyl)-2-methoxyacetic acid (0.101 g, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of iodomethane (0.12 mL, 0.274

g, 1.93 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched after 2 h, and product **3-11** (90.1 mg, 0.419 mmol, 84% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_2=34.6 min (major); t_1=30.1 min). $[\alpha]_D^{23}$ +39.9 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.50 (brs, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.28 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 176.1, 137.7, 134.5, 128.7, 127.6, 80.9, 51.8, 20.9. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{10}H_{10}ClO_3$, 213.0318; found, 213.0314.

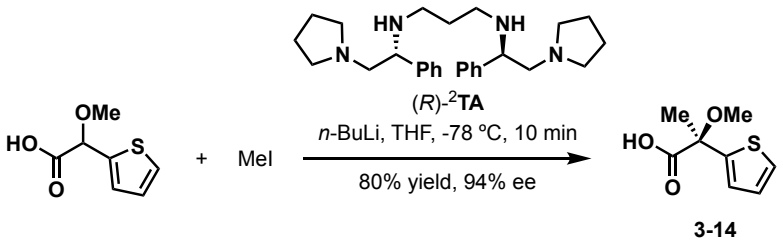


(*S*)-2-(3-Chlorophenyl)-2-methoxypropanoic acid (3-12). The title compound was prepared according to **general procedure I** using (±)-2-(3-chloropheyl)-2-methoxyacetic acid (0.101 g, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of iodomethane (0.12 mL, 0.274 g, 1.93 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched after 2 h, and product **3-12** (74.1mg, 0.344 mmol, 69% yield) was obtained after purification by column chromatography on silica gel (40% diethyl ether in hexanes with 0.5% acetic acid). Ee 82% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_2=34.8 min (major); t_1=29.1 min). $[\alpha]_D^{23}$ +38.5 (c 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.48 (s, 1H), 7.38-7.34 (m, 1H), 7.33-7.29 (m, 2 H), 3.30 (s, 3H), 1.83 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ (ppm) 175.5, 141.3, 134.7, 129.6, 128.6, 126.5, 124.4, 80.9, 51.9, 20.9. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{10}H_{10}ClO_3$, 213.0318; found, 213.0320.

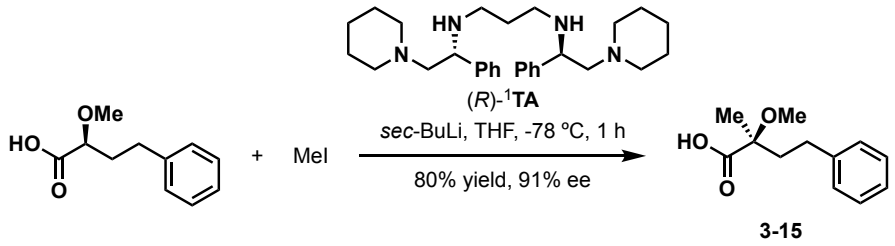


(*R*)-2-(2-Chlorophenyl)-2-methoxypropanoic acid (3-13). The title compound was prepared according to **general procedure I** using (±)-2-(2-chloropheyl)-2-methoxyacetic acid (0.101 g, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of iodomethane (0.12 mL, 0.274 g, 1.93 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched after 2 h, and product **3-13** (55.1 mg, 0.256 mmol, 51% yield) was obtained after purification by column chromatography on silica gel (40% diethyl ether in hexanes with 0.5% acetic acid). Ee 84% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_2=60.7 min (major); t_1=49.1 min). $[\alpha]_D^{25}$ –22.3 (c 0.33, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.84 (brs, 1 H), 7.57 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.33-7.27 (m, 2H), 3.19 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 174.8, 136.0, 133.3, 130.9, 129.9, 128.9, 126.7, 80.6, 51.3, 20.9. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{10}H_{10}ClO_3$, 213.0318; found, 213.0318.



3-14

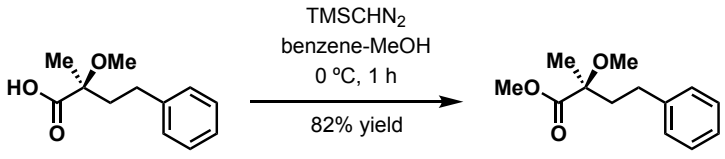
(*R*)-2-Methoxy-2-(thiophen-2-yl)propanoic acid (3-14). The title compound was prepared according to **general procedure I** using (±)-2-methoxy-2-(thiophen-2-yl)acetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of iodomethane (0.12 mL, 0.274 g, 1.93 mmol, 3.9 equiv) at –78 °C over 10 min. The reaction was quenched immediately, and product **3-14** (89.2 mg, 0.348 mmol, 80% yield) was obtained after purification by column chromatography on silica gel (3% methanol in dichloromethane). Ee 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_2=53.9 min (major); t_1=50.4 min). $[\alpha]_D^{24}$ –15.1 (c 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.33 (d, J = 5.1 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 7.00 (t, J = 4.3 Hz, 1H), 3.33 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 174.5, 142.7, 126.9, 126.43, 126.37, 79.6, 52.0, 22.2. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_8H_9O_3S$, 185.0272; found, 185.0271.



3-15

(*S*)-2-Methoxy-2-methyl-4-phenylbutanoic acid (3-15). A solution of *sec*-BuLi (1.38 mL, 1.45 M in cyclohexane, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*S*)-2-

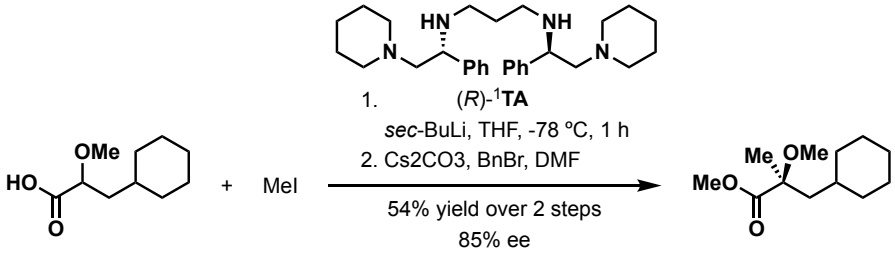
methoxy-4-phenylbutyric acid (97.1 mg, 0.500 mmol) and (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (4 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. The reaction mixture was then cooled to −78 °C and stirred for an additional 5 min. Iodomethane (0.12 mL, 0.274 g, 1.93 mmol, 3.9 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 50 min before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at −78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with a mixture of 1 M aqueous solution of HCl and drops of saturated aqueous solution of sodium sulfite, brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford the pure product **3-15** (83.1 mg, 0.400 mmol, 80% yield). $[\alpha]_D^{23}$ – 2.0 (c 1.47, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.08 (brs, 1H), 7.31– 7.25 (m, 2H), 7.21–7.16 (m, 3H), 3.39 (s, 3H), 2.71 (ddd, J = 13.8, 12.2, 5.1 Hz, 1H), 2.60 (ddd, J = 13.8, 12.2, 5.0 Hz, 1H), 2.15 (ddd, J = 14.2, 12.2, 5.0 Hz, 1H), 2.05 (ddd, J = 14.2, 12.2, 5.1 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 178.1, 141.2, 128.4, 128.3, 126.0, 79.9, 51.3, 38.6, 29.8, 20.9. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{12}H_{15}O_3$, 207.1021; found, 207.1019.



3-15 **3-15 methyl ester**

(*S*)-Methyl 2-methoxy-2-methyl-4-phenylbutanoate (3-15 methyl ester). A solution of $TMSCHN_2$ (0.16 mL, 1.1 M in hexanes, 0.176 mmol) was added dropwise to a solution of

carboxylic acid **3-15** (18.7 mg, 89.9 μmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the product **3-15 methyl ester** (16.4 mg, 73.9 μmol, 82% yield). Ee 91% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=7.8 min (major); t_2=10.5 min). $[\alpha]_D^{24}$ –13.3 (c 0.49, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.29–7.25 (m, 2H), 7.20–7.15 (m, 3H), 3.74 (s, 3H), 3.33 (s, 3H), 2.70 (ddd, J = 13.7, 11.8, 5.5 Hz, 1H), 2.57 (ddd, J = 13.7, 11.8, 5.3 Hz, 1H), 2.12–1.99 (m, 2H), 1.47 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 174.5, 141.6, 128.4, 128.3, 125.9, 80.0, 52.1, 51.9, 39.8, 29.8, 20.9. LRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{13}H_{19}O_3$, 223; found, 223.



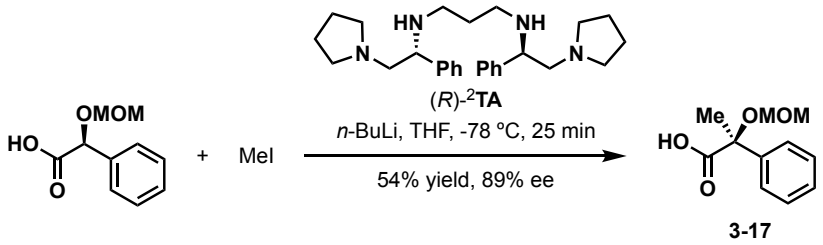
3-16 benzyl ester

(*S*)-3-Cyclohexyl-2-methoxy-2-methylpropanoic acid (3-16). A solution of *sec*-BuLi (1.4 mL, 1.43 M in cyclohexane, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of 3-cyclohexyl-2-methoxypropionic acid (93.2 mg, 0.500 mmol) and (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (4 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Iodomethane (0.16 mL, 0.365 g, 2.57 mmol, 5.1 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 50 min

before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with a mixture of 1 M aqueous solution of HCl and drops of saturated aqueous solution of sodium sulfite, brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford the product **3-16** (65.9 mg, 0.329 mmol, 66% yield) together with inseparable starting material 3-cyclohexyl-2-methoxypropionic acid (8.2 mg, 43.9 μmol, 9% yield).

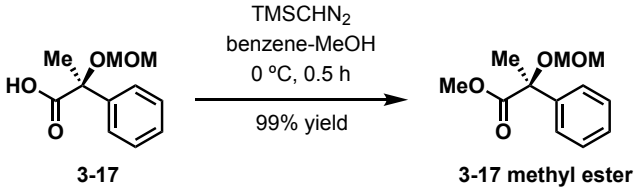
(*S*)-Benzyl 3-cyclohexyl-2-methoxy-2-methylpropanoate (3-16 benzyl ester). Cesium carbonate (0.240 g, 0.737 mmol) and benzyl bromide (90 μL, 0.129 g, 0.757 mmol) were added sequentially to a solution of the above mixture (74.1 mg) in DMF (4 mL). The resultant mixture was stirred at 23 °C for 16 h before a quench with water. Then the reaction mixture was extracted with 10% ethyl acetate in hexanes. The combined organic phase was sequentially washed with water (three times), brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford the product **3-16 benzyl ester** (78.0 mg, 0.269 mmol, 82% yield) together with benzyl 3-cyclohexyl-2-methoxypropionate (10.3 mg, 37.3 μmol, 85% yield). The analytically pure product **3-16 benzyl ester** was obtained using preparative HPLC (YMC-Pack- SIL 250x30 mm; 10% MTBE in hexanes; flow rate = 20 mL/min; detection at 215 nm, t = 15 min). Ee: 85% (Chiralcel® AD-H; 1% i-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=6.1 min (major); t_1=5.7 min). $[\alpha]_D^{23}$ –35.3 (c 1.12, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.40–7.29 (m, 5H), 5.17 (s, 2H), 3.25 (s, 3H), 1.70–1.53 (m, 7H), 1.41 (s, 3H), 1.43-1.34 (m, 1 H), 1.21–1.02 (m, 3H), 0.94–0.80 (m, 2H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm)

174.4, 135.8, 128.5, 128.4, 128.2, 80.2, 66.6, 51.7, 45.8, 34.6, 34.2, 33.2, 26.30, 26.27, 26.2, 21.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{26}O_3Na$, 313.1780; found, 313.1771.

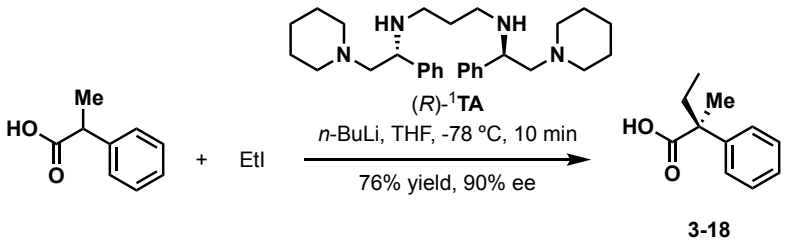


(*S*)-2-(Methoxymethoxy)-2-phenylpropanoic acid (3-17). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*S*)-2-(methoxymethoxy)-2-phenylacetic acid (98.1 mg, 0.500 mmol) and (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv) in THF (4.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 hours. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Iodomethane (0.284 g, 2.00 mmol, 4.0 equiv) was then added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 15 min before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford the pure product **3-17** (56.5 mg, 0.269 mmol 54% yield). $[\alpha]_D^{26}$ +28.9 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.55–7.48 (m, 2H), 7.43–7.36 (m, 2 H), 7.35-7.29 (m, 1H), 4.76 (d, J = 7.2 Hz, 1H), 4.74 (d, J = 7.2 Hz, 1H), 3.42 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 176.1, 139.5, 128.6,

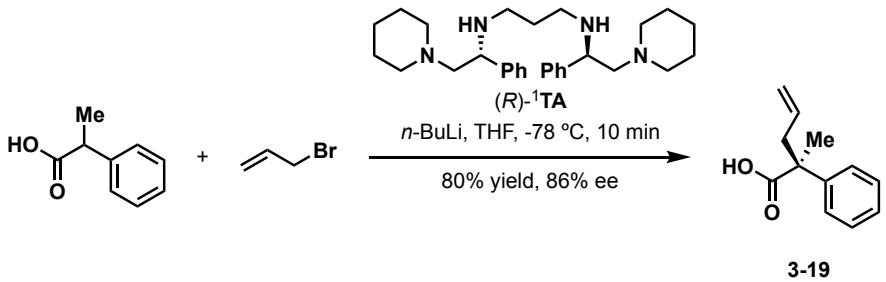
128.5, 126.0, 92.8, 81.6, 56.2, 23.1. HRMS-CI (m/z): $[M+H]^+$ calcd for $C_{11}H_{15}O_4$, 211.0970; found, 211.0979.



(*S*)-Methyl 2-(methoxymethoxy)-2-phenylpropanoate (3-17 methyl ester). A solution of $TMSCHN_2$ in hexanes (0.31 mL, 1.03 M, 0.308 mmol) was added dropwise to a solution of carboxylic acid **3-17** (32.4 mg, 0.154 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the product 3g methyl ester (34.3 mg, 0.153 mmol, 99% yield). Ee: 89% (Chiralcel® AD-H; 1% i-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=10.8 min (major); t_1=8.4 min). $[\alpha]_D^{25}$ +4.6 (c 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.51–7.45 (m, 2H), 7.38–7.33 (m, 2H), 7.32–7.27 (m, 1H), 4.81 (d, J = 7.3 Hz, 1H), 4.79 (d, J = 7.3 Hz, 1H), 3.72 (s, 3H), 3.42 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 173.6, 141.3, 128.3, 127.9, 125.5, 92.8, 81.2, 56.0, 52.5, 23.8. LRMS-FD (m/z): $[M]^+$ calcd for $C_{12}H_{16}O_4$, 224; found, 224.

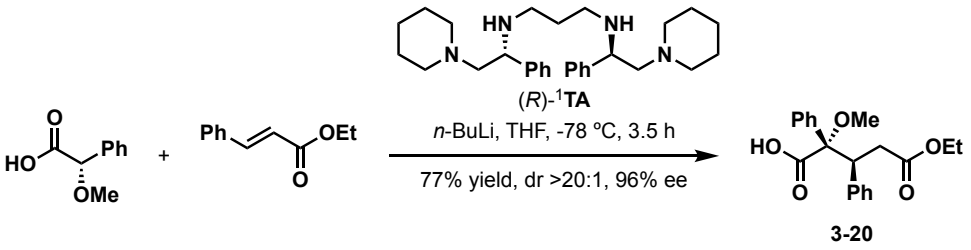


(*S*)-2-Methyl-2-phenyl-butanoic acid (3-18). A solution of *n*-BuLi (0.55 mL, 2.46 M in hexanes, 1.35 mmol, 4.0 equiv) was added dropwise to a solution of 2-phenylpropanoic acid (51.0 mg, 0.338 mmol) and (R)-1TA (0.155 g, 0.346 mmol, 1.03 equiv) in THF (2.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then cooled to –78 °C and stirred for an additional 10 min. Iodoethane (0.11 mL, 1.35 mmol, 4.0 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was immediately quenched with a mixture of THF-MeOH (3:1, 1.0 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (40% diethyl ether in hexanes with 0.5% acetic acid) to afford the pure product as a white crystalline solid **3-18** (46.1 mg, 0.257 mmol, 76% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=22.6 min (major); t_1=19.9 min). $[\alpha]_D^{20}$ +24.2 (c 1.00, benzene). ^{1}H NMR (500 MHz, C_6D_6) δ (ppm) 7.23-7.20 (m, 2H), 7.05-7.01 (m, 2H), 6.98-6.94 (m, 1H), 2.00-1.92 (m, 1H), 1.83-1.75 (m, 1H), 1.36 (s, 3H), 0.64 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ (ppm) 183.4, 143.3, 128.7, 127.0, 126.6, 50.8, 32.0, 21.8, 9.2. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{11}H_{13}O_2$, 177.0916; found, 177.0911.



3-19

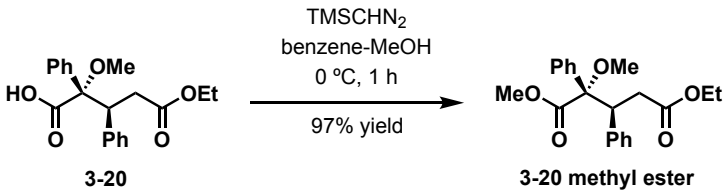
(*S*)-2-Methyl-2-phenyl-pent-4-enoic acid (3-19). A solution of *n*-BuLi (0.55 mL, 2.46 M in hexanes, 1.35 mmol, 4.0 equiv) was added dropwise to a solution of 2-phenylpropanoic acid (51 mg, 0.338 mmol) and (*R*)-**[1]TA** (0.155 g, 0.346 mmol, 1.03 equiv) in THF (2.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was then cooled to –78 °C and stirred for an additional 10 min. Allylbromide (0.12 ml, 1.35 mmol, 4.0 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was immediately quenched with a mixture of THF-MeOH (3:1, 1.0 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (40% diethyl ether in hexanes with 0.5% acetic acid) to afford the pure product and a colorless film (51 mg, 0.270 mmol, 80% yield). Ee: 86% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=34.1min (major); t_1=32.4 min). $[\alpha]_D^{20}$ +50.5 (c 1.00, EtOH). ^{1}H NMR (500 MHz, C_6D_6) δ (ppm) 7.23-7.18 (m, 2H), 7.05-7.00 (m, 2H), 6.98-6.93 (m, 1H), 5.52 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.09 (m, 2H), 2.73 (ddt, J = 13.8, 7.4, 1.2 Hz, 1H), 2.52 (ddt, J = 13.8, 17.1, 1.2, 1H), 1.40 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ (ppm) 182.8, 142.8, 134.1, 128.7, 127.2, 126.5, 118.6, 50.0, 43.8, 22.2. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{12}H_{13}O_2$, 189.0916; found, 189.0913.



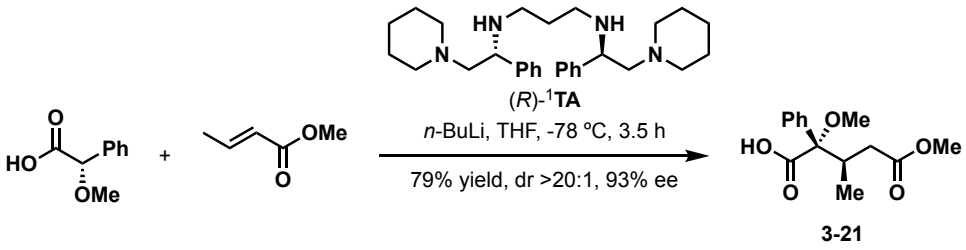
"General Procedure II"

(2*S*,3*S*)-5-Ethoxy-2-methoxy-5-oxo-2,3-diphenylpentanoic acid (3-20). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), and (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. A solution of ethyl cinnamate (85.0 μL, 88.9 mg, 0.505 mmol, 1.01 equiv) in THF (0.30 mL, plus 2 × 0.10 mL) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 3.5 h before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2-4% methanol in dichloromethane) to afford product **3-20** (0.132 g, 0.384 mmol, 77% yield). $[\alpha]_D^{25}$ –53.5 (c 0.57, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.97 (brs, 1H), 7.39– 7.30 (m, 5H), 7.23-7.17 (m, 3H), 7.16-7.11 (m, 2H), 4.11 (dd, J = 11.3, 3.7 Hz, 1H), 3.99–3.84 (m, 2H), 3.22 (s, 3H), 2.99 (dd, J = 16.3, 11.3 Hz, 1H), 2.80 (dd, J = 16.3, 3.7 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ (ppm) 175.2, 172.1, 137.6, 135.0, 129.8, 128.4, 128.2,

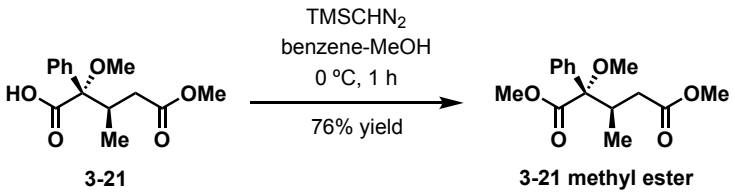
128.0, 127.7, 127.3, 87.9, 60.3, 53.9, 49.7, 36.1, 13.9. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{22}O_5Na$, 365.1365; found, 365.1352.



(2*S*,3*S*)-5-Ethyl 1-methyl-2-methoxy-2,3-diphenylpentanedioate (3-20 methyl ester). A solution of $TMSCHN_2$ (0.13 mL, 0.57 M in hexanes, 74.1 μmol) was added dropwise to a solution of carboxylic acid **3-20** (12.1 mg, 35.4 μmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the product **3-20 methyl ester** (12.2 mg, 34.2 μmol, 97% yield). Ee: 96% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=14.5 min; t_2=16.8 min). $[\alpha]_D^{26}$ –42.2 (c 0.60, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.28–7.24 (m, 3H), 7.23–7.19 (m, 2H), 7.17–7.14 (m, 3H), 7.00–6.96 (m, 2H), 4.02 (dd, J = 11.0, 4.3 Hz, 1H), 3.95–3.83 (m, 2H), 3.80 (s, 3H), 3.22 (s, 3H), 2.81 (dd, J = 16.0, 11.0 Hz, 1H), 2.73 (dd, J = 16.0, 4.3 Hz, 1H), 1.00 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.0, 171.7, 137.9, 135.7, 129.9, 128.3, 128.0, 127.6, 127.5, 127.1, 88.5, 60.2, 54.4, 51.9, 51.2, 35.7, 13.9. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{24}O_5Na$, 379; found, 379.



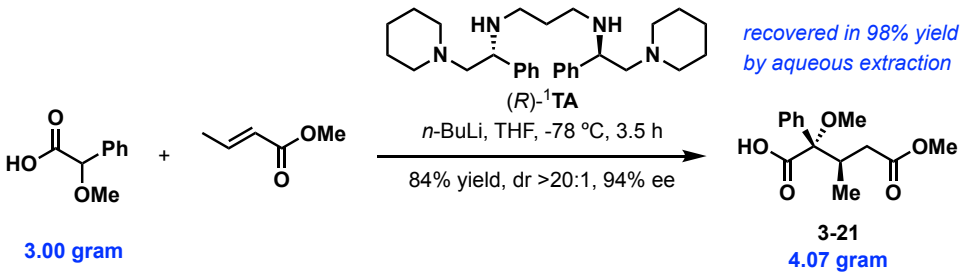
(2*S*,3*R*)-2,5-Dimethoxy-3-methyl-5-oxo-2-phenylpentanoic acid (3-21). The title compound was prepared according to **general procedure II** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of methyl crotonate (50.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at –78 °C. The reaction was quenched after 3.5 h, and product **3-21** (0.105 g, 0.394 mmol, 79% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{26}$ –42.4 (c 0.92, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.47–7.42 (m, 2H), 7.41–7.37 (m, 2H), 7.36–7.32 (m, 1H), 3.64 (s, 3H), 3.19 (s, 3H), 3.10–2.99 (m, 1H), 2.52 (dd, J = 16.4, 2.7 Hz, 1H), 2.16 (dd, J = 16.4, 10.7 Hz, 1H), 1.07 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ (ppm) 174.6, 173.5, 135.1, 128.6, 128.4, 128.1, 87.6, 53.0, 51.7, 37.1, 36.2, 15.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{18}O_5Na$, 289.1052; found, 289.1039.



(2*S*,3*R*)-Dimethyl 2-methoxy-3-methyl-2-phenylpentanedioate (3-21 methyl ester). The title compound was prepared using carboxylic acid **3-21** (22.3 mg, 83.7 μmol), $TMSCHN_2$

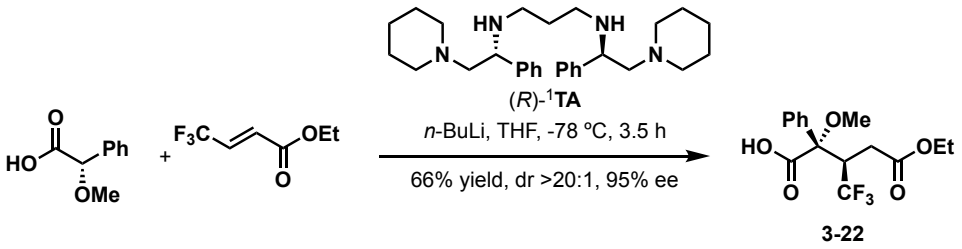
(0.30 mL, 0.57 M in hexanes, 0.171 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-21 methyl ester** (19.5 mg, 69.6 μmol, 83% yield). Ee: 93% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=9.9 min (major); t_2=11.8 min). $[\alpha]_D^{25}$ –28.9 (c 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41–7.28 (m, 5H), 3.84 (s, 3H), 3.62 (s, 3H), 3.20 (s, 3H), 2.92 (dqd, J = 10.7, 6.7, 3.0 Hz, 1H), 2.47 (dd, J = 15.8, 3.0 Hz, 1H), 1.91 (dd, J = 15.8, 10.7 Hz, 1H), 0.96 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.4, 171.8, 136.1, 128.0, 128.0, 127.9, 88.1, 53.8, 52.0, 51.5, 38.4, 36.8, 15.5. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{20}O_5Na$, 303; found, 303.

4-Gram Scale Procedure for Conjugate Addition with the Recovery of Chiral Tetraamine



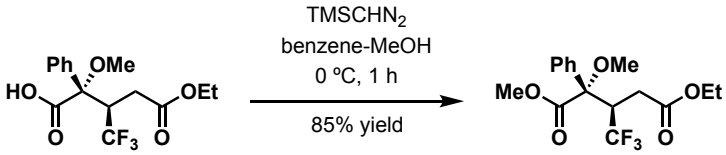
A three-neck round-bottom flask was equipped with a gas-inlet adapter, glass-stopper, and thermometer adapter fitted with a low-temperature thermometer. After flame drying under vacuum and back filling with argon, the flask was charged with (±)-2-methoxy-2- phenylacetic acid (3.00 g, 18.1 mmol), and (*R*)-**^{1}TA** (8.35 g, 18.6 mmol, 1.03 equiv) and THF (126 mL) under a positive pressure of argon gas. The reaction mixture was cooled in an ice-water bath to 0 °C, and a solution of *n*-BuLi (29.0 mL, 2.50 M in hexanes, 72.2 mmol, 4.0 equiv) over 30

min, keeping the internal reaction temperature below 15 °C. After stirring in an ice-water bath for 2 h, the reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. A solution of (*E*)-methyl crotonate (1.93 mL, 1.82 g, 18.2 mmol, 1.01 equiv) in THF (16 mL, plus 2 × 1 mL rinses) was added to the reaction mixture dropwise over 30 min. The resultant mixture was stirred for additional 3 h before a quench with a mixture of THF-MeOH (3:1, 23.4 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 6 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **3-21** (4.07 g, 15.3 mmol, 84% yield). Ee: 94% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=9.9 min (major); t_2=11.8 min).

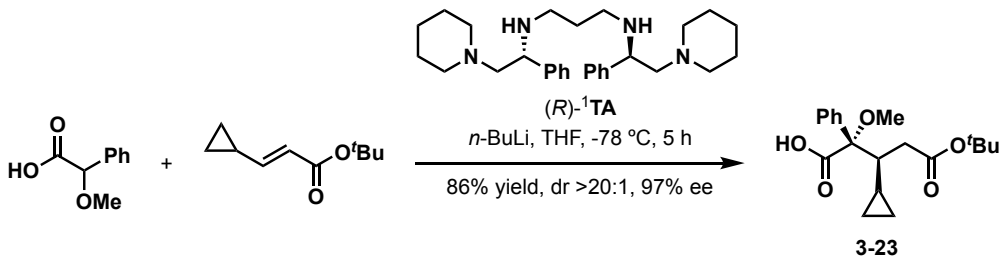


(2*S*,3*R*)-5-Ethoxy-2-methoxy-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoic acid (3-22). The title compound was prepared according to **general procedure II** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of ethyl (*E*)-4,4,4-trifluoro-2-butenoate (84.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at –78 °C. The reaction was quenched after 3.5 h, and product **3-22** (0.110 g, 0.330 mmol, 66% yield) was obtained after purification by column chromatography

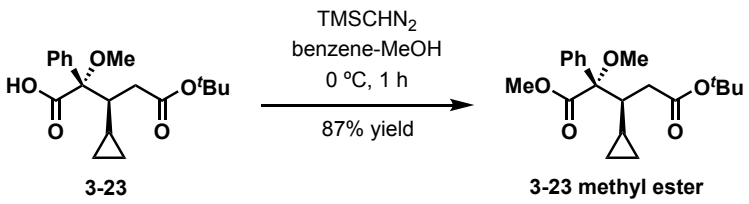
on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{21}$ –58.3 (c 0.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.78 (brs, 1H), 7.48–7.37 (m, 5H), 4.21–4.06 (m, 3H), 3.15 (s, 3H), 2.75–2.61 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.4, 171.4, 133.7, 129.0, 128.9, 127.9, 126.2 (q, J = 281 Hz), 83.8, 61.3, 53.0, 45.5, 31.7, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –65.5 (d, J = 8.6 Hz). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{17}O_5F_3Na$, 357.0926; found, 357.0915.



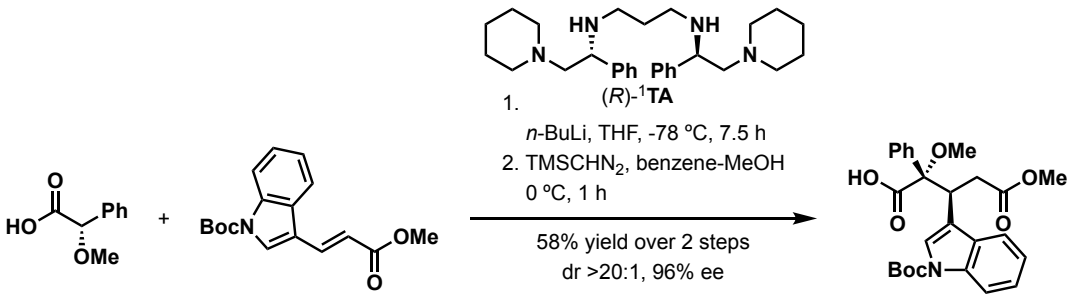
(2*S*,3*R*)-5-Ethyl 1-methyl 2-methoxy-2-phenyl-3-(trifluoromethyl)pentanedioate (3-22 methyl ester). The title compound was prepared using carboxylic acid **3-22** (27.1 mg, 81.1 μmol), $TMSCHN_2$ (0.29 mL, 0.57 M in hexanes, 0.165 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-22 methyl ester** (24.0 mg, 68.9 μmol, 85% yield). Ee: 95% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=6.7 min (major); t_2=7.6 min). $[\alpha]_D^{21}$ –39.0 (c 0.63, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.44–7.33 (m, 5H), 4.18–4.04 (m, 2H), 4.05–3.92 (m, 1H), 3.89 (s, 3H), 3.15 (s, 3H), 2.56 (dd, J = 17.3, 3.3 Hz, 1H), 2.48 (dd, J = 17.3, 7.8 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.1, 170.4, 134.2, 128.9, 128.4, 128.2, 126.1 (q, J = 282 Hz), 84.4 (q, J = 1.6 Hz), 61.0, 53.8, 52.5, 48.7 (q, J = 25.3 Hz), 31.2 (q, J = 2.5 Hz), 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –64.8 (d, J = 8.8 Hz). LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{19}O_5F_3Na$, 371; found, 371.



(2*S*,3*S*)-5-(*tert*-Butoxy)-3-cyclopropyl-2-methoxy-5-oxo-2-phenylpentanoic acid (3-23). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2- phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.47 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of tert-butyl (*E*)- 3-cyclopropylacrylate (88.2 mg, 0.525 mmol, 1.05 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 5 h, and product **3-23** (0.143 g, 0.427 mmol, 86% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{24}$ +3.2 (c 0.92, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.52–7.49 (m, 2H), 7.41–7.36 (m, 2H), 7.36–7.32 (m, 1H), 3.14 (s, 3H), 2.53–2.44 (m, 2H), 2.14–2.05 (m, 1H), 1.43 (s, 9H), 0.66–0.58 (m, 1H), 0.55–0.48 (m, 1H), 0.45–0.37 (m, 2H), 0.30–0.23 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 175.7, 172.7, 135.0, 128.6, 128.1, 127.8, 88.0, 80.3, 53.2, 46.3, 37.4, 28.0, 12.6, 4.4, 2.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{26}O_5Na$, 357.1678; found, 357.1683.



(2*S*,3*S*)-5-(*tert*-Butyl) 1-methyl 3-cyclopropyl-2-methoxy-2-phenylpentanedioate (3-23 methyl ester). The title compound was prepared using carboxylic acid **3-23** (40.1 mg, 0.120 mmol), $TMSCHN_2$ (0.42 mL, 0.57 M in hexanes, 0.239 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-23 methyl ester** (36.2 mg, 0.104 mol, 87% yield). Ee: 97% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; t_1=11.5 min (major); t_2=12.1 min). $[\alpha]_D^{24}$ +43.8 (c 1.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54–7.48 (m, 2H), 7.39–7.32 (m, 2H), 7.34–7.27 (m, 1H), 3.83 (s, 3H), 3.19 (s, 3H), 2.50 (dd, J = 15.1, 4.0 Hz, 1H), 2.31 (virt. td, J = 9.1, 3.9 Hz, 1H), 1.81 (dd, J = 15.1, 9.0 Hz, 1H), 1.42 (s, 9H), 0.47–0.29 (m, 3H), 0.26–0.15 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.6, 172.1, 135.5, 128.7, 127.7, 127.5, 88.0, 80.0, 53.5, 51.8, 47.8, 37.3, 28.0, 12.8, 4.3, 3.3. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{28}O_5Na$, 371; found, 371.

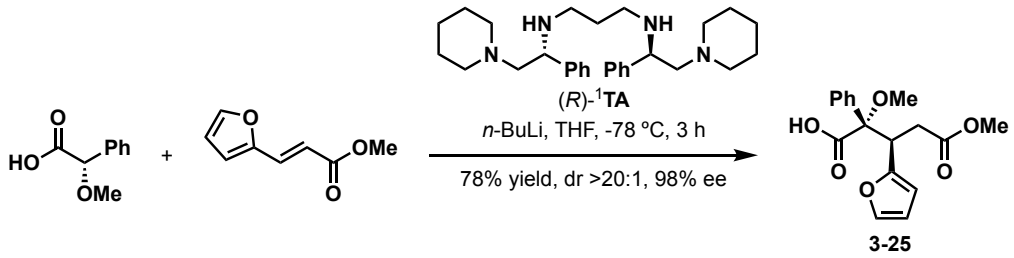


3-24 methyl ester

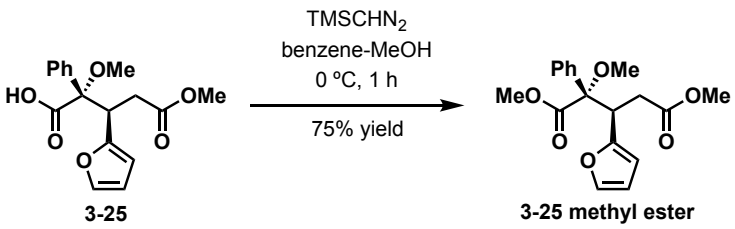
(2*S*,3*S*)-3-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-2,5-dimethoxy-5-oxo-2-phenylpentan-oic acid (3-24). The title compound was prepared according to **general procedure II** using (*S*)-2- methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv)

in THF (3.5 mL) followed by addition of a solution of *tert*-butyl (*E*)-3-(3-methoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate (0.151 g, 0.501 mmol, 1.0 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 7.5 h and the product **3-24** (0.160 g), contaminated with inseparable impurity, was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane).

(2*S*,3*S*)- Dimethyl 3-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-methoxy-2-phenyl pentane-dioate (4e methyl ester). The title compound was prepared using above crude acid **3-24** (0.160 g), $TMSCHN_2$ (1.3 mL, 0.57 M in hexanes, 0.741 mmol) in a mixture of benzene-MeOH (4:1, 5 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-24 methyl ester** (0.139 g, 0.288 mmol, 58% yield over 2 steps). Ee: 96% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=13.4 min (major); t_2=15.1 min). $[\alpha]_D^{23}$ –62.4 (c 0.72, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.14–7.97 (m, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.40–7.34 (m, 2H), 7.33–7.27 (m, 3H), 7.28–7.20 (m, 1H), 7.19–7.12 (m, 1H), 7.08 (s, 1H), 4.37 (dd, J = 10.9, 3.9 Hz, 1H), 3.77 (s, 3H), 3.43 (s, 3H), 3.23 (s, 3H), 2.84 (dd, J = 16.3, 3.9 Hz, 1H), 2.75 (dd, J = 16.3, 10.9 Hz, 1H), 1.64 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.3, 171.6, 149.6, 135.7, 134.8, 131.1, 128.3, 128.2, 127.7, 124.5, 124.0, 122.2, 120.0, 118.6, 114.7, 88.5, 83.4, 54.3, 51.9, 51.5, 42.2, 36.6, 28.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{31}NO_7Na$, 504.1998; found, 504.1975.

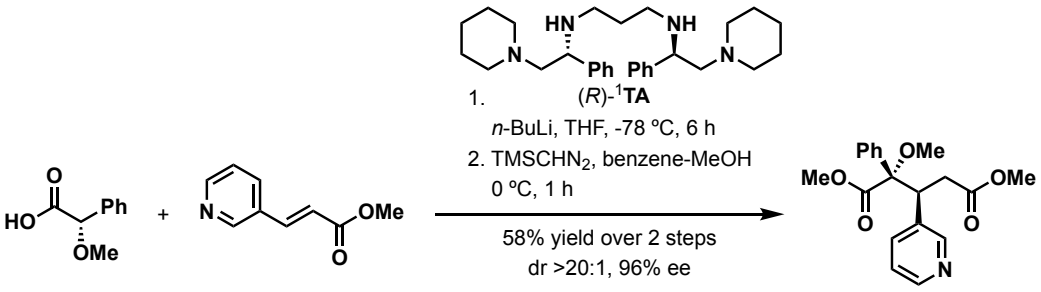


(2*S*,3*S*)-3-(Furan-2-yl)-2,5-dimethoxy-5-oxo-2-phenylpentanoic acid (3-25). The title compound was prepared according to **general procedure II** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.79 mL, 2.52 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of methyl (*E*)-3-(2-furyl)acrylate (78.3 mg, 0.515 mmol, 1.03 equiv) at –78 °C. The reaction was quenched after 3 h, and product **3-25** (0.125 g, 0.392 mmol, 78% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{23}$ –20.3 (c 2.13, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.91 (s, 1H), 7.39–7.31 (m, 3H), 7.33–7.26 (m, 3H), 6.28 (dd, J = 3.2, 1.9 Hz, 1H), 6.14 (d, J = 3.2 Hz, 1H), 4.38 (dd, J = 10.7, 3.7 Hz, 1H), 3.57 (s, 3H), 3.25 (s, 3H), 2.82 (dd, J = 16.7, 10.7 Hz, 1H), 2.75 (dd, J = 16.7, 3.7 Hz, 1H). ^{3}C NMR (126 MHz, $CDCl_3$) δ (ppm) 174.9, 172.4, 151.7, 141.8, 134.5, 128.6, 128.1, 127.8, 110.3, 108.6, 87.0, 53.6, 51.8, 42.8, 34.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{18}O_6Na$, 341.1001; found, 341.1001.



(2*S*,3*S*)-Dimethyl 3-(furan-2-yl)-2-methoxy-2-phenylpentanedioate (3-25 methyl ester). The title compound was prepared using carboxylic acid **3-25** (21.1 mg, 66.4 μmol), $TMSCHN_2$

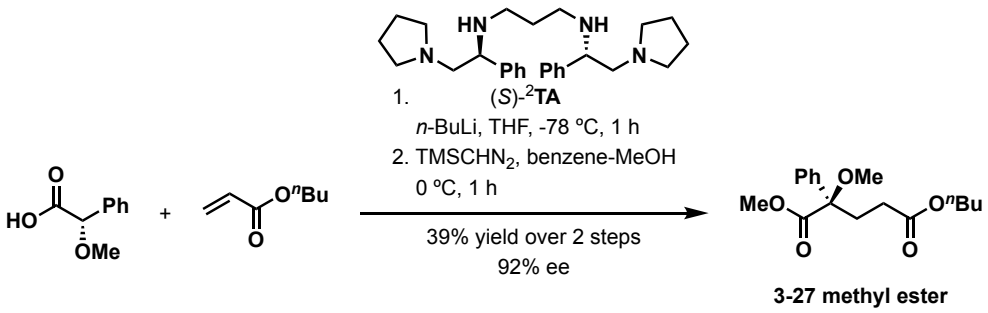
(0.12 mL, 1.1 M in hexanes, 0.132 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-25methyl ester** (16.6 mg, 50.0 μmol, 75% yield). Ee: 98% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=20.6 min (major); t_2=23.4 min). $[\alpha]_D^{23}$ +16.0 (c 0.56, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.25 (m, 3H), 7.26 (dd, J = 1.9, 0.8 Hz, 1H), 7.15–7.07 (m, 2H), 6.25 (dd, J = 3.2, 1.8 Hz, 1H), 5.99 (dt, J = 3.2, 0.8 Hz, 1H), 4.29 (dd, J = 11.2, 3.5 Hz, 1H), 3.87 (s, 3H), 3.55 (s, 3H), 3.24 (s, 3H), 2.73 (dd, J = 16.4, 3.5 Hz, 1H), 2.55 (dd, J = 16.4, 11.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.4, 171.2, 152.1, 141.5, 135.0, 128.1, 127.8, 127.7, 110.3, 108.6, 87.4, 54.2, 52.2, 51.7, 44.5, 33.2. LRMS-CI (m/z): $[M+C_2H_5]^+$ calcd for $C_{20}H_{25}O_6$, 361; found, 361.



(2*S*,3*S*)-2,5-Dimethoxy-5-oxo-2-phenyl-3-(pyridin-3-yl)pentanoic acid (3-26). The title compound was prepared according to **general procedure II** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of methyl (*E*)-3-(pyridin-3-yl)acrylate (82.1 mg, 0.503 mmol, 1.0 equiv) in THF (0.5 mL) at –78 °C. The resultant mixture was stirred for additional 6 h before a quench with a

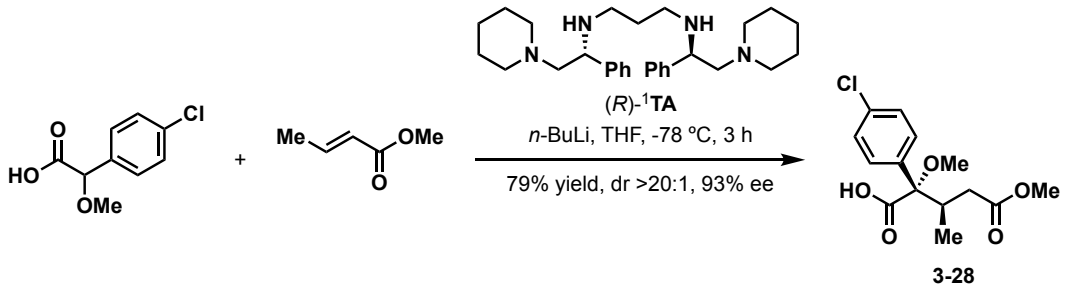
mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified to PH value around 4-5 using 1 M aqueous solution of HCl (4 mL) and drops of 1 M aqueous solution of NaOH. The reaction mixture was then extracted with ethyl acetate, and the combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the crude product **3-26** (0.154 g) was directly used for the next step.

(2*S*,3*S*)-Dimethyl 2-methoxy-2-phenyl-3-(pyridin-3-yl)pentanedioate (3-26 methyl ester). The title compound was prepared using above crude acid **3-26** (0.154 g), $TMSCHN_2$ (2.2 mL, 0.65 M in hexanes, 1.43 mmol) in a mixture of benzene-MeOH (4:1, 7.5 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (33-50% ethyl acetate in hexanes) to afford product **3-26 methyl ester** (94.8 mg, 0.276 mmol, 55% yield over 2 steps). Ee: 93% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=10.0 min (major); t_2=12.7 min). $[\alpha]_D^{23}$ –60.6 (c 1.20, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.40 (d, J = 4.2 Hz, 1H), 8.24 (s, 1H), 7.31–7.23 (m, 4H), 7.18–7.14 (m, 2H), 7.09 (dd, J = 7.9, 4.8 Hz, 1H), 3.98 (dd, J = 11.2, 3.9 Hz, 1H), 3.81 (s, 3H), 3.45 (s, 3H), 3.27 (s, 3H), 2.90 (dd, J = 16.4, 11.2 Hz, 1H), 2.77 (dd, J = 16.4, 3.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.0, 171.5, 151.2, 148.3, 137.1, 135.6, 133.8, 128.3, 128.0, 127.7, 122.5, 88.0, 54.7, 52.1, 51.6, 49.2, 35.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{21}NO_5Na$, 366.1317; found, 366.1313.

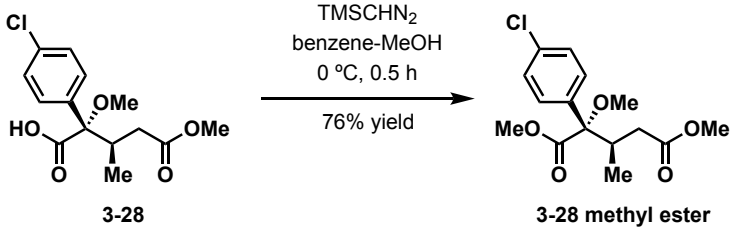


(*R*)-5-Butoxy-2-methoxy-5-oxo-2-phenylpentanoic acid (3-27). The title compound was prepared according to **general procedure II** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of *n*-butyl acrylate (75 μL, 67.1 mg, 0.523 mmol, 1.05 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 1 h and the product **3-27** (0.116 g), contaminated with inseparable impurity, was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane).

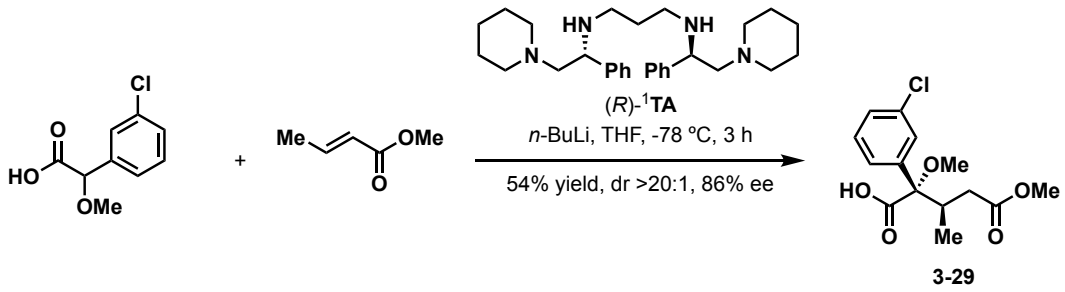
(*R*)-5-Butyl 1-methyl 2-methoxy-2-phenylpentanedioate (3-27 methyl ester). The title compound was prepared using above crude acid **3-27** (0.116 g), $TMSCHN_2$ (1.3 mL, 0.57 M in hexanes, 0.741 mmol) in a mixture of benzene-MeOH (4:1, 5 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-27 methyl ester** (60.0 mg, 0.195 mmol, 39% yield over 2 steps). Ee: 92% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=15.3 min (major); t_2=16.0 min). $[\alpha]_D^{23}$ +18.9 (c 1.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.47–7.43 (m, 2H), 7.38–7.30 (m, 2H), 7.32–7.25 (m, 1H), 4.02 (t, J = 6.5 Hz, 2H), 3.71 (s, 3H), 3.24 (s, 3H), 2.64 (ddd, J = 15.5, 9.8, 6.6 Hz, 1H), 2.51 (ddd, J = 15.0, 9.7, 6.7 Hz, 1H), 2.18 (ddd, J = 9.7, 6.1, 3.1 Hz, 2H), 1.61–1.52 (m, 2H), 1.40–1.29 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.1, 172.5, 138.7, 128.4, 128.0, 125.9, 83.4, 64.4, 52.5, 51.8, 30.6, 28.8, 28.1, 19.0, 13.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_5Na$, 331.1521; found, 331.1505.



(2*S*,3*R*)-2-(4-Chlorophenyl)-2,5-dimethoxy-3-methyl-5-oxopentanoic acid (3-28). The title compound was prepared according to **general procedure II** using 2-(4-chlorophenyl)-2-methoxyacetic acid (0.100 g, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of methyl crotonate (50.6 mg, 0.505 mmol, 1.01 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 3 h and the product **3-28** (0.118 g, 0.393 mmol, 79% yield) was obtained after purification by column chromatography on silica gel (2-4% methanol in dichloromethane). $[\alpha]_D^{25}$ –36.2 (c 1.03, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.41 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 3.64 (s, 3H), 3.21 (s, 3H), 2.96 (dqd, J = 10.5, 6.7, 2.9 Hz, 1H), 2.47 (dd, J = 16.1, 2.9 Hz, 1H), 2.07 (dd, J = 16.1, 10.5 Hz, 1H), 1.02 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 174.7, 173.3, 134.5, 133.8, 129.5, 128.5, 87.3, 53.4, 51.8, 37.3, 36.9, 15.2. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{14}H_{16}ClO_5$, 299.0686; found, 299.0686.



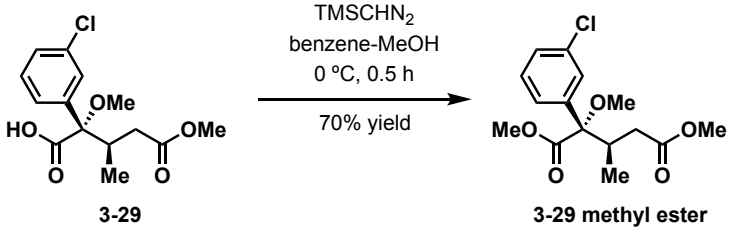
(2*S*,3*R*)-Dimethyl 2-(4-chlorophenyl)-2-methoxy-3-methylpentanedioate (3-28 methyl ester). The title compound was prepared using above acid **3-28** (54.1 mg, 0.180 mmol), $TMSCHN_2$ (0.33 mL, 1.13 M in hexanes, 0.373 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford product **3-28 methyl ester** (43.3 mg, 0.138 mmol, 76% yield). Ee: 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=10.3 min (major); t_2=13.3 min). $[\alpha]_D^{25}$ –20.8 (c 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38–7.31 (m, 4H), 3.83 (s, 3H), 3.62 (s, 3H), 3.19 (s, 3H), 2.89 (dqd, J = 10.6, 6.8, 3.2 Hz, 1H), 2.44 (dd, J = 15.8, 3.2 Hz, 1H), 1.85 (dd, J = 15.8, 10.6 Hz, 1H), 0.92 (d, J = 6.8, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.1, 171.4, 134.5, 134.0, 129.4, 128.1, 87.6, 53.8, 52.1, 51.6, 38.5, 36.5, 15.5. LRMS-FD (m/z): $[M]^+$ calcd for $C_{15}H_{19}ClO_5$, 314; found, 314.



3-29

(2*S*,3*R*)-2-(3-Chlorophenyl)-2,5-dimethoxy-3-methyl-5-oxopentanoic acid (3-29). The title compound was prepared according to **general procedure II** using 2-(3-chlorophenyl)-2-methoxyacetic acid (100.3 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of methyl crotonate (50.6 mg, 0.505 mmol, 1.01 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 3 h and the product **3-29** (81.9 mg, 0.272 mmol,

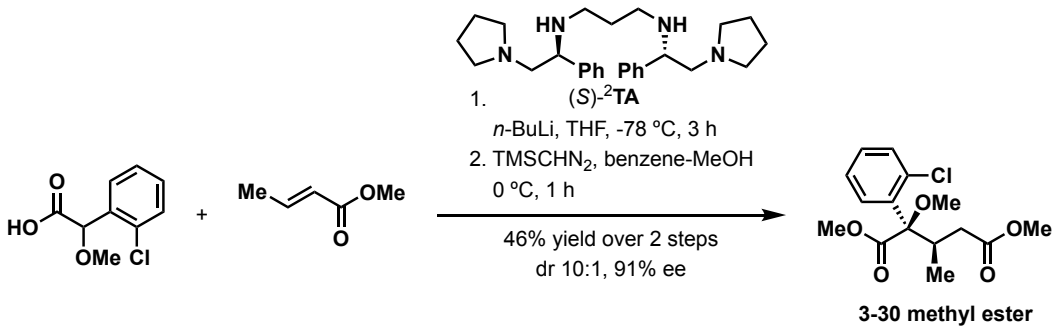
54% yield) was obtained after purification by column chromatography on silica gel (2-4% methanol in dichloromethane). $[\alpha]_D^{25}$ –28.8 (c 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.49–7.45 (m, 1H), 7.39–7.31 (m, 3H), 3.65 (s, 3H), 3.23 (s, 3H), 3.08–2.86 (m, 1H), 2.51 (dd, J = 16.2, 2.8 Hz, 1H), 2.10 (dd, J = 16.2, 10.6 Hz, 1H), 1.04 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 174.0, 173.2, 137.4, 134.5, 129.5, 128.8, 128.2, 126.2, 87.2, 53.4, 51.8, 36.8, 15.2. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{14}H_{16}ClO_5$, 299.0686; found, 299.0676.



3-29 3-29 methyl ester

(2*S*,3*R*)-Dimethyl 2-(3-chlorophenyl)-2-methoxy-3-methylpentanedioate (3-29 methyl ester). The title compound was prepared using above acid **3-29** (26.5 mg, 88.1 μmol), $TMSCHN_2$ (0.16 mL, 1.13 M in hexanes, 0.181 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford product **3-29 methyl ester** (19.2 mg, 61.0 μmol, 70% yield). Ee: 86% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; t_1=26.8 min (major); t_2=28.3 min). $[\alpha]_D^{25}$ –18.4 (c 0.96, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.43–7.41 (m, 1H), 7.33–7.29 (m, 3H), 3.85 (s, 3H), 3.63 (s, 3H), 3.22 (s, 3H), 2.94–2.84 (m, 1H), 2.47 (dd, J = 15.7, 3.2 Hz, 1H), 1.86 (dd, J = 15.7, 10.7 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

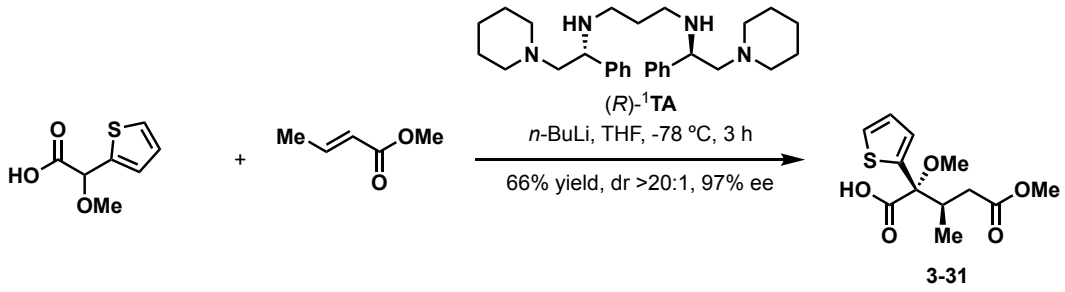
(ppm) 173.1, 171.3, 138.3, 134.1, 129.2, 128.2, 128.1, 126.1, 87.6, 54.0, 52.2, 51.6, 38.5, 36.5, 15.5. LRMS-FD (m/z): $[M]^+$ calcd for $C_{15}H_{19}ClO_5$, 314; found, 314.



(2*R*,3*S*)-2-(2-Chlorophenyl)-2,5-dimethoxy-3-methyl-5-oxopentanoic acid (3-30). The title compound was prepared according to **general procedure II** using 2-(2-chlorophenyl)-2-methoxyacetic acid (100.3 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of methyl crotonate (50.6 mg, 0.505 mmol, 1.01 equiv) in THF (0.50 mL) at –78 °C. The resultant mixture was stirred for additional 3 h before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified using 1 M aqueous solution of HCl (4 mL). The reaction mixture was then extracted with ethyl acetate, and the combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the crude product **3-30** (85.3 mg) was directly used for the next step.

(2*R*,3*S*)-Dimethyl 2-(2-chlorophenyl)-2-methoxy-3-methylpentanedioate (3-30 methyl ester). The title compound was prepared using above crude acid **3-30** (36.3 mg), $TMSCHN_2$ (0.22 mL, 1.13 M in hexanes, 0.249 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford product **3-30 methyl ester** (28.9 mg, 91.8 μmol, 46% yield over steps). Ee: 91% (Chiralcel® OD-H; 1% *i*-PrOH in

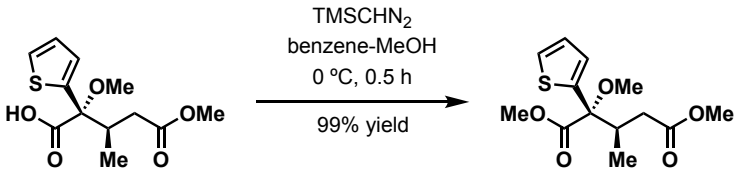
hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=13.7 min (major), t_1=11.6 min). $[\alpha]_D^{25}$ +37.1 (c 0.69, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 (dd, J = 7.8, 1.8 Hz, 1H), 7.39 (dd, J = 7.7, 1.6 Hz, 1H), 7.34–7.26 (m, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 3.32–3.24 (m, 1H), 3.18 (s, 3H), 2.80 (d, J = 15.9 Hz, 1H), 1.98 (dd, J = 16.1, 10.5 Hz, 1H), 0.97 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.6, 170.6, 135.2, 133.8, 131.2, 129.5, 129.3, 126.4, 85.3, 52.24, 52.21, 51.7, 37.2, 33.7, 15.7. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{19}ClO_5Na$, 337.0819; found, 337.0806.



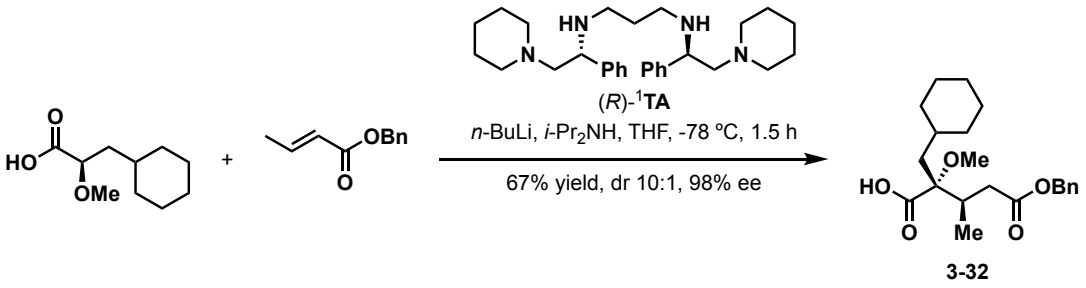
3-31

(2*R*,3*R*)-2,5-Dimethoxy-3-methyl-5-oxo-2-(thiophen-2-yl)pentanoic acid (3-31). The title compound was prepared according to **general procedure II** using 2-methoxy-2-(thiophen-2- yl)acetic acid (86.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of methyl crotonate (50.6 mg, 0.505 mmol, 1.01 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 3 h and the product **3-31** (89.6 mg, 0.329 mmol, 66% yield) was obtained after purification by column chromatography on silica gel (2-4% methanol in dichloromethane). $[\alpha]_D^{25}$ –31.2 (c 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.36 (dd, J = 5.1, 1.1 Hz, 1H), 7.19 (dd, J = 3.6, 1.1 Hz, 1H), 7.02 (dd, J = 5.1, 3.6 Hz, 1H), 3.65 (s, 3H), 3.26 (s, 3H), 2.26–2.17 (m, 1H), 2.64 (dd, J = 16.2, 2.8 Hz, 1H), 2.18 (dd, J = 16.2, 10.6 Hz, 1H), 1.06 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 174.2,

173.4, 138.7, 128.3, 126.6, 126.4, 86.0, 53.7, 51.7, 39.9, 37.0, 15.1. HRMS-EI (m/z): $[M]^+$ calcd for $C_{12}H_{16}O_5S$, 272.0718; found, 272.0707.



(2*R*,3*R*)-Dimethyl 2-methoxy-3-methyl-2-(thiophen-2-yl)pentanedioate (3-31 methyl ester). The title compound was prepared using above carboxylic acid **3-31** (22.2 mg, 81.5 μmol), $TMSCHN_2$ (0.15 mL, 1.13 M in hexanes, 0.171 mmol) in a mixture of benzene-MeOH (4:1, 1 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **3-31 methyl ester** (23.2 mg, 81.0 μmol, 99% yield). Ee: 97% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=14.0 min (major); t_1=12.6 min). $[\alpha]_D^{25}$ –25.5 (c 1.08, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32 (dd, J = 5.1, 1.2 Hz, 1H), 7.11 (dd, J = 3.6, 1.2 Hz, 1H), 7.00 (dd, J = 5.1, 3.6 Hz, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 3.23 (s, 3H), 2.86 – 2.69 (m, 1H), 2.57 (dd, J = 15.8, 3.1 Hz, 1H), 2.00 (dd, J = 15.8, 10.8 Hz, 1H), 0.96 (d, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.1, 171.2, 139.5, 127.8, 126.21, 126.16, 86.8, 54.1, 52.3, 51.6, 41.0, 36.7, 15.2. LRMS-FD (m/z): $[M]^+$ calcd for $C_{13}H_{18}O_5S$, 286; found, 286.

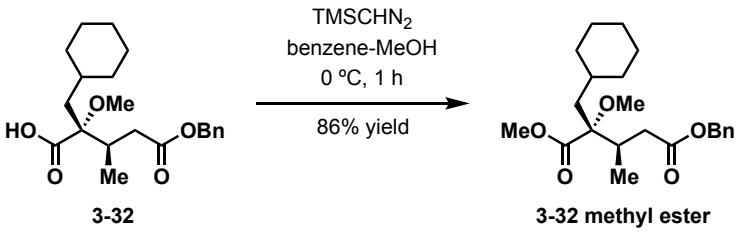


3-32

"General Procedure III"

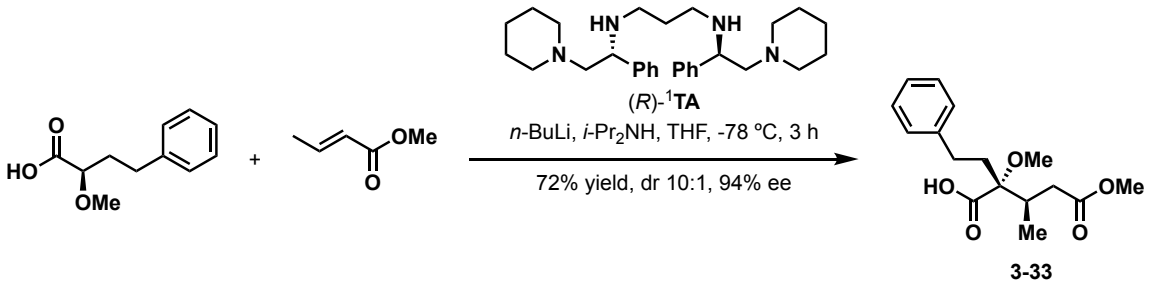
(2*R*,3*R*)-5-(Benzyloxy)-2-(cyclohexylmethyl)-2-methoxy-3-methyl-5-oxopentanoic acid (3-32). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of *i*-Pr_2NH (0.14 mL, 0.101 g, 1.00 mmol) and (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Then, (*R*)-3-cyclohexyl-2-methoxypropionic acid (93.2 mg, 0.500 mmol) in THF (1.0 mL) was added dropwise. After additional 1 h at 0 °C, the reaction mixture was cooled to –78 °C. After 5 min, a solution of benzyl crotonate (90.6 mg, 0.515 mmol, 1.03 equiv) in THF (0.30 mL, plus 2 × 0.10 mL rinses) was added to the reaction mixture dropwise over 10 min. After stirring for further 1.5 h, the reaction mixture was quenched with a mixture of THF-MeOH (3:1, 0.64 mL). After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **3-32** (0.122 g, 0.337 mmol, 67% yield). $[\alpha]_D^{23}$ +16.8 (c 2.36, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39–7.27 (m, 5H), 5.14 (d, J = 12.4 Hz, 1H), 5.10 (d, J = 12.4 Hz, 1H), 3.32 (s, 3H), 2.70 (dd, J = 16.0, 3.3 Hz, 1H), 2.49 (dqd, J = 9.9, 6.6, 3.3 Hz, 1H), 2.40 (dd, J = 16.0, 9.9 Hz, 1H), 1.87 (dd, J = 14.8, 8.3 Hz, 1H), 1.70–1.55 (m, 6H), 1.40-1.29 (m, 1H), 1.28–1.05 (m, 3H), 1.01-0.81 (m, 2 H), 0.91 (d, J = 6.6 Hz,

3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.9, 135.8, 128.5, 128.2, 128.1, 83.8, 66.3, 49.9, 38.7, 36.7, 34.4, 34.2, 33.2, 33.0, 26.4, 26.0, 26.0, 14.3. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{21}H_{29}O_5$, 361.2015; found, 361.2003.

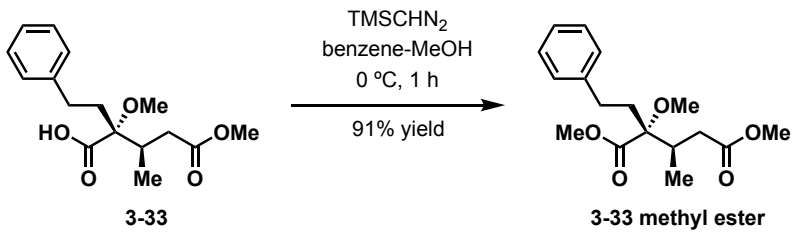


3-32 3-32 methyl ester

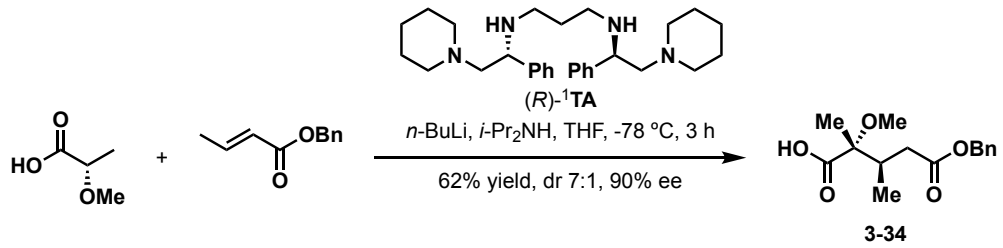
(2*R*,3*R*)-5-Benzyl 1-methyl 2-(cyclohexylmethyl)-2-methoxy-3-methylpentanedioate (3-32 methyl ester). The title compound was prepared using acid **3-32** (28.4 mg, 78.4 μmol), $TMSCHN_2$ (80 μL, 2.0 M in hexanes, 0.160 mmol) in a mixture of benzene-MeOH (4:1, 1 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (11% ethyl acetate in hexanes) to afford product **3-32 methyl ester** (25.5 mg, 67.7 μmol, 86% yield). Ee: 98% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=8.0 min (major); t_2=9.9 min). $[\alpha]_D^{23}$ +8.5 (c 1.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38–7.29 (m, 5H), 5.12 (s, 2H), 3.71 (s, 3H), 3.27 (s, 3H), 2.61 (dd, J = 15.7, 3.0 Hz, 1H), 2.54 (dqd, J = 9.9, 6.8, 3.1 Hz, 1H), 2.22 (dd, J = 15.7, 10.6 Hz, 1H), 1.77 (dd, J = 14.9, 7.6 Hz, 1H), 1.72–1.55 (m, 6H), 1.48-1.38 (m, 1H), 1.29–1.05 (m, 3H), 1.01–0.81 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.3, 172.9, 135.9, 128.5, 128.21, 128.17, 84.0, 66.3, 51.8, 50.7, 38.9, 37.3, 34.9, 34.7, 33.3, 33.0, 26.4, 26.3, 26.2, 14.6. LRMS-CI (m/z): $[M+H]^+$ calcd for $C_{22}H_{33}O_5$, 377; found, 377.



(2*R*,3*R*)-2,5-Dimethoxy-3-methyl-5-oxo-2-phenethylpentanoic acid (3-33). The title compound was prepared according to **general procedure III** using *i*-Pr_2NH (0.14 mL, 0.101 g, 1.00 mmol, 2 eq), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3 mL), followed by addition of a solution of (*R*)-2-methoxy-4-phenylbutyric acid (97.2 mg, 0.500 mmol) in THF (1 mL). After stirring at 0 ºC for 1 h, a solution of methyl crotonate (55 μL, 51.9 mg, 0.519 mmol, 1.04 equiv) in THF (0.5 mL) was added at –78 °C. The reaction was quenched after 3 h, and product **3-33** (0.106 g, 0.360 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{23}$ +15.0 (c 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.31–7.24 (m, 2H), 7.23–7.13 (m, 3H), 3.65 (s, 3H), 3.42 (s, 3H), 2.68–2.44 (m, 4H), 2.38 (dd, J = 16.0, 10.0 Hz, 1H), 2.27 (ddd, J = 14.5, 12.2, 4.8 Hz, 1H), 2.00 (ddd, J = 14.5, 12.3, 4.7 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.3, 140.8, 128.5, 128.2, 126.2, 84.8, 51.7, 49.9, 36.6, 33.7, 33.4, 29.9, 14.6. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{16}H_{21}O_5$, 293.1389; found, 293.1376.

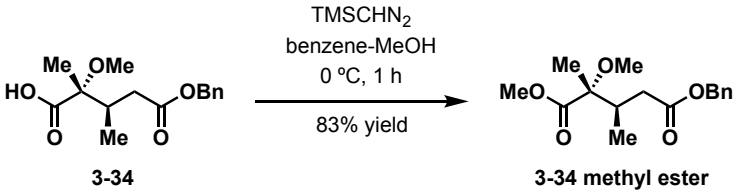


(2*R*,3*R*)-Dimethyl 2-methoxy-3-methyl-2-phenethylpentanedioate (3-33 methyl ester). The title compound was prepared using acid **3-33** (31.2 mg, 0.106 mmol), $TMSCHN_2$ (0.19 mL, 1.1 M in hexanes, 0.209 mmol) in a mixture of benzene-MeOH (4:1, 1 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (11% ethyl acetate in hexanes) to afford product **3-33 methyl ester** (29.6 mg, 96.0 μmol, 91% yield). Ee: 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=15.6 min (major); t_2=20.4 min). $[\alpha]_D^{23}$ +14.0 (c 0.86, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.25 (m, 2H), 7.22–7.17 (m, 3H), 3.75 (s, 3H), 3.68 (s, 3H), 3.38 (s, 3H), 2.79–2.69 (m, 1H), 2.64–2.48 (m, 3H), 2.24–2.03 (m, 3H), 1.00 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.3, 172.9, 141.6, 128.4, 128.2, 126.0, 84.2, 51.8, 51.7, 51.3, 37.0, 34.9, 33.5, 29.8, 14.6. LRMS-CI (m/z): $[M+H]^+$ calcd for $C_{17}H_{25}O_5$, 309; found, 309.



(2*R*,3*R*)-5-(Benzyloxy)-2-methoxy-2,3-dimethyl-5-oxopentanoic acid (3-34). The title compound was prepared according to **general procedure III** using *i*-Pr_2NH (0.14 mL, 0.101 g, 1.00 mmol, 2.0 equiv), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3 mL), followed by addition of a solution of (*S*)-2-methoxypropionic acid (52.3 mg, 0.500 mmol) in THF (1 mL). After stirring at 0 ºC for 1 h, a solution of benzyl crotonate (90.6 mg, 0.515 mmol, 1.03 equiv) in THF (0.5 mL) was added

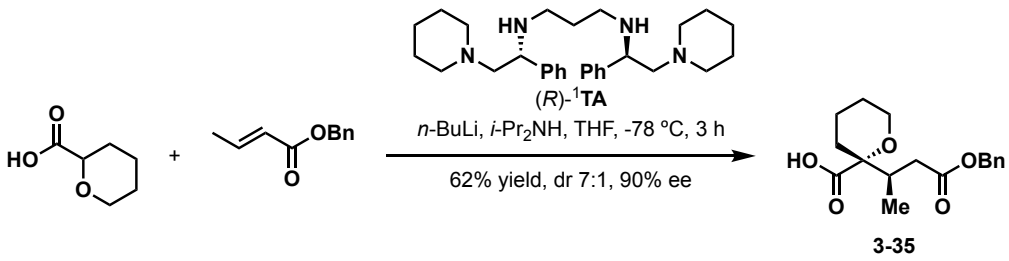
at –78 °C. The reaction was quenched after 3 h, and product **3-34** (87.2 mg, 0.311 mmol, 62% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{22}$ +25.2 (c 0.94, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.75 (brs, 1H), 7.39–7.27 (m, 5H), 5.12 (s, 2H), 3.28 (s, 3H), 2.67 (dd, J = 15.6, 3.9 Hz, 1H), 2.54 (dqd, J = 9.9, 6.8, 3.3 Hz, 1H), 2.24 (dd, J = 15.6, 10.0 Hz, 1H), 1.35 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 177.7, 172.9, 135.8, 128.5, 128.1, 82.3, 66.3, 51.9, 37.1, 36.3, 15.9, 14.6. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{15}H_{19}O_5$, 279.1233; found, 279.1227.



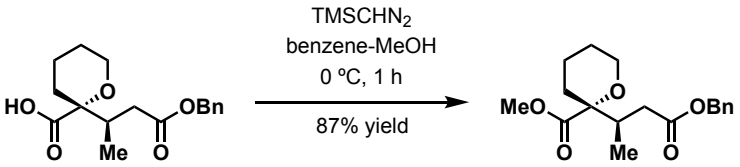
3-34 3-34 methyl ester

(2*R*,3*R*)-5-Benzyl 1-methyl 2-methoxy-2,3-dimethylpentanedioate (3-34 methyl ester). The title compound was prepared using acid **3-34** (21.9 mg, 78.1 μmol), $TMSCHN_2$ (80 μL, 2.0 M in hexanes, 0.160 mmol) in a mixture of benzene-MeOH (4:1, 1 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (11% ethyl acetate in hexanes) to afford product **3-34 methyl ester** (19.1 mg, 64.9 μmol, 83% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=12.2 min (major); t_2=19.7 min). $[\alpha]_D^{23}$ +29.6 (c 0.56, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.40–7.27 (m, 5H), 5.11 (d, J = 12.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 3.73 (s, 3H), 3.21 (s, 3H), 2.65 (dd, J = 15.6, 3.7 Hz, 1H), 2.53 (dqd, J = 10.5, 6.9, 3.7 Hz, 1H), 2.14 (dd, J = 15.6, 10.2 Hz, 1H), 1.30 (s, 3H), 0.89 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125

MHz, $CDCl_3$) δ (ppm) 174.0, 172.8, 136.0, 128.5, 128.2, 128.1, 82.6, 66.2, 52.2, 52.0, 37.5, 36.2, 15.5, 14.9. LRMS-CI (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}O_5$, 295; found, 295.

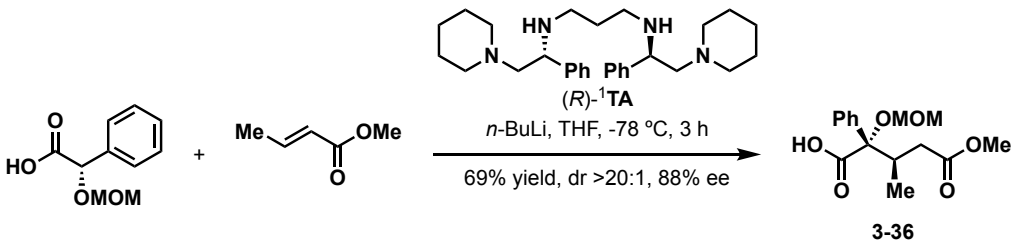


(*R*)-2-((*R*)-4-Methoxy-4-oxobutan-2-yl)tetrahydro-2*H*-pyran-2-carboxylic acid (3-35). The title compound was prepared according to **general procedure III** using *i*-Pr_2NH (0.14 mL, 0.101 g, 1.00 mmol, 2.0 eq), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.49 M in hexanes, 1.99 mmol, 4.0 equiv) in THF (3 mL), followed by addition of a solution of tetrahydro-2*H*-pyran-2-carboxylic acid (65.1 mg, 0.500 mmol) in THF (1 mL). After stirring at 0 ºC for 1 h, a solution of benzyl crotonate (90.6 mg, 0.515 mmol, 1.03 equiv) in THF (0.5 mL) was added at –78 °C. The reaction was quenched after 3 h, and product **3-35** (0.113 g, 0.369 mmol, 74% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{23}$ +44.4 (c 1.90, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.00 (brs, 1 H), 7.39–7.29 (m, 5H), 5.13 (d, J = 13.0 Hz, 1H), 5.10 (d, J = 13.0 Hz, 1H), 3.87–3.80 (m, 1H), 3.63 (ddd, J = 11.6, 8.9, 4.4 Hz, 1H), 2.74 (dd, J = 15.6, 4.0 Hz, 1H), 2.45 (dqd, J = 10.7, 6.9, 3.9 Hz, 1H), 2.22 (dd, J = 15.6, 9.8 Hz, 1H), 2.10-2.03 (m, 1H), 1.78–1.70 (m, 1H), 1.56-1.42 (m, 4H), 0.97 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 176.9, 172.9, 135.9, 128.5, 128.20, 128.17, 81.8, 66.3, 65.1, 37.5, 36.4, 27.5, 25.0, 20.1, 14.4. HRMS-ESI (m/z): $[M–H]^-$ calcd for $C_{17}H_{21}O_5$, 305.1389; found, 305.1380.



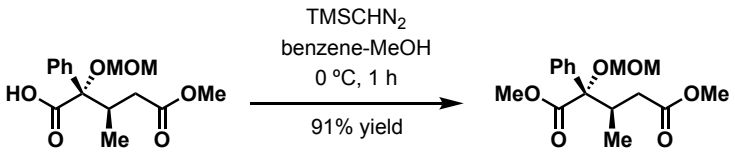
3-35 **3-35 methyl ester**

(*R*)-Methyl 2-((*R*)-4-(benzyloxy)-4-oxobutan-2-yl)tetrahydro-2*H*-pyran-2-carboxylate (3-35 methyl ester). The title compound was prepared using acid **3-35** (41.6 mg, 0.136 mmol), $TMSCHN_2$ (0.13 mL, 2.0 M in hexanes, 0.260 mmol) in a mixture of benzene-MeOH (4:1, 2 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (11% ethyl acetate in hexanes) to afford product **3-35 methyl ester** (37.9 mg, 0.118 mmol, 87% yield). Ee: 98% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=14.3 min(major); t_1=13.6 min). $[\alpha]_D^{23}$ +49.2 (c 1.83, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39–7.27 (m, 5H), 5.11 (d, J = 12.5 Hz, 1H), 5.10 (d, J = 12.5 Hz, 1H), 3.88–3.80 (m, 1H), 3.75 (s, 3H), 3.53 (td, J = 11.7, 3.1 Hz, 1H), 2.71 (dd, J = 15.6, 3.7 Hz, 1H), 2.38 (dqd, J = 10.5, 6.9, 3.7 Hz, 1H), 2.14 (dd, J = 15.6, 10.2 Hz, 1H), 2.11–2.05 (m, 1H), 1.79–1.68 (m, 1H), 1.55–1.33 (m, 4H), 0.91 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.6, 172.8, 136.0, 128.5, 128.2, 128.1, 82.2, 66.2, 65.2, 51.9, 38.2, 36.3, 27.8, 25.2, 20.5, 14.4. LRMS-CI (m/z): $[M+H]^+$ calcd for $C_{18}H_{25}O_5$, 321; found, 321.



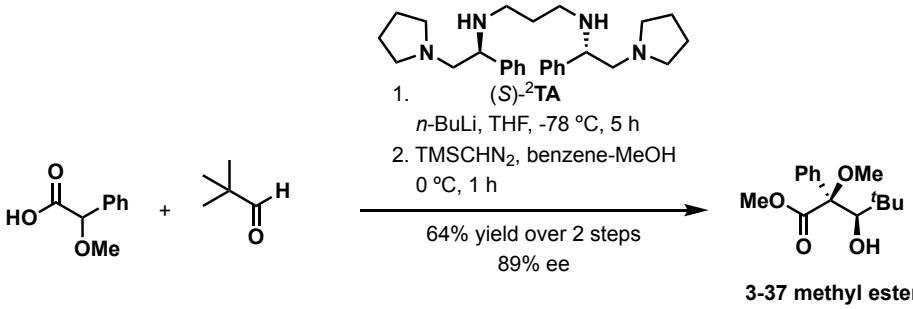
3-36

(2*S*,3*R*)-5-Methoxy-2-(methoxymethoxy)-3-methyl-5-oxo-2-phenylpentanoic acid (3-36). The title compound was prepared according to **general procedure II** using (*S*)-2-(methoxymethoxy)-2-phenylacetic acid (98.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.49 M in hexanes, 1.99 mmol, 4.0 equiv) in THF (7 mL). After stirring at 0 °C for 2 h, a solution of benzyl crotonate (90.6 mg, 0.515 mmol, 1.03 equiv) in THF (1.0 mL) was added at –78 °C. The reaction was quenched after 3 h, and product **3-36** (0.102 g, 0.345 mmol, 69% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{23}$ –34.4 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.47–7.42 (m, 2H), 7.41–7.31 (m, 3H), 4.66 (d, J = 6.7 Hz, 1H), 4.63 (d, J = 6.7 Hz, 1H), 3.61 (s, 3H), 3.43 (s, 3H), 3.02-2.94 (m, 1 H), 2.38 (dd, J = 16.3, 2.9 Hz, 1H), 2.27 (dd, J = 16.3, 10.5 Hz, 1H), 1.09 (dd, J = 6.7, 0.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.3, 135.4, 128.8, 128.5, 127.9, 93.6, 89.26, 56.5, 51.6, 39.4, 37.1, 15.1. HRMS-CI (m/z): $[M+H]^+$ calcd for $C_{15}H_{21}O_6$, 297.1338; found, 297.1329.



(2*S*,3*R*)-Dimethyl 2-(methoxymethoxy)-3-methyl-2-phenylpentanedioate (3-36 methyl ester). A solution of $TMSCHN_2$ in hexane (0.26 mL, 1.03 M, 0.262 mmol) was added dropwise to a solution of carboxylic acid **3-36** (25.1 mg, 84.7 μmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the product **3-36 methyl**

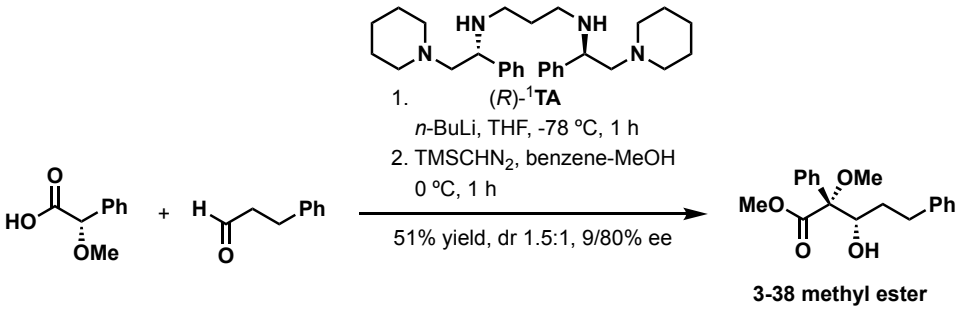
ester (24.0 mg, 77.3 μmol, 91% yield). Ee: 88% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_2=21.4 min (major), t_1=16.6 min). $[\alpha]_D^{26}$ –77.5 (c 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38-7.35 (m, 4H), 7.34–7.28 (m, 1H), 4.80 (d, J = 6.5 Hz, 1H), 4.64 (d, J = 6.5 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.38 (s, 3H), 3.04 (dqd, J = 10.3, 6.8, 3.4 Hz, 1H), 2.52 (dd, J = 15.7, 3.4 Hz, 1H), 1.91 (dd, J = 15.7, 10.3 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.4, 172.0, 136.1, 128.1, 127.9, 127.8, 93.5, 86.9, 56.1, 52.3, 51.5, 38.4, 36.7, 15.4. LRMS-FD (m/z): $[M]^+$ calcd for $C_{16}H_{22}O_6$, 310; found, 310.



(2*S*,3*R*)-3-Hydroxy-2-methoxy-4,4-dimethyl-2-phenylpentanoic acid (3-37). A solution of *n*- BuLi (0.81 mL, 2.47 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), and (S)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Then pivaldehyde (0.11 mL, 87.2 mg, 1.01 mmol, 2.03 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 5 h before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of

HCl and brine, dried over Na_2SO_4, concentrated, and the residue was directly used for the next step without further purification.

(2*S*,3*R*)-Methyl 3-hydroxy-2-methoxy-4,4-dimethyl-2-phenylpentanoate (3-37 methyl ester). The title compound was prepared using above crude acid **3-37**, $TMSCHN_2$ in hexane (1.75 mL, 0.57 M, 1.00 mmol) in a mixture of benzene-MeOH (4:1, 5 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-37 methyl ester** (84.9 mg, 0.319 mmol, 64% yield over steps). Ee: 89% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=7.1 min (major); t_2=7.6 min). $[\alpha]_D^{23}$ +21.2 (c 1.60, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54–7.48 (m, 2H), 7.39–7.31 (m, 2H), 7.34–7.26 (m, 1H), 4.03 (d, J = 8.2 Hz, 1H), 3.83 (s, 3H), 3.30 (s, 3H), 3.18 (d, J = 8.2 Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.8, 138.3, 128.2, 128.0, 127.2, 87.2, 83.0, 54.6, 52.2, 36.5, 27.7. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{22}O_4Na$, 289.1416; found, 289.1403.



3-38 methyl ester

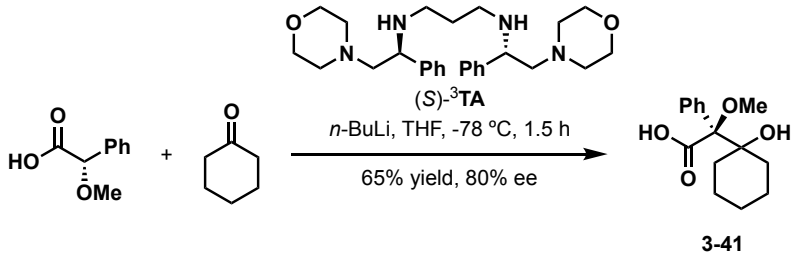
(2*R*,3*S*)-3-Hydroxy-2-methoxy-2,5-diphenylpentanoic acid (3-38). A solution of *n*-BuLi (0.79 mL, 2.53 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*S*)-2- methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), and (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 2 h. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min.

Then a solution of hydrocinnamaldehyde (70 μL, 71.3 mg, 0.531 mmol, 1.06 equiv) in THF (0.5 mL) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 50 min before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was directly used for the next step without further purification.

(2*R*,3*S*)-Methyl 3-hydroxy-2-methoxy-2,5-diphenylpentanoate (3-38 methyl ester). The title compound was prepared using above crude acid **3-38**, $TMSCHN_2$ in hexane (0.9 mL, 1.1 M, 0.99 mmol) in a mixture of benzene-MeOH (4:1, 5 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford products diastereomeric mixtures **3-38 methyl ester-1** and **3-38 methyl ester-2** (79.7 mg, 0.254 mmol, 51% yield). The analytically pure products was obtained using preparative HPLC (YMC-Pack-SIL 250x30 mm; 1% *i*-PrOH in hexanes; flow rate = 5 mL/min; detection at 215 nm, t_1=6.5 min (major), t_2=7.2 min (minor)).

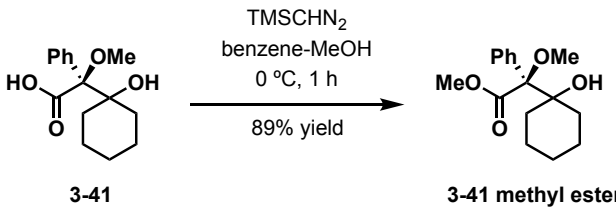
Major diastereomer **3-38 methyl ester-1**: Ee: 9% (Chiralcel® AD-H; 1% ^{i}-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=24.6 min; t_2=33.8 min). $[\alpha]_D^{25}$ –14.4 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.45–7.38 (m, 2H), 7.38–7.30 (m, 3H), 7.23 (t, J = 7.4 Hz, 2H), 7.19–7.13 (m, 1H), 7.09 (d, J = 6.8 Hz, 2H), 4.19 (ddd, J = 10.4, 6.5, 2.1 Hz, 1H), 3.81 (s, 3H), 3.46 (s, 3H), 2.94–2.84 (m, 2H), 2.58 (ddd, J = 13.9, 9.5, 7.3 Hz, 1H), 1.85-1.76 (m, 1H), 1.68-1.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.1, 141.9, 136.6, 128.4, 128.3, 128.2, 128.1, 126.7, 125.7, 87.1, 55.0, 52.4, 32.3, 32.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{22}O_4Na$, 337.1416; found, 337.1403.

Minor diastereomer **3-38 methyl ester-2**: Ee: 80% (Chiralcel® AD-H; 1% ^{i}-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=31.4 min; t_2=38.8 min). $[\alpha]_D^{25}$ –31.7 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.43–7.28 (m, 5H), 7.24 (t, J = 7.2 Hz, 2H), 7.19–7.12 (m, 1H), 7.14–7.08 (m, 2H), 4.16 (ddd, J = 10.5, 3.6, 1.8 Hz, 1H), 3.84 (s, 3H), 3.21 (s, 3H), 2.90 (d, J = 2.4 Hz, 1H), 2.83 (ddd, J = 13.9, 9.3, 4.8 Hz, 1H), 2.57 (dt, J = 13.8, 8.4 Hz, 1H), 1.69 (dt, J = 15.5, 8.3 Hz, 1H), 1.53 (dddd, J = 14.0, 10.5, 8.8, 4.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.1, 141.8, 135.4, 128.6, 128.23, 128.19, 128.1, 127.5, 125.7, 87.6, 75.2, 53.8, 52.2, 32.3, 32.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{22}O_4Na$, 337.1416; found, 337.1415.

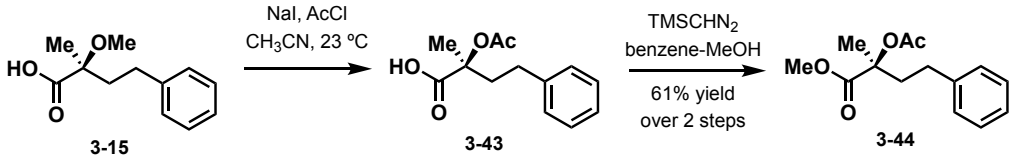


(*S*)-2-(1-Hydroxycyclohexyl)-2-methoxy-2-phenylacetic acid (3-41). The title compound was prepared according to **general procedure II** using (*S*)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*S*)-**^{3}TA** (0.233 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.47 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of a solution of cyclohexanone (65 µL, 61.6 mg, 0.628 mmol, 1.26 equiv) in THF (0.5 mL) at –78 °C. The reaction was quenched after 1.5 h, and product **3-41**(90.3 mg, 0.324 mmol, 65% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). $[\alpha]_D^{23}$ –50.4 (c 1.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.47-7.41 (m, 2H), 7.40–7.32 (m, 3H), 3.35 (s, 3H), 3.17 (brs, 1H), 1.82–1.75 (m, 2H), 1.71–1.41 (m,

6H), 0.96–0.83 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.6, 133.5, 129.2, 128.1, 127.4, 89.9, 77.9, 54.4, 31.4, 30.4, 25.2, 20.9, 20.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{20}O_4Na$, 287.1259; found, 287.1251.

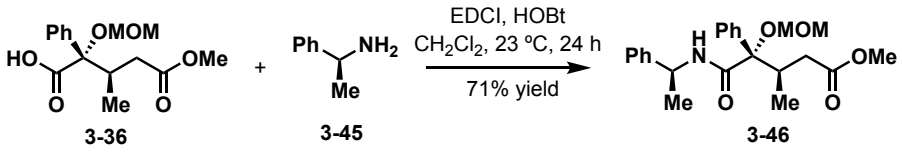


(*S*)-Methyl 2-(1-hydroxycyclohexyl)-2-methoxy-2-phenylacetate (3-41 methyl ester). The title compound was prepared using carboxylic acid **3-41** (24.5 mg, 92.7 μmol), TMSCHN2 (0.33 mL, 0.57 M in hexanes, 0.188 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3-41 methyl ester** (22.9 mg, 82.3 μmol, 89% yield). Ee: 80% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; t_1=17.6 min (major); t_2=20.5 min). $[\alpha]_D^{23}$ +6.90 (c 1.23, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.66–7.60 (m, 2H), 7.38–7.29 (m, 3H), 3.85 (s, 3H), 3.33 (s, 3H), 2.81 (s, 1H), 1.77–1.69 (m, 1H), 1.63–1.36 (m, 7H), 1.32–1.22 (m, 1H), 1.05–0.93 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.5, 134.6, 128.9, 127.9, 127.5, 91.0, 76.7, 55.4, 51.9, 32.3, 31.6, 25.6, 21.7, 21.6. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$, 301; found, 301.

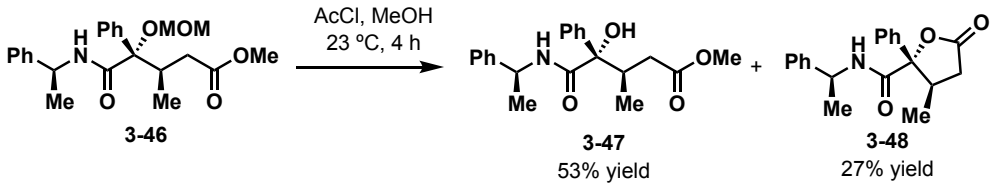


(*S*)-2-Acetoxy-2-methyl-4-phenylbutanoic acid (3-43). A 10-mL round flask was charged with sodium iodide (87.0 mg, 0.580 mmol) under an argon atmosphere through a gas inlet. Then the flask was flame-dried under vacuum and back filled with argon. After cooling to 23 °C, a solution of **3-15** (29.2 mg, 0.132 mmol) in CH_3CN (2 mL) was added and followed by acetyl chloride (40 μL, 44.0 mg, 0.561 mmol). The flask was wrapped with aluminium foil and the resultant mixture was stirred for 24 h at 23 °C before quenched with a mixture of 1 M aqueous solution of HCl and saturated aqueous solution of $NaHSO_3$. The aqueous solution was extracted with ethyl acetate and the combination of the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford crude product **3-43**. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32–7.27 (m, 2H), 7.23–7.16 (m, 3H), 2.76 (ddd, J = 13.7, 11.8, 5.3 Hz, 1H), 2.68 (ddd, J = 13.7, 11.8, 5.3 Hz, 1H), 2.32–2.26 (m, 1H), 2.18–2.10 (m, 1H), 2.07 (s, 3H), 1.67 (s, 3H). **3-43** was directly used to the next step without further characterization.

Methyl (*S*)-2-acetoxy-2-methyl-4-phenylbutanoate (3-44). A solution of $TMSCHN_2$ (0.25 mL, 1.03 M in hexanes, 0.258 mmol) was added dropwise to a solution of above crude acid **3-43** in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the product **3-44** (20.2 mg, 80.7 μmol, 61% yield over 2 steps). $[\alpha]_D^{22}$ –6.9 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32–7.25 (m, 2H), 7.23–7.15 (m, 3H), 3.72 (s, 3H), 2.70 (ddd, J = 13.8, 11.6, 5.5 Hz, 1H), 2.63 (ddd, J = 13.8, 11.6, 5.5 Hz, 1H), 2.23 (ddd, J = 14.0, 11.6, 5.5 Hz, 1H), 2.11 (ddd, J = 14.0, 11.6, 5.5 Hz, 1H), 2.06 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.5, 170.0, 141.0, 128.4, 128.3, 126.1, 80.4, 52.3, 39.8, 29.6, 21.5, 21.1. LRMS-FD (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}O_4$, 251; found, 251.



(3*R*,4*S*)-Methyl 4-(methoxymethoxy)-3-methyl-5-oxo-4-phenyl-5-(((*S*)-1-phenylethyl) amino) pentanoate (3-46). Hydroxybenzotriazole monohydrate (HOBt•H2O, 28.3 mg, 0.185 mmol, 1.5 equiv)，*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI• HCl, 35.4 mg, 0.185 mmol, 1.5 equiv) and (*S*)-α-methylbenzylamine (29.9 mg, 0.246 mmol, 2.0 equiv) were added sequentially to a solution of acid **3-36** (36.5 mg, 0.123 mmol, 1.0 equiv) in dichloromethane (2 mL). The solution was stirred at room temperature for 24 h. The reaction mixture was then diluted with hexanes/ethyl acetate (10 mL, 5:1) and quenched with 0.5 M aqueous solution of HCl. The aqueous solution was extracted with ethyl acetate and the combination of the organic layer was washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate with hexanes) to afford the pure amide product (34.7 mg, 86.9 μmol, 71% yield). $[\alpha]_D^{26}$ –72.1 (c 1.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.86 (d, J = 7.9 Hz, 1H), 7.55–7.44 (m, 2H), 7.42–7.26 (m, 8H), 5.18 (virt. p, J = 7.0 Hz, 1H), 4.50 (d, J = 6.5 Hz, 1H), 4.44 (d, J = 6.5 Hz, 1H), 3.59 (s, 3H), 3.33 (s, 3H), 3.00-2.94 (m, 1H), 2.41 (dd, J = 16.6, 2.8 Hz, 1H), 2.33 (dd, J = 16.6, 10.4 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.8, 170.2, 143.3, 137.4, 128.6, 128.5, 128.4, 128.2, 127.3, 126.2, 93.5, 88.6, 56.2, 51.4, 48.8, 38.3, 37.5, 22.0, 15.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{29}NO_5Na$, 422.1943; found, 422.1935.

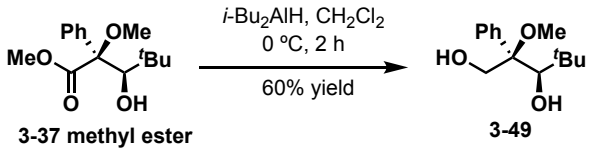


(3*R*,4*S*)-Methyl 4-hydroxy-3-methyl-5-oxo-4-phenyl-5-(((*S*)-1-phenylethyl)amino) pentanoate (3-47). Acetyl chloride (3.6 mg, 45.3 μmol, 1.0 equiv) was added to a solution of amide **3-46** (18.1 mg, 45.3 μmol) in methanol (0.5 mL) at 0 °C. After 5 min, the reaction mixture was warmed up to 23 °C and stirred for further 4 h. The reaction mixture was then concentrated and the residue was purified by column chromatography on silica gel (10% ethyl acetate with hexanes) to afford **3-47** (8.6 mg, 24.2 μmol, 53% yield) and 3-48 (4.0 mg, 12.4 μmol, 27% yield).

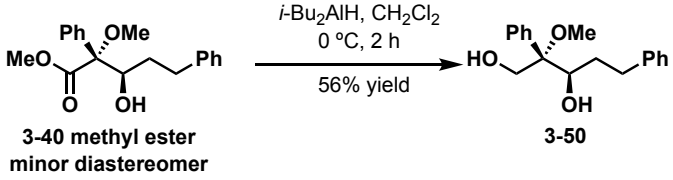
3-47: $[\alpha]_D^{25}$ –29.2 (c 0.53, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.76–7.70 (m, 2H), 7.41– 7.32 (m, 3H), 7.31–7.25 (m, 3H), 7.25–7.21 (m, 3H), 5.71 (brs, 1H), 4.96 (virt. p, J = 7.1 Hz, 1H), 3.68 (s, 3H), 2.95 (virt. qt, J = 7.1, 4.8 Hz, 1H), 2.55 (dd, J = 17.2, 4.6 Hz, 1H), 2.48 (dd, J = 17.2, 5.1 Hz, 1H), 1.36 (d, J = 7.0 Hz, 3H), 0.77 (d, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 176.1, 173.8, 143.9, 141.4, 128.5, 128.1, 127.3, 127.1, 125.8, 125.4, 80.8, 52.2, 48.8, 37.3, 37.0, 22.0, 12.3. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{25}NO_4Na$, 378.1681; found, 378.1681.

(2*R*,3*R*)-3-Methyl-5-oxo-2-phenyl-*N*-((*S*)-1-phenylethyl)tetrahydrofuran-2-carboxamide (3-48). $[\alpha]_D^{25}$ –78.7 (c 0.27, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.61–7.52 (m, 2H), 7.43–7.30 (m, 5H), 7.30–7.22 (m, 3H), 6.60 (d, J = 7.8 Hz, 1H), 5.00 (virt. p, J = 7.1 Hz, 1H), 3.35 (virt. pd, J = 7.2, 3.9 Hz, 1H), 2.62 (dd, J = 17.5, 7.6 Hz, 1H), 2.22 (dd, J = 17.5, 4.0 Hz, 1H), 1.36 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 174.9, 169.9, 142.9, 135.0, 128.8, 128.51, 128.47, 127.5, 125.7, 124.9, 90.8,

49.5, 37.4, 36.6, 21.8, 16.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{21}NO_3Na$, 346.1419; found, 346.1423.

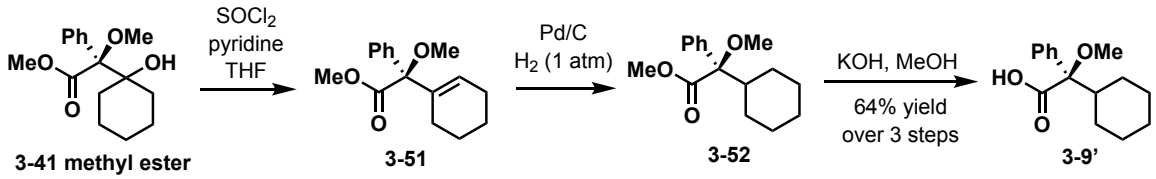


(2*R*,3*R*)-2-Methoxy-4,4-dimethyl-2-phenylpentane-1,3-diol (3-49). To a solution of **3-37 methyl ester** (66.1 mg, 0.248 mmol) in CH_2Cl_2 (4 mL) was added *i*-Bu_2AlH (1 mL, 1.0 M in toluene, 1.00 mmol) at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with a saturated solution of sodium potassium tartrate. The reaction mixture was stirred at 23 °C for 0.5 h, and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexanes) to afford product **3-49** (35.4 mg, 0.149 mmol, 60% yield). $[\alpha]_D^{23}$ +53.8 (c 0.92, CHCl3). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm): 7.45–7.42 (m, 2H), 7.34–7.30 (m, 2H),7.25–7.21 (m, 1H), 4.39 (d, J = 12.2 Hz, 1H), 4.01 (d, J = 12.2 Hz, 1H), 3.71 (s, 1H), 3.41 (s, 3H), 0.72 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD) δ (ppm): 142.5, 128.9, 128.5, 128.0, 85.1, 84.9, 66.4, 52.1, 37.6, 28.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{22}O_3Na$, 261.1467; found, 261.1473.



(2*S*,3*R*)-2-Methoxy-2-phenyl-5-phenylpentane-1,3-diol (3-50). To a solution of **3-40 methyl ester minor diastereomer** (14.2 mg, 45.2 μmol) in CH_2Cl_2 (2 mL) was added *i*-

Bu_2AlH (0.26 mL, 1.0 M in toluene, 0.260 mmol) at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with a saturated solution of sodium potassium tartrate. The reaction mixture was stirred at 23 °C for 0.5 h, and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (40% ethyl acetate in hexanes) to afford product **3-50** (7.2 mg, 25.1 μmol, 56% yield). $[\alpha]_D^{23}$ +1.88 (c 0.35, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36–7.27 (m, 3H), 7.23–7.18 (m, 4H), 7.16–7.12 (m, 1H), 7.03–7.00 (m, 2H), 4.51 (d, J = 12.2 Hz, 1H), 4.12 (dd, J = 12.2, 1.6 Hz, 1H), 3.85 (virt. dt, J = 10.2, 1.9 Hz, 1H), 3.21 (s, 3H), 2.87 (ddd, J = 14.4, 9.9, 5.0 Hz, 1H), 2.49 (ddd, J = 13.8, 9.4, 7.3 Hz, 1H), 1.75–1.57 (m, 2H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm): 141.6, 138.4, 128.5, 128.34, 128.27, 127.9, 126.7, 125.8, 81.3, 78.8, 61.3, 50.6, 32.7, 32.4. LRMS-FD (m/z): $[M+H]^+$ calcd for $C_{18}H_{23}O_3$, 287; found, 287.



(*R*)-2-Cyclohexyl-2-methoxy-2-phenylacetic acid (3-9'). Thionyl chloride (20 μL, 32.8 mg, 0.276 mmol) and pyridine (30 μL, 29.4 mg, 0.372 mmol) were added sequentially to a solution of **3-41 methyl ester** (22.9 mg, 82.3 μmol) in THF (1 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 2 h and quenched with water, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was concentrated to afford crude alkene product **3-51** (21.1 mg). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.56–7.50 (m, 2H), 7.36–7.29 (m, 2H), 7.31–7.25 (m,

1H), 5.99 (virt. tt, J = 3.8, 1.6 Hz, 1H), 3.72 (s, 3H), 3.31 (s, 3H), 2.21-2.15 (m, 2H), 1.81-1.75 (m, 2H), 1.63–1.56 (m, 4H). The product was directly used to the next step without further characterization.

A solution of crude product **3-51** (21.1 mg), 10% Pd/C (8.8 mg, 8.30 μmol) in MeOH (1 mL) was stirred at 23 °C under 1 atm of hydrogen atmosphere for 18 h. The mixture was then filtered through a pad of celite and rinsed with ethyl acetate. The combined filtrate was concentrated to afford the crude product **3-52** (19.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.46–7.40 (m, 2H), 7.37–7.32 (m, 2H), 7.31–7.27 (m, 1H), 3.82 (s, 3H), 3.19 (s, 3H), 2.10 (tt, J = 12.0, 2.9 Hz, 1H), 1.89–1.81 (m, 1H), 1.75–1.52 (m, 4H), 1.30–1.11 (m, 2H), 1.06–0.94 (m, 1H), 0.96–0.77 (m, 2H). The product was directly used to the next step without further characterization.

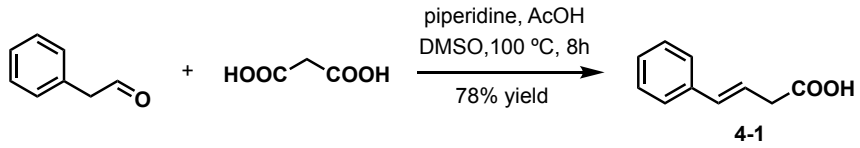
A solution of crude product **3-52** (19.0 mg) and KOH (56.0 mg, 1.00 mmol) in a mixture of MeOH-H_2O (3:1, 1.0 mL) was heated for 40 h at 80 °C. After cooling, the reaction mixture was extracted with ether. Then the aqueous phase was acidified, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated to product 2h (13.1 mg, 52.8 μmol, 64% combined yield over 3 steps). $[\alpha]_D^{23}$ +4.2 (c 0.62, $CHCl_3$). Ee: 83% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_1=16.5 min (major); t_2=20.2 min).

7.4 Enantioselective and Regioselective Alkylation of β,γ-Unsaturated Carboxylic Acids

Preparation of Substrates: β,γ-Unsaturated Carboxylic Acids

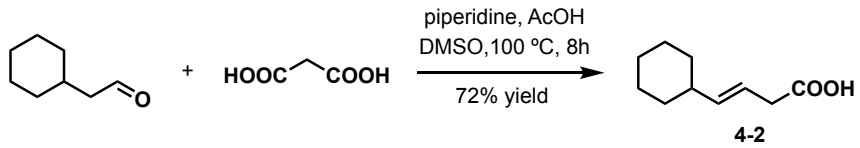
"General Procedure IV" (Aldol Condensation)

4-1, **4-2**, and the starting materials of **4-24~26** were prepared using the following procedure.[2]



4-1

To a stirred solution of phenylacetaldehyde (18.5 mL, 20.0 g, 0.167 mol, 1.0 equiv) in DMSO (1M), malonic acid (19.1 g, 0.183 mol, 1.1 equiv), piperidine (0.32 mL) and acetic acid (0.19 mL) were added in one portion. The mixture was heated at 100 °C for 8 h and then poured into water. After extraction with ethyl acetate for three times, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude material was purified by recrystallization (hexanes/ethyl acetate) to afford product **4-1** (21.1g, 0.130 mol, 78% yield). The spectral data matched with those reported in the literature.[3]

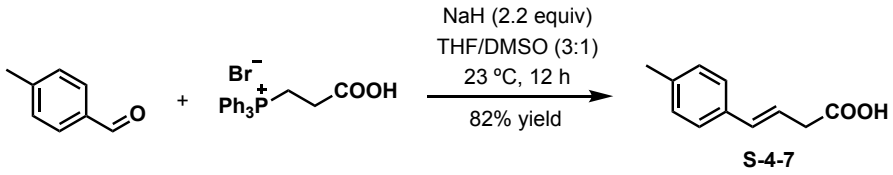


4-2

To a stirred solution of 2-cyclohexylacetaldehyde (2.00 g, 15.8 mol, 1.0 equiv) in DMSO (1M), malonic acid (1.81 g, 17.4 mmol, 1.1 equiv), piperidine (48 μL) and acetic acid (30 μL) were added in one portion. The mixture was heated at 100 °C for 8 h and then poured into water. After extraction with ethyl acetate for three times, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **4-2** (1.92 g, 11.4 mol, 72% yield). The spectral data matched with those reported in the literature.[2]

"General Procedure V" (Wittig Reaction)

The starting materials of **4-7~19, 4-28** were prepared using the following procedure.[2]

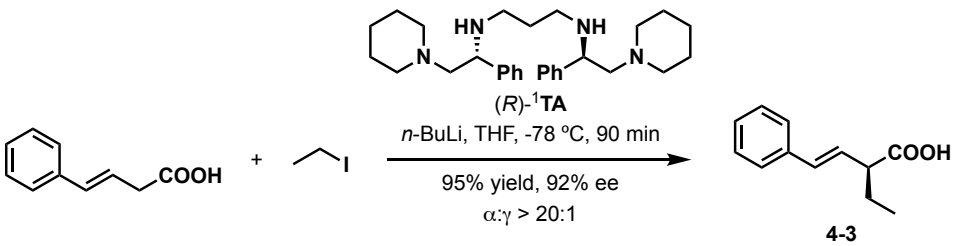


S-4-7

To a suspension of 2-(carboxyethyl)triphenylphosphonium bromide[4] (9.14 g, 22.0 mmol, 1.1 equiv) in THF/DMSO (v/v=3:1, 80 mL), sodium hydride (60% in mineral oil, 1.76 g, 44.0 mmol, 2.2 equiv) was added at room temperature (23 °C). After the evolution of hydrogen gas, 4-methylbenzaldehyde (2.4 mL, 2.40 g, 20.0 mmol, 1.0 equiv) was added dropwise at this temperature. The resulting mixture was stirred at room temperature overnight and then acidified with 1M HCl. After extraction with ethyl acetate for three times, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **S-4-7** (1.92 g, 11.4 mol, 72% yield). The spectral data matched with those reported in the literature.[3]

The starting materials of **4-21**,[5] **4-22**,[6] **4-23**,[7] **4-27**,[8] were prepared using the procedures described in the corresponding references. The starting materials of **4-29**, **4-30** are commercially available.

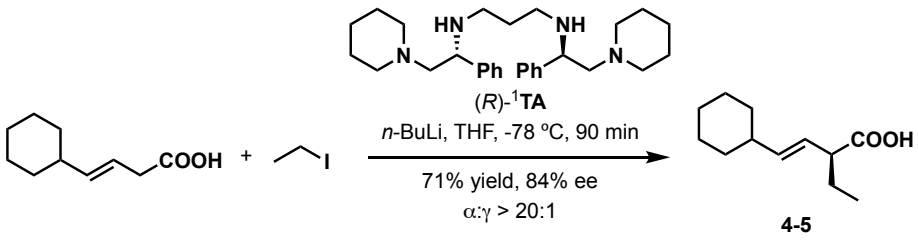
Selective Alkylation on β,γ-Unsaturated Carboxylic Acids



4-3

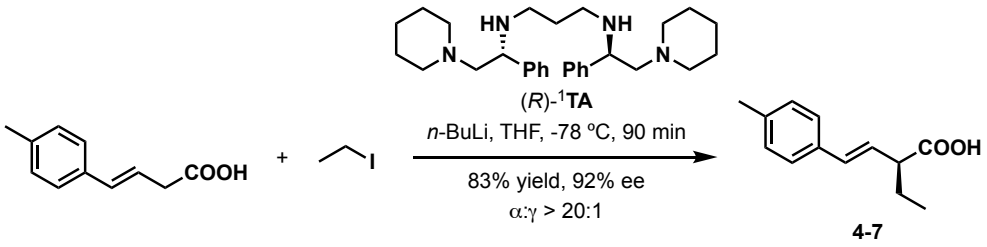
"General Procedure VI"

(*S*,*E*)-2-Ethyl-4-phenyl-3-butenoic acid (4-3). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol) and (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (4.0 mL) at 0 °C and the resulting mixture was stirred at this temperature for 45 min. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 80 min, then a mixture of THF-MeOH (3:1, 0.64 mL) was added at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous HCl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **4-3** (90.8 mg, 0.477 mmol, 95% yield). Ee 92% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=18.4 min (major); t_1=16.1 min). $[\alpha]_D^{23}$ +56.4 (*c* 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 8.9 Hz, 1H), 3.11 (dt, J = 9.0, 7.1 Hz, 1H), 1.91 (dqd, J = 13.4, 7.4, 7.2 Hz, 1H), 1.70 (ddq, J = 13.6, 7.5, 7.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 180.2, 136.7, 132.8, 128.5, 127.6, 126.8, 126.3, 51.0, 25.8, 11.6. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{12}H_{13}O_2Na_2$, 235.0711; found, 235.0718.

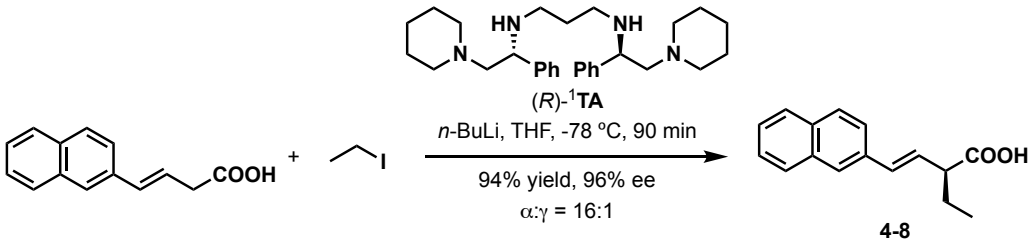


"General Procedure VII"

(*S*,*E*)-4-Cyclohexyl-2-ethyl-3-butenoic acid (4-5). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of (*E*)-4-cyclohexyl-3-butenoic acid (84.1 mg, 0.500 mmol) and (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (4.0 mL) at 0 °C and the resulting mixture was warmed to room temperature (23 °C) and stirred for 45 min. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for 80 min and quenched with a THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous HCl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (1-2% methanol in dichloromethane) to afford product **2b** (69.2 mg, 0.353 mmol, 71% yield). Ee 84% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 215 nm; t_2=5.2 min (major); t_1=4.9 min). $[\alpha]_D^{23}$ +56.4 (*c* 0.94, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.52 (dd, J = 15.5, 6.6 Hz, 1H), 5.35 (dd, J = 15.5, 8.7 Hz, 1H), 2.84 (virt. q, J = 7.7 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.85 – 1.56 (m, 6H), 1.53 (dqd, J = 14.5, 7.3, 7.0 Hz, 1H), 1.35 – 0.97 (m, 5H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 181.1, 140.0, 124.3, 50.8, 40.6, 32.84, 32.78, 26.1, 26.0, 25.7, 11.5. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{12}H_{19}O_2Na_2$, 241.1180; found, 241.1176.



(*S*,*E*)-2-Ethyl-4-(p-tolyl)-3-butenoic acid (4-7). The title compound was prepared according to **general procedure VI** using (*E*)-4-(*p*-tolyl)-3-butenoic acid (88.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-7** (84.5 mg, 0.414 mmol, 83% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 92% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 225 nm; t_2=12.5 min (major); t_1=8.6 min). $[\alpha]_D^{23}$ +88.2 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.49 (d, J = 15.8 Hz, 1H), 6.14 (dd, J = 15.8, 9.0 Hz, 1H), 3.09 (dt, J = 9.1, 7.3 Hz, 1H), 1.91 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.70 (ddq, J = 14.8, 7.4, 7.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ (ppm) 180.7, 137.4, 133.9, 132.7, 129.2, 126.2, 125.6, 51.1, 25.8, 21.2, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{13}H_{15}O_2$, 203.1072; found, 203.1066.



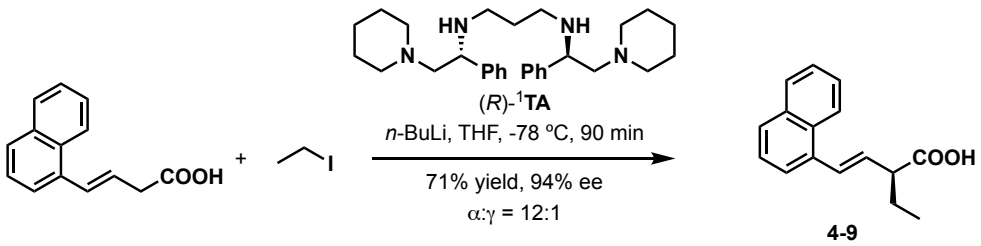
(*S*,*E*)-2-Ethyl-4-(naphthalen-2-yl)-3-butenoic acid (4-8). The title compound was prepared according to **general procedure VI** using (*E*)-4-(naphthalene-2-yl)-3-butenoic acid (0.106 g, 0.500 mmol), (R)-^{1}TA (0.231 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16

mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-8** (0.113 g, 0.470 mmol, 94% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 96% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=15.9 min (major); t_1=13.0 min). $[\alpha]_D^{23}$ +67.5 (c 0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.83 – 7.75 (m, 3H), 7.73 (s, 1H), 7.63– 7.57 (m, 1H), 7.51 – 7.40 (m, 2H), 6.68 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 8.9 Hz, 1H), 3.17 (virt. q, J = 7.7 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.81 – 1.69 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.7, 134.1, 133.5, 133.00, 132.96, 128.2, 128.0, 127.6, 127.1, 126.3, 126.2, 125.9, 123.5, 51.0, 25.8, 11.7. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{16}H_{15}O_2Na_2$, 285.0867; found, 285.0856.

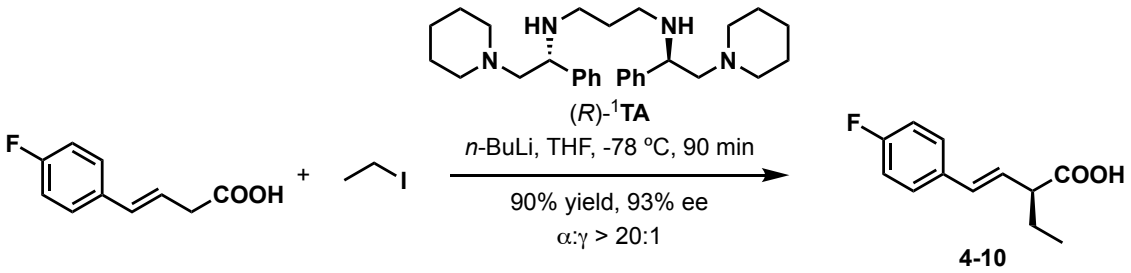
One-gram Scale Synthesis of 4-8

A solution of *n*-BuLi (8.0 mL, 2.50 M in hexanes, 20.0 mmol, 4.0 equiv) was added dropwise to a solution of (*E*)-4-phenyl-3-butenoic acid (1.06 g, 5.00 mmol) and (*R*)-**^{1}TA** (2.31 g, 5.15 mmol, 1.03 equiv) in THF (40.0 mL) at 0 °C and the resulting mixture was stirred at this temperature for 45 min. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Iodoethane (1.6 mL, 3.12 g, 20.0 mmol, 4.0 equiv) was added to the above reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 80 min before a quench with a mixture of THF-MeOH (3:1, 6.4 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column

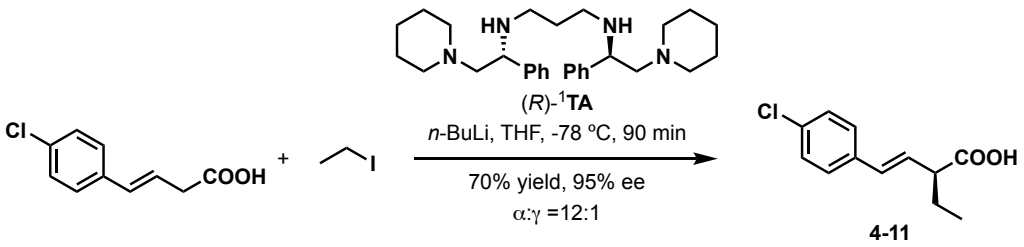
chromatography on silica gel (2% methanol in dichloromethane) to afford product **4-8** (1.08 g, 4.49 mmol, 90% yield). Ee 90% (measured as in the preceding experiment).



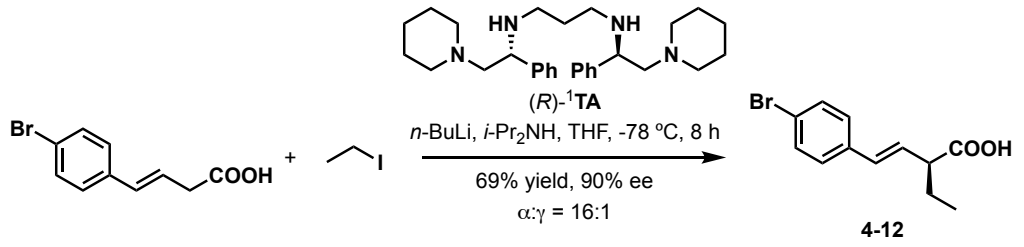
(*S*,*E*)-2-Ethyl-4-(naphthalen-1-yl)-3-butenoic acid (4-9). The title compound was prepared according to **general procedure VI** using (*E*)-4-(naphthalene-1-yl)-3-butenoic acid (0.106 g, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-9** (85.3 mg, 0.355 mmol, 71% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Er 94% ee (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=62.1 min (major); t_1=40.9 min). $[\alpha]_D^{23}$ +65.9 (*c* 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 7.1 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.27 (d, J = 15.6 Hz, 1H), 6.23 (dd, J = 15.6, 9.0 Hz, 1H), 3.27 (virt. q, J = 7.7 Hz, 1H), 2.07 – 1.92 (m, 1H), 1.88 – 1.72 (m, 1H), 1.06 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 179.7, 134.5, 133.6, 131.0, 130.2, 130.0, 128.5, 128.0, 126.1, 125.8, 125.6, 124.0, 123.7, 51.2, 25.9, 11.7. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{16}H_{15}O_2Na_2$, 285.0867; found, 285.0871.



(*S*,*E*)-2-Ethyl-4-(4-fluorophenyl)-3-butenoic acid (4-10). The title compound was prepared according to **general procedure VI** using (*E*)-4-(4-fluorophenyl)-3-butenoic acid (90.1 mg, 0.500 mmol), (R)-[1]TA (0.231 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-10** (94.1 mg, 0.452 mmol, 90% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 93% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=30.3 min (major); t_1=25.4 min). $[\alpha]_D^{23}$ +40.8 (*c* 0.96, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.31 (m, 2H), 7.03 – 6.96 (m, 2H), 6.47 (d, J = 15.9 Hz, 1H), 6.10 (dd, J = 15.9, 9.0 Hz, 1H), 3.09 (dt, J = 9.1, 7.2 Hz, 1H), 1.91 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.69 (ddq, J = 14.9, 7.5, 7.5 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ (ppm) 180.4, 162.3 (d, J = 246.9 Hz), 132.8 (d, J = 3.3 Hz), 131.6, 127.8 (d, J = 8.0 Hz), 126.5 (d, J = 2.3 Hz), 115.4 (d, J = 21.6 Hz), 51.0, 25.7, 11.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -114.4. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{12}H_{12}FO_2Na_2$, 253.0617; found, 253.0611.

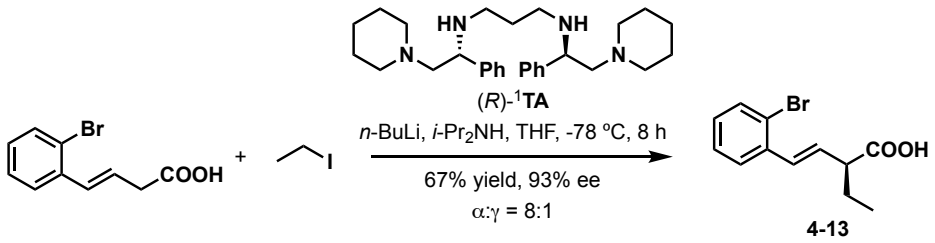


(*S*,*E*)-4-(4-Chlorophenyl)-2-ethyl-3-butenoic acid (4-11). The title compound was prepared according to **general procedure VI** using (*E*)-4-(4-chlorophenyl)-3-butenoic acid (98.3 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-11** (78.5 mg, 0.349 mmol, 70% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 95% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=36.7 min (major); t_1=29.3 min). $[\alpha]_D^{23}$ +45.0 (*c* 0.60, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.33 – 7.24 (m, 4H), 6.46 (d, J = 15.9 Hz, 1H), 6.16 (dd, J = 15.9, 9.0 Hz, 1H), 3.09 (dt, J = 9.0, 7.7 Hz, 1H), 1.91 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.70 (ddq, J = 14.8, 7.4, 7.4 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ (ppm) 180.2, 135.1, 133.3, 131.6, 128.7, 127.5, 127.4, 50.9, 25.7, 11.6. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{12}H_{12}ClO_2Na_2$, 269.0321; found, 269.0315.

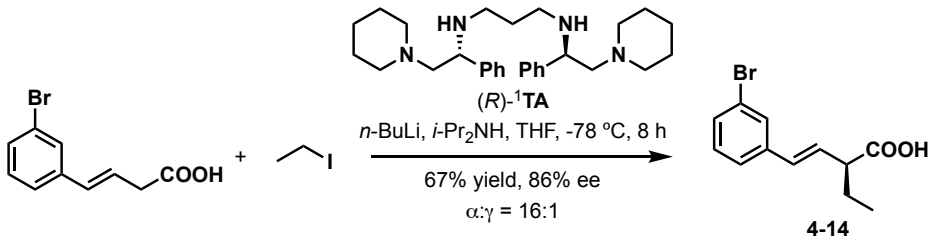


"General Procedure VIII"

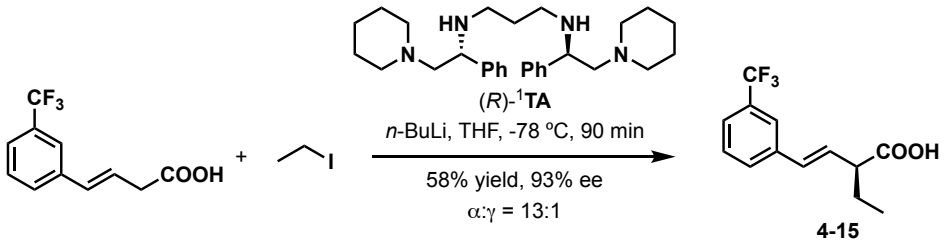
(*S*,*E*)-4-(4-Bromophenyl)-2-ethyl-3-butenoic acid (4-12). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of diisopropylamine (0.14 mL, 0.101 g, 1.00 mmol, 2.0 equiv) and (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.0 mL) at 0 °C and the reaction mixture was stirred for 30 min. Then, the solution of (*E*)-4-(4-bromophenyl)-3-butenoic acid (0.120 g, 0.500 mmol) in THF (1.0 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature (23 °C). After additional 45 min at 23 °C, the reaction mixture was cooled to –78 °C. After 5 min, iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) was added dropwise over 10 min. After 8 h, the reaction mixture was quenched with THF-MeOH (3:1, 0.64 mL). After 5 min, the reaction mixture was acidified with 1 M aqueous of HCl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (1-2% methanol in dichloromethane) to afford product **4-12** (92.8 mg, 0.345 mmol, 69% yield). Ee 90% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_1=70.1 min (major); t_2=83.5 min). $[\alpha]_D^{23}$ +28.7 (*c* 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.45 – 7.39 (m, 2H), 7.25 – 7.21 (m, 2H), 6.44 (d, J = 15.8 Hz, 1H), 6.18 (dd, J = 15.9, 8.9 Hz, 1H), 3.09 (dt, J = 9.0, 7.2 Hz, 1H), 1.91 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.69 (ddq, J = 14.9, 7.5, 7.5 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.9, 135.6, 131.7, 131.6, 127.9, 127.5, 121.4, 50.9, 25.7, 11.6. HRMS-ESI (m/z): $[M-H+2Na]^+$ calcd for $C_{12}H_{12}BrO_2Na_2$, 312.9816; found, 312.9811.



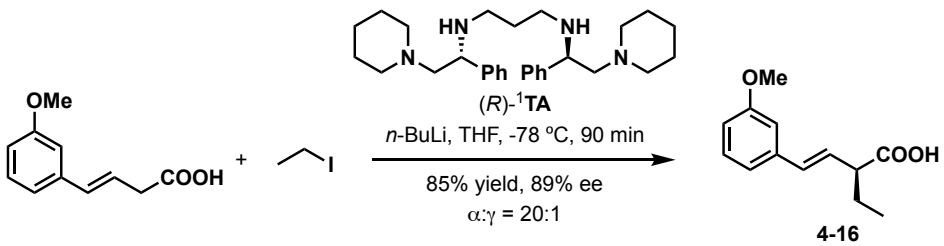
(*S*,*E*)-4-(2-Bromophenyl)-2-ethyl-3-butenoic acid (4-13). The title compound was prepared according to **general procedure VIII** using diisopropylamine (0.14 mL, 0.101 g, 1.00 mmol, 2.0 equiv), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.0 mL) followed by addition of a solution of (*E*)-4-(3-bromophenyl)-3-butenoic acid (0.120 g, 0.500 mmol) in THF (1.0 mL). After stirring at room temperature (23 °C) for 45 min, iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) was added at –78 °C over 10 min. The reaction was quenched after additional 8 h, and product **4-13** (90.2 mg, 0.335 mmol, 67% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=42.0 min (major); t_1=23.8 min). $[\alpha]_D^{23}$ +44.9 (*c* 0.87, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.56 – 7.49 (m, 2H), 7.29 – 7.23 (m, 1H), 7.13 – 7.06 (m, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.15 (dd, J = 15.8, 9.0 Hz, 1H), 3.18 (dt, J = 9.0, 7.6 Hz, 1H), 1.94 (ddq, J = 14.5, 7.4, 7.4 Hz, 1H), 1.72 (ddq, J = 14.8, 7.4, 7.4 Hz, 1H), 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.4, 136.6, 132.9, 131.7, 129.7, 128.9, 127.5, 127.1, 123.5, 50.9, 25.8, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{12}H_{12}BrO_2$, 267.0021; found, 267.0020.



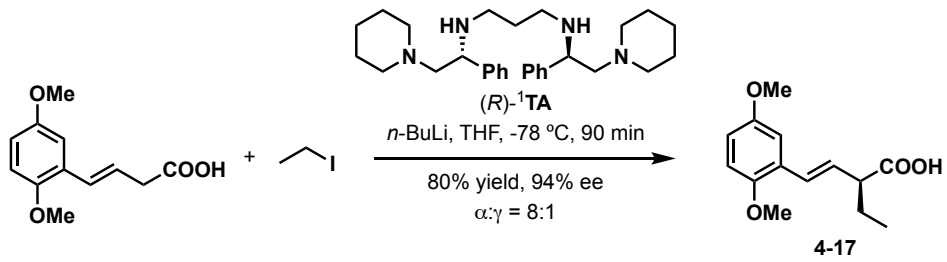
(*S*,*E*)-4-(3-Bromophenyl)-2-ethyl-3-butenoic acid (4-14). The title compound was prepared according to **general procedure VIII** using diisopropylamine (0.14 mL, 0.101 g, 1.00 mmol, 2.0 equiv), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), n-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.0 mL) followed by addition of a solution of (*E*)-4-(3-bromophenyl)-3-butenoic acid (0.120 g, 0.500 mmol) in THF (1.0 mL). After stirring at room temperature (23 °C) for 45 min, iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) was added at –78 °C over 10 min. The reaction was quenched after additional 8 h, and product **4-14** (89.6 mg, 0.333 mmol, 67% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 86% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=39.2 min (major); t_1=24.9 min). $[\alpha]_D^{23}$ +25.8 (*c* 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 (t, J = 1.8 Hz, 1H), 7.36 (ddd, J = 7.9, 2.0, 1.1 Hz, 1H), 7.28 (dt, J = 7.8, 1.4 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 15.9, 8.9 Hz, 1H), 3.10 (dt, J = 9.0, 7.2 Hz, 1H), 1.91 (ddq, J = 14.5, 7.4, 7.4 Hz, 1H), 1.70 (ddq, J = 14.9, 7.5, 7.4 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.7, 138.8, 131.4, 130.5, 130.0, 129.2, 128.4, 125.1, 122.7, 50.8, 25.7, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{12}H_{12}BrO_2$, 267.0021; found, 267.0010.



(*S*,*E*)-2-Ethyl-4-(3-trifluoromethylphenyl)-3-butenoic acid (4-15). The title compound was prepared according to **general procedure VI** using (*E*)-4-(3-trifluoromethylphenyl)-3-butenoic acid (0.115 g, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-15** (75.2 mg, 0.291 mmol, 58% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 93% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=19.0 min (major); t_1=13.9 min). $[\alpha]_D^{23}$ +34.8 (c 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (s, 1H), 7.58 – 7.38 (m, 3H), 6.54 (d, J = 15.9 Hz, 1H), 6.28 (dd, J = 15.9, 9.0 Hz, 1H), 3.13 (dt, J = 9.0, 7.7 Hz, 1H), 2.01 – 1.86 (m, 1H), 1.80 – 1.64 (m, 1H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.4, 137.4, 131.5, 129.51, 129.50, 129.0, 128.8, 124.2 (q, J = 3.9 Hz), 123.0 (q, J = 3.8 Hz), 50.8, 25.7, 11.6. ^{19}F NMR (376 MHz, CDCl3) δ (ppm) -62.8. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{13}H_{12}F_3O_2$, 257.0789; found, 257.0798.

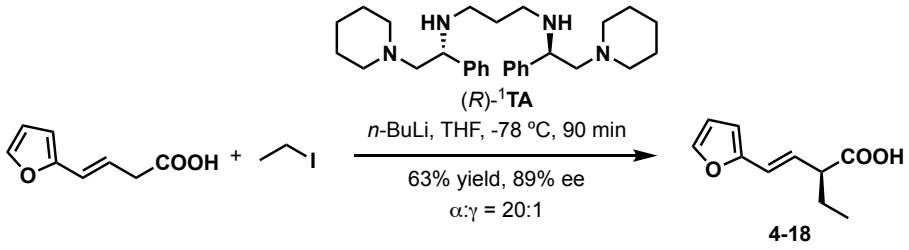


(*S*,*E*)-2-Ethyl-4-(3-methoxyphenyl)-3-butenoic acid (4-16). The title compound was prepared according to **general procedure VI** using (*E*)-4-(3-methoxyphenyl)-3-butenoic acid (96.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-16** (93.9 mg, 0.426 mmol, 85% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 89% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=27.7 min (major); t_1=14.0 min). $[\alpha]_D^{23}$ +38.0 (c 0.98, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.22 (t, J = 7.9 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 6.19 (dd, J = 15.8, 8.9 Hz, 1H), 3.82 (s, 3H), 3.10 (dt, J = 9.0, 7.7 Hz, 1H), 1.91 (ddq, J = 14.3, 7.2, 7.2 Hz, 1H), 1.70 (ddq, J = 14.6, 7.5, 7.5 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 179.8, 159.8, 138.1, 132.8, 129.5, 127.0, 119.1, 113.4, 111.5, 55.2, 50.9, 25.8, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{13}H_{15}O_2$, 219.1021; found, 219.1017.



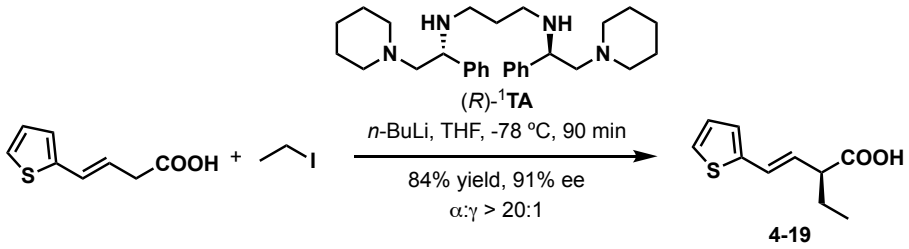
(*S*,*E*)-4-(2,5-Dimethoxyphenyl)-2-ethyl--3-butenoic acid (4-17). The title compound was prepared according to **general procedure VI** using (*E*)-4-(2,5-dimethoxyphenyl)-3-butenoic acid (0.111 g, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL,

2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after 80 min, and product **4-17** (0.100 g, 0.402 mmol, 80% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 94% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=20.8 min (major); t_1=17.8 min). $[\alpha]_D^{23}$ +44.2 (c 0.62, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, J = 2.9 Hz, 1H), 6.85 – 6.75 (m, 3H), 6.19 (dd, J = 16.0, 9.0 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.12 (dt, J = 8.8, 7.3 Hz, 1H), 1.91 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.70 (ddq, J = 14.8, 7.4, 7.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.1, 153.7, 151.1, 127.4, 126.5, 113.9, 112.3, 111.9, 105.0, 56.2, 55.8, 51.3, 25.9, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{14}H_{17}O_4$, 249.1127; found, 249.1122.



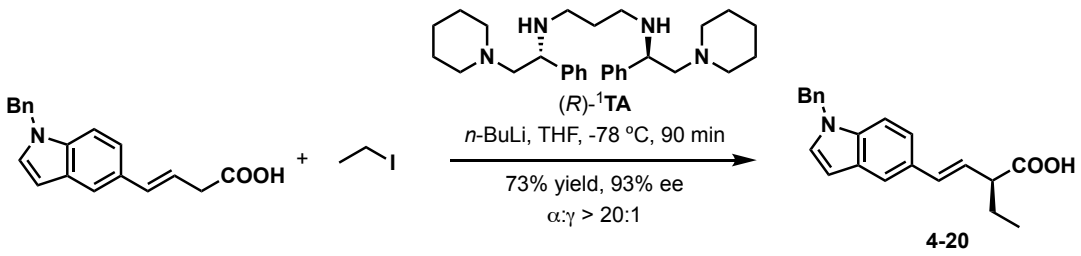
(*S*,*E*)-2-Ethyl-4-(furan-2-yl)-3-butenoic acid (4-18). The title compound was prepared according to **general procedure VI** using (*E*)-4-(furan-2-yl)-3-butenoic acid (76.2 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-18** (57.1 mg, 0.317 mmol, 63% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 89% (Chiralcel® OD-

H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=13.0 min (major); t_1=9.9 min). $[\alpha]_D^{23}$ +19.8 (c 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (d, J = 1.8 Hz, 1H), 6.35 (dd, J = 3.3, 1.8 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 6.22 (d, J = 3.3 Hz, 1H), 6.12 (dd, J = 15.8, 9.0 Hz, 1H), 3.04 (dt, J = 9.0, 7.2 Hz, 1H), 1.88 (ddq, J = 14.5, 7.3, 7.2 Hz, 1H), 1.68 (ddq, J = 14.9, 7.4, 7.4 Hz, 1H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 180.2, 152.1, 141.9, 125.3, 121.2, 111.2, 107.9, 50.7, 25.6, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{10}H_{11}O_3$, 179.0708; found, 179.0710.



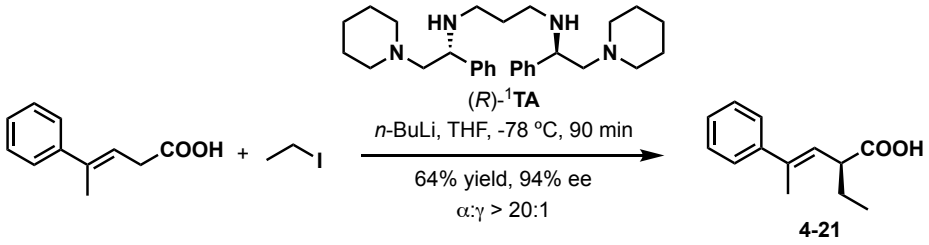
(*S*,*E*)-2-Ethyl-4-(thiophen-2-yl)-3-butenoic acid (4-19). The title compound was prepared according to **general procedure VI** using (*E*)-4-(thiophen-2-yl)-3-butenoic acid (84.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-19** (82.4 mg, 0.420 mmol, 84% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 91% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 225 nm; t_2=17.9 min (major); t_1=10.4 min). $[\alpha]_D^{23}$ +43.9 (c 0.72, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20 – 7.10 (m, 1H), 7.05 – 6.89 (m, 2H), 6.64 (d, J = 15.7 Hz, 1H), 6.02 (dd, J = 15.7, 8.9 Hz, 1H), 3.05 (dt, J = 9.4, 7.0 Hz, 1H), 1.90 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.69 (ddq, J

= 14.9, 7.5, 7.5 Hz, 1H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 180.4, 141.7, 127.3, 126.2, 126.0, 125.7, 124.2, 50.8, 25.7, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{10}H_{11}O_2S$, 195.0480; found, 195.0475.

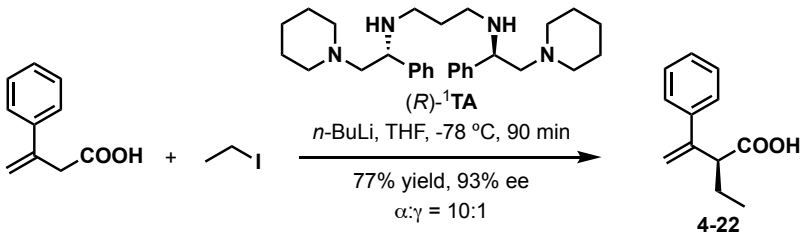


(*S*,*E*)-4-(1-Benzyl-1H-indol-5-yl)-2-ethyl-3-butenoic acid (4-20). The title compound was prepared according to **general procedure VI** using (*E*)-4-(1-benzyl-1H-indol-5-yl)-3-butenoic acid (0.146 g, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-20** (0.116 g, 0.365 mmol, 73% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 93% ee. (Determined by the HPLC analysis after a portion of **4-20** was reduced by lithium aluminum hydride in diethyl ether at 23 °C for 10 min to the corresponding alcohol). (Chiralcel® AD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 195 nm; t_2=17.0 min (major); t_1=15.0 min).) $[\alpha]_D^{23}$ +15.7 (c 1.04, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.33 – 7.22 (m, 4H), 7.20 (d, J = 8.6 Hz, 1H), 7.13 – 7.04 (m, 3H), 6.62 (d, J = 15.8 Hz, 1H), 6.52 (d, J = 3.1 Hz, 1H), 6.12 (dd, J = 15.8, 9.0 Hz, 1H), 5.30 (s, 2H), 3.11 (dt, J = 9.0, 7.3 Hz, 1H), 1.92 (ddq, J = 14.4, 7.3, 7.2 Hz, 1H), 1.70 (ddq, J = 14.8, 7.4, 7.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.8, 137.4,

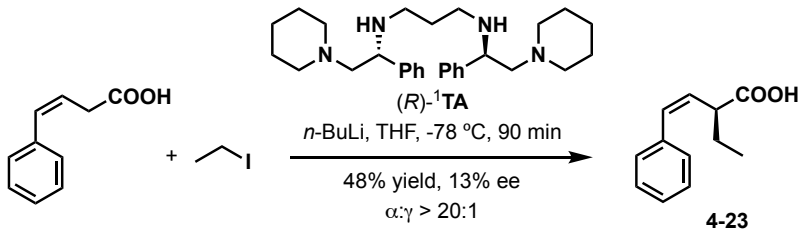
136.0, 133.8, 128.9, 128.8, 128.7, 128.6, 127.6, 126.6, 123.9, 120.2, 119.4, 109.8, 102.0, 51.2, 50.1, 25.9, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{21}H_{20}NO_2$, 318.1494; found, 318.1501.



(*S*,*E*)-2-Ethyl-4-phenylpent-3-enoic acid (4-21). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenylpent-3-enoic acid (88.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-21** (65.3 mg, 0.383 mmol, 64% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 220 nm; t_2=40.8 min (major); t_1=21.2 min). $[\alpha]_D^{23}$ +62.8 (c 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.43 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 7.29 – 7.21 (m, 1H), 5.74 (dq, J = 9.7, 1.4 Hz, 1H), 3.37 (dt, J = 9.6, 7.2 Hz, 1H), 2.11 (d, J = 1.4 Hz, 3H), 1.91 (ddq, J = 14.3, 7.4, 7.4 Hz, 1H), 1.68 (ddq, J = 14.6, 7.5, 7.5 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 179.9, 143.1, 138.2, 128.2, 127.2, 125.9, 125.1, 46.8, 26.1, 16.4, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{13}H_{15}O_2$, 203.1072; found, 203.1068.

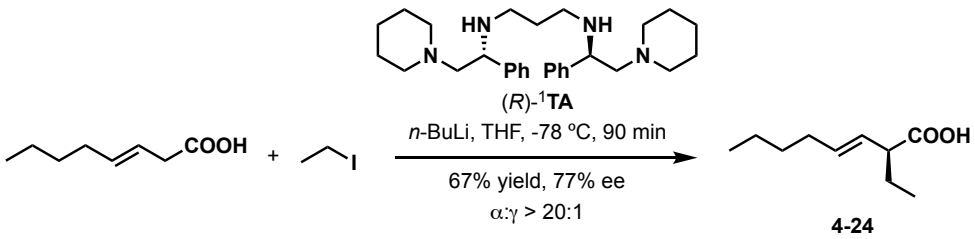


(*S*)-2-Ethyl-3-phenyl-3-butenoic acid (4-22). The title compound was prepared according to **general procedure VI** using 3-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-22** (72.9 mg, 0.383 mmol, 77% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 254 nm; t_1=15.7 min (major); t_2=21.3 min). $[\alpha]_D^{23}$ +54.5 (c 1.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.44 – 7.40 (m, 2H), 7.36 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 5.45 (s, 1H), 5.33 (s, 1H), 3.47 (t, J = 7.4 Hz, 1H), 1.96 (ddq, J = 14.9, 7.5, 7.5 Hz, 1H), 1.75 (ddq, J = 14.1, 6.9, 6.9 Hz, 1H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.1, 146.3, 141.2, 128.3, 127.7, 126.5, 115.1, 51.9, 25.2, 12.2. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{12}H_{13}O_2$, 189.0916; found, 189.0909.



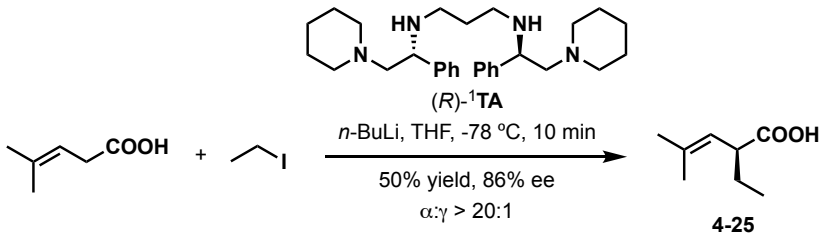
(*S*,*Z*)-2-Ethyl-4-phenyl-3-butenoic acid (4-23). The title compound was prepared according to **general procedure VI** using (*Z*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500

mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min and product **4-23** (36.7 mg, 0.193 mmol, 48% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 13% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=31.1 min (major); t_1=14.4 min). $[\alpha]_D^{23}$ –40.4 (*c* 1.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.29 (m, 4H), 7.22 – 7.15 (m, 1H), 6.67 (d, J = 11.5 Hz, 1H), 5.66 (t, J = 11.0 Hz, 1H), 3.53 (dt, J = 10.6, 7.0 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.69 – 1.57 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 180.1, 136.5, 132.1, 128.9, 128.7, 128.3, 127.2, 45.9, 26.3, 11.4. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{12}H_{13}O_2$, 189.0916; found, 189.0912.



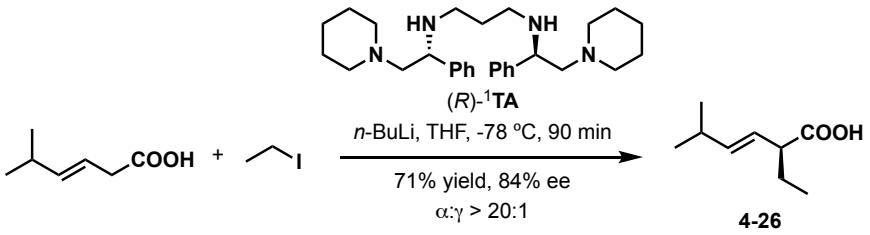
(*S*,*E*)-2-Ethyl-3-octenoic acid (4-24). The title compound was prepared according to **general procedure VI** using (*E*)-3-octenoic acid (71.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-24** (56.8 mg, 0.334 mmol, 67% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 77% (Chiralcel® AD-H; 2% *i*-PrOH in

hexanes; flow rate = 1.0 mL/min; detection at 190 nm; t_2=7.6 min (major); t_1=7.2 min). $[\alpha]_D^{23}$ +42.0 (*c* 1.03, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.57 (dt, J = 15.2, 6.7 Hz, 1H), 5.40 (ddt, J = 15.4, 8.8, 1.4 Hz, 1H), 2.87 (q, J = 7.5 Hz, 1H), 2.03 (q, J = 7.1 Hz, 2H), 1.78 (ddq, J = 14.4, 7.3, 7.3 Hz, 1H), 1.55 (ddq, J = 13.7, 7.5, 7.5 Hz, 1H), 1.43 – 1.20 (m, 4H), 0.99 – 0.83 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.8, 134.3, 126.7, 50.7, 32.1, 31.3, 25.6, 22.2, 13.9, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{10}H_{17}O_2$, 169.1228; found, 169.1221.

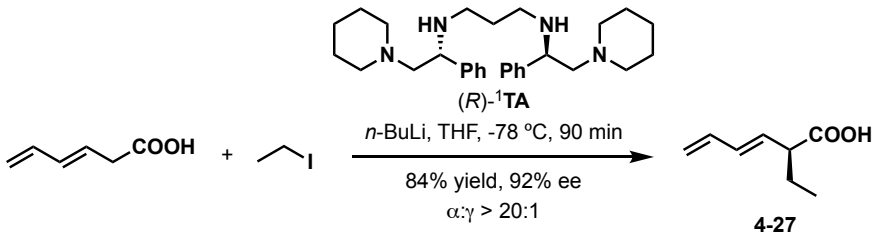


(*S*)-2-Ethyl-4-methyl-3-pentenoic acid (4-25). The title compound was prepared according to **general procedure VII** using 4-methyl-3-pentenoic acid (57.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched immediately, and product **4-25** (35.7 mg, 0.251 mmol, 50% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 86% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=8.0 min (major); t_1=7.5 min). $[\alpha]_D^{23}$ +149.9 (c 0.98, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 5.11 (dp, J = 9.5, 1.4 Hz, 1H), 3.14 (dt, J = 9.5, 7.2 Hz, 1H), 1.78 (ddq, J = 13.4, 7.2, 7.2 Hz, 1H), 1.74 (d, J = 1.4 Hz, 3H), 1.67 (d, J = 1.4 Hz, 3H), 1.52 (ddq, J = 13.4, 7.5, 7.5 Hz, 1H), 0.91 (t, J = 7.4

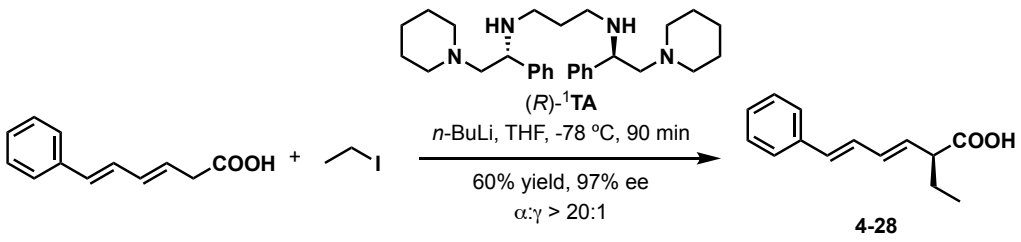
Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 181.2, 135.6, 121.9, 46.3, 26.0, 25.8, 18.2, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_8H_{13}O_2$, 141.0916; found, 141.0915.



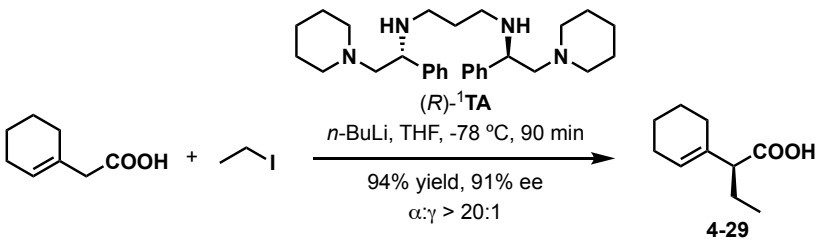
(*S*,*E*)-2-Ethyl-5-methylhex-3-enoic acid (4-26). The title compound was prepared according to **general procedure VII** using (*E*)-5-methylhex-3-enoic acid (64.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-26** (55.4 mg, 0.355 mmol, 71% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 84% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 197 nm; t_2=7.5 min (major); t_1=6.9 min). $[\alpha]_D^{23}$ +56.7 (*c* 1.18, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (dd, J = 15.4, 6.6 Hz, 1H), 5.35 (ddd, J = 15.4, 8.8, 1.4 Hz, 1H), 2.85 (dt, J = 8.2, 7.5 Hz, 1H), 2.28 (dqqd, J = 6.7, 6.7, 6.7, 1.2 Hz, 1H), 1.78 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.54 (ddq, J = 13.4, 7.5, 7.5 Hz, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 181.0, 141.1, 123.9, 50.7, 31.0, 25.7, 22.32, 22.28, 11.5. LRMS-ESI (m/z): $[M-H]^-$ calcd for $C_9H_{15}O_2$, 155.1; found, 155.1.



(*S*,*E*)-2-Ethylhexa-3,5-dienoic acid (4-27). The title compound was prepared according to **general procedure VII** using (*E*)-hexa-3,5-dienoic acid (56.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-27** (58.9 mg, 0.420 mmol, 84% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 92% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 220 nm; t_2=10.8 min (major); t_1=9.7 min). $[\alpha]_D^{23}$ +135.4 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.32 (dt, J = 17.0, 10.3 Hz, 1H), 6.16 (dd, J = 15.4, 10.4 Hz, 1H), 5.68 (dd, J = 15.3, 8.9 Hz, 1H), 5.19 (d, J = 16.9 Hz, 1H), 5.08 (d, J = 10.0 Hz, 1H), 2.97 (dt, J = 8.9, 7.3 Hz, 1H), 1.83 (ddq, J = 14.6, 7.4, 7.4 Hz, 1H), 1.62 (ddq, J = 13.6, 7.4, 7.4 Hz, 1H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.0, 136.3, 133.7, 130.6, 117.3, 50.5, 25.6, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_8H_{11}O_2$, 139.0759; found, 139.0765.

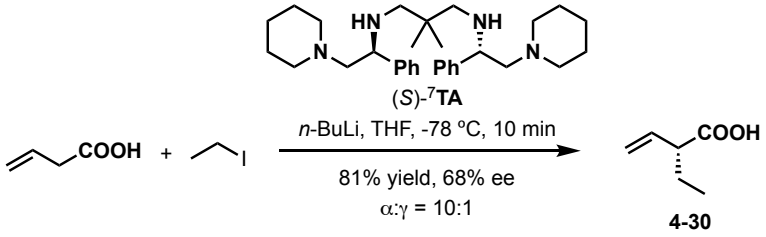


(*R,3E,5E*)-2-Ethyl-6-phenylhexa-3,5-dienoic acid (4-28). The title compound was prepared according to **general procedure VI** using (3*E,5E*)-6-phenylhexa-3,5-dienoic acid (90.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-28** (65.0 mg, 0.301 mmol, 60% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 97% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% Et_3N; flow rate = 1.0 mL/min; detection at 210 nm; t_2=13.2 min (major); t_1=11.8 min). $[\alpha]_D^{23}$ +109.3 (*c* 1.22, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.39 (d, J = 8.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.23 (t, J = 6.9 Hz, 1H), 6.77 (dd, J = 15.7, 10.4 Hz, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.33 (dd, J = 15.4, 10.3 Hz, 1H), 5.80 (dd, J = 15.3, 8.9 Hz, 1H), 3.04 (dt, J = 8.9, 7.2 Hz, 1H), 1.88 (ddq, J = 14.4, 7.1, 7.0 Hz, 1H), 1.67 (ddq, J = 13.6, 7.2, 6.9 Hz, 1H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 180.4, 137.1, 133.3, 132.5, 130.6, 128.6, 128.2, 127.5, 126.3, 50.7, 25.7, 11.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{14}H_{15}O_2$, 215.1072; found, 215.1071.



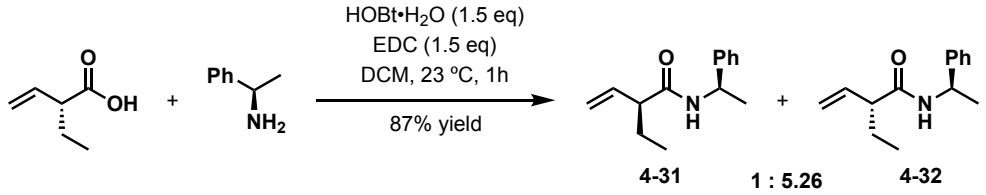
(*S*)-2-(Cyclohex-1-en-1-yl)butanoic acid (4-29). The title compound was prepared according to **general procedure VII** using 2-(cyclohex-1-en-1-yl)acetic acid (70.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodoethane (0.16 mL, 0.312 g, 2.00

mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-29** (79.3 mg, 0.471 mmol, 94% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 91% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_1=10.0 min (major); t_2=13.3 min). $[\alpha]_D^{23}$ +120.9 (*c* 0.71, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.63 (tt, J = 3.6, 1.6 Hz, 1H), 2.82 (t, J = 7.7 Hz, 1H), 2.10 – 1.94 (m, 4H), 1.80 (ddq, J = 14.8, 7.4, 7.3 Hz, 1H), 1.68 – 1.49 (m, 5H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 179.9, 134.4, 125.6, 54.9, 26.0, 25.4, 22.9, 22.8, 22.2, 12.0. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{10}H_{15}O_2$, 167.1072; found, 167.1066.

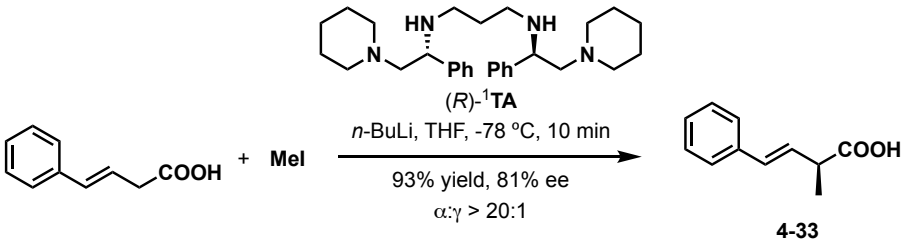


(*R*)-2-Ethyl-3-butenoic acid (4-30). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of 3-butenoic acid (43.0 mg, 0.500 mmol) and (*S*)-**^{7}TA** (0.246 g, 0.515 mmol, 1.03 equiv) in THF (4.0 mL) at 0 °C and the resulting mixture was stirred at this temperature for 90 min. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Iodoethane (0.16 mL, 0.312 g, 2.00 mmol, 4.0 equiv) was added dropwise over 10 min. Then, the resultant mixture was quenched immediately with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 °C. After 5 min, the mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel

(1% methanol in dichloromethane) to afford product **4-30** (46.3 mg, 0.406 mmol, 81% yield). Ee 68%. $[\alpha]_D^{23}$ –45.7 (*c* 1.01, $CHCl_3$)[9]. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.82 (ddd, J = 15.9, 11.4, 8.6 Hz 1H), 5.18 (d, J = 15.9 Hz, 1H), 5.17 (d, J = 11.4 Hz, 1H), 2.94 (dt, J = 8.6, 7.3 Hz, 1H), 1.82 (ddq, J = 14.5, 7.3, 7.3 Hz, 1H), 1.60 (ddq, J = 14.9, 7.5, 7.4 Hz, 1H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 180.6, 135.2, 117.8, 51.7, 25.2, 11.5. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_6H_9O_2$, 113.0603; found, 113.0609.

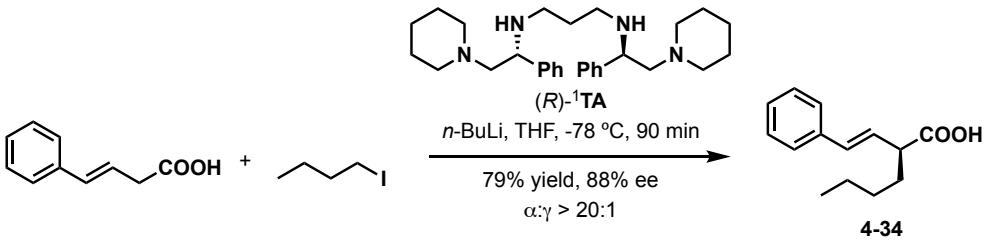


Determination of the enantiomeric excess of 4-30 (46.3 mg, 0.406 mmol) was dissolved in CH_2Cl_2 (2.0 mL) at room temperature (23 °C), then (*R*)-1-phenylehan-1-amine (54.2 mg, 0.447 mmol, 1.1 equiv), HOBt•H_2O (82.3 mg, 0.609 mmol, 1.5 equiv), and EDC (94.5 mg, 0.609 mmol, 1.5 equiv) were added. The resulting solution was kept stirring at room temperature for 1 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate = 5:1) to afford the product (76.8 mg, 87% yield), as a mixture of diastereomers **4-31** and **4-32** in 1:5.26 (16:84) ratio. Therefore, the ee of **4-30** is 68%.



4-33

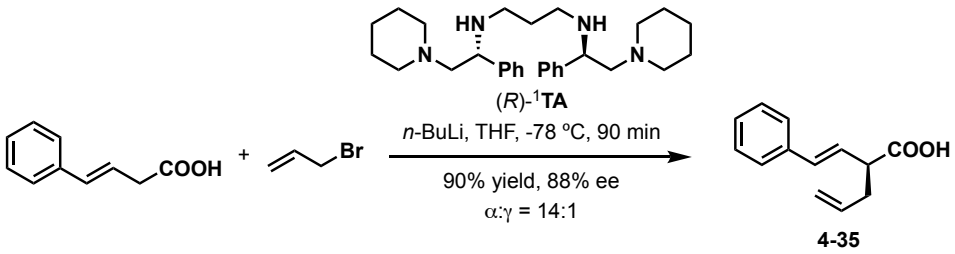
(*S*,*E*)-2-Methyl-4-phenyl-3-butenoic acid (4-33). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodomethane (0.12 mL, 0.284 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched immediately, and product **4-33** (82.1 mg, 0.466 mmol, 93% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 81% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=21.5 min (major); t_1=12.4 min). $[\alpha]_D^{23}$ +18.9 (c 1.01, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.38 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 6.53 (d, J = 15.9 Hz, 1H), 6.29 (dd, J = 15.9, 7.9 Hz, 1H), 3.36 (dq, J = 8.2, 7.0 Hz, 1H), 1.41 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 180.8, 136.7, 131.7, 128.5, 127.9, 127.6, 126.3, 43.0, 17.2. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{11}H_{11}O_2$, 175.0759; found, 175.0751.



4-34

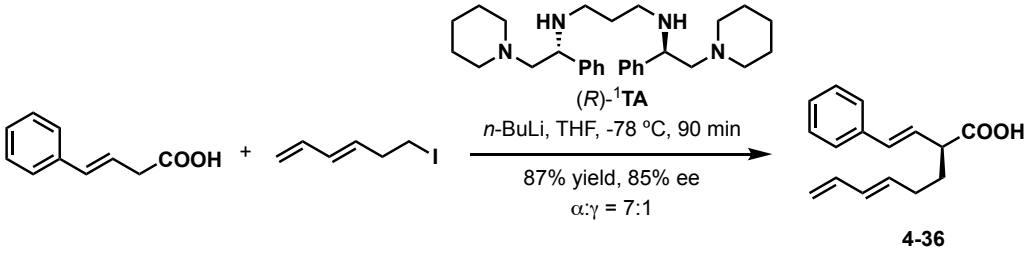
(*S*,*E*)-2-Styrylhexanoic acid (4-34). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA**

(0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of 1-iodobutane (0.368 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-34** (86.5 mg, 0.396 mmol, 79% yield) was obtained after purification by column chromatography on silica gel (3:1 hexanes/ethyl acetate). Ee 88% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=20.5 min (major); t_1=16.5 min). $[\alpha]_D^{23}$ +47.3 (c 0.54, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.34 (m, 2H), 7.35 – 7.27 (m, 2H), 7.27 – 7.19 (m, 1H), 6.50 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.8, 9.0 Hz, 1H), 3.17 (virt. q, J = 7.9 Hz, 1H), 1.96 – 1.81 (m, 1H), 1.73 – 1.59 (m, 1H), 1.43 – 1.27 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 180.5, 136.7, 132.7, 128.5, 127.6, 127.0, 126.3, 49.4, 32.2, 29.2, 22.4, 13.9. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{14}H_{17}O_2$, 217.1228; found, 217.1225.



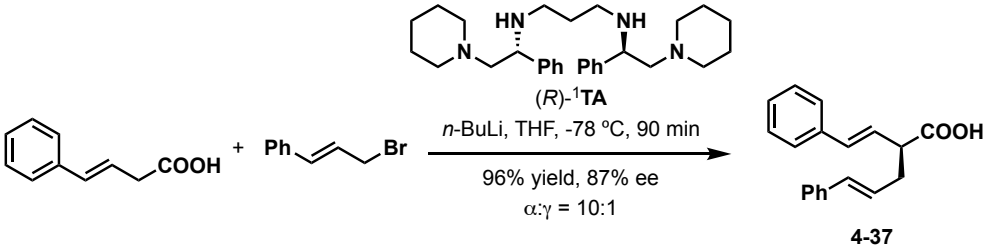
(*S*,*E*)-2-Styryl-4-pentenoic acid (4-35). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of allyl bromide (0.17 mL, 0.242 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-35** (91.0 mg, 0.450 mmol, 90% yield) was obtained after purification by column

chromatography on silica gel (3:1 hexanes/ethyl acetate). Ee 88% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=23.0 min (major); t_1=19.5 min). $[\alpha]_D^{23}$ +44.5 (c 0.54, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.34 (m, 2H), 7.35 – 7.27 (m, 2H), 7.27 – 7.19 (m, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 15.9, 8.8 Hz, 1H), 5.80 (ddt, J = 17.1, 10.1, 6.9 Hz, 1H), 5.14 (virt. dq, J = 17.1, 1.6 Hz, 1H), 5.08 (virt. dq, J = 10.2, 1.3 Hz, 1H), 3.29 (dt, J = 9.1, 6.8 Hz, 1H), 2.62 (dtt, J = 14.4, 7.3, 1.3 Hz, 1H), 2.45 (dtt, J = 14.0, 6.9, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 179.4, 136.5, 134.4, 133.1, 128.5, 127.7, 126.4, 126.1, 117.5, 49.1, 36.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{13}H_{13}O_2$, 201.0916; found, 201.0910.



(*S*,*E*)-2-((*E*)-Styryl)octa-5,7-dienoic acid (4-36). The title compound was prepared according to **general procedure VI** using (E)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of (E)-6-iodohexa-1,3-diene (0.125 g, 0.600 mmol, 1.20 equiv) in THF (1.0 mL) at –78 °C over 5 min. The reaction was quenched after additional 80 min, and product **4-36** (0.105 g, 0.435 mmol, 87% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 85% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes with 0.1% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=102.1 min (major); t_1=38.9 min). $[\alpha]_D^{23}$ +116.2 (c

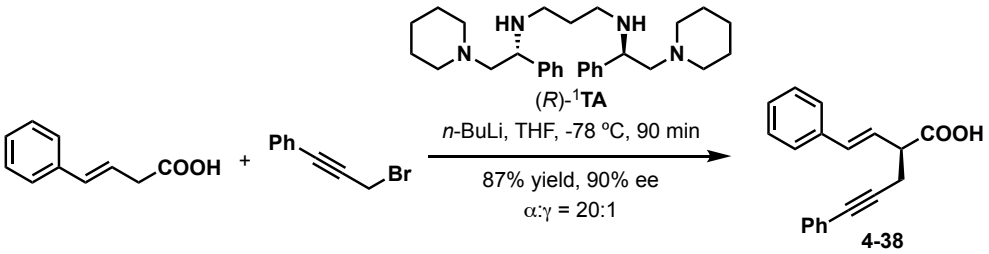
1.04, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.21 (m, 1H), 6.52 (d, J = 15.8 Hz, 1H), 6.32 (dt, J = 17.1, 10.3 Hz, 1H), 6.18 (dd, J = 15.8, 9.0 Hz, 1H), 6.09 (dd, J = 15.2, 10.4 Hz, 1H), 5.68 (dt, J = 14.6, 6.9 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.00 (d, J = 10.1 Hz, 1H), 3.22 (ddd, J = 8.8, 7.7, 6.7 Hz, 1H), 2.25 – 2.12 (m, 2H), 2.00 (ddt, J = 13.5, 8.8, 6.7 Hz, 1H), 1.77 (dtd, J = 13.9, 8.3, 6.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.1, 136.9, 136.5, 133.3, 133.2, 132.1, 128.6, 127.7, 126.40, 126.36, 115.4, 48.7, 31.7, 29.8. LRMS-ESI (m/z): $[M\text{-}CO_2H]^-$ calcd for $C_{15}H_{17}$, 197.1; found, 197.1.



4-37

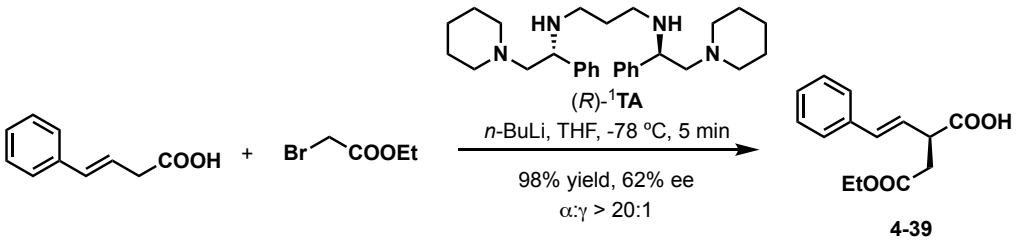
(*S*,*E*)-5-Phenyl-2-((*E*)-styryl)pent-4-enoic acid (4-37). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of (*E*)-(3-bromoprop-1-en-1-yl)benzene (0.394 g, 2.00 mmol, 4.0 equiv) in THF (1.0 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-37** (0.133 g, 0.479 mmol, 96% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 87% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=46.0 min (major); t_1=22.0 min). $[\alpha]_D^{23}$ +76.4 (c 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.38 – 7.34 (m, 2H), 7.34 – 7.26 (m, 5H), 7.26 – 7.16 (m, 3H), 6.55 (d, J = 15.9 Hz, 1H), 6.47 (d, J = 15.7 Hz, 1H), 6.23 (dd, J = 15.9, 8.8 Hz,

1H), 6.17 (dt, J = 15.4, 7.2 Hz, 1H), 3.35 (virt. q, J = 7.5 Hz, 1H), 2.76 (ddd, J = 14.4, 7.3, 7.3 Hz, 1H), 2.59 (ddd, J = 14.1, 6.9, 6.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 179.5, 137.2, 136.5, 133.2, 132.7, 128.55, 128.48, 127.8, 127.3, 126.4, 126.2, 126.06, 126.05, 49.5, 35.9. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{19}H_{17}O_2$, 277.1229; found, 277.1219.

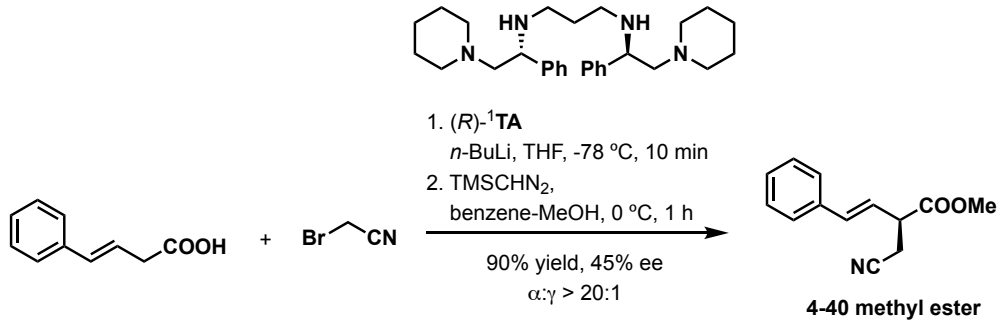


(*S*,*E*)-5-Phenyl-2-styrylpent-4-ynoic acid (4-38). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of (3-bromoprop-1-yn-1-yl)benzene (0.390 g, 2.00 mmol, 4.0 equiv) in THF (1.0 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-38** (0.120 g, 0.434 mmol, 87% yield) was obtained after purification by column chromatography on silica gel (2% methanol in dichloromethane). Ee 90% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=57.1 min (major); t_1=24.2 min). $[\alpha]_D^{23}$ +83.9 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.43 – 7.37 (m, 2H), 7.38 – 7.35 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.28 – 7.23 (m, 4H), 6.65 (d, J = 15.8 Hz, 1H), 6.29 (dd, J = 15.9, 8.6 Hz, 1H), 3.53 (virt. q, J = 7.5 Hz, 1H), 2.96 (dd, J = 16.8, 6.9 Hz, 1H), 2.83 (dd, J = 16.8, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 178.2, 136.4, 133.9, 131.6, 128.6, 128.2, 127.91,

127.88, 126.5, 125.0, 123.3, 86.1, 82.8, 48.5, 22.9. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{19}H_{15}O_2$, 275.1072; found, 275.1078.



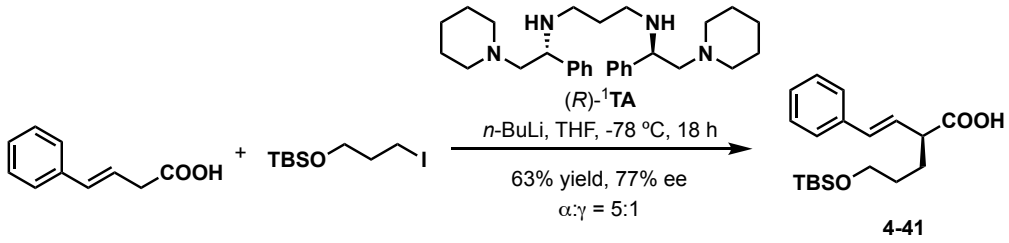
(*S*,*E*)-2-(2-Ethoxy-2-oxoethyl)-4-phenyl-3-butenoic acid (4-39). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of ethyl 2-bromoacetate (0.334 g, 2.00 mmol, 4.0 equiv) in THF (1.0 mL) at –78 °C over 5 min. The reaction was quenched immediately, and product **4-39** (0.122 g, 0.491 mmol, 98% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 62% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_2=70.1 min (major); t_1=67.9 min). $[\alpha]_D^{23}$ +67.8 (c 0.51, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39 – 7.33 (m, 2H), 7.34 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 6.59 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.9, 8.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.72 (ddd, J = 8.5, 8.5, 5.9 Hz, 2H), 2.93 (dd, J = 16.6, 8.5 Hz, 1H), 2.66 (dd, J = 16.6, 5.9 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 177.7, 171.1, 136.2, 133.7, 128.6, 128.0, 126.5, 124.7, 60.9, 44.7, 36.3, 14.1. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{14}H_{15}O_4$, 247.0970; found, 247.0963.



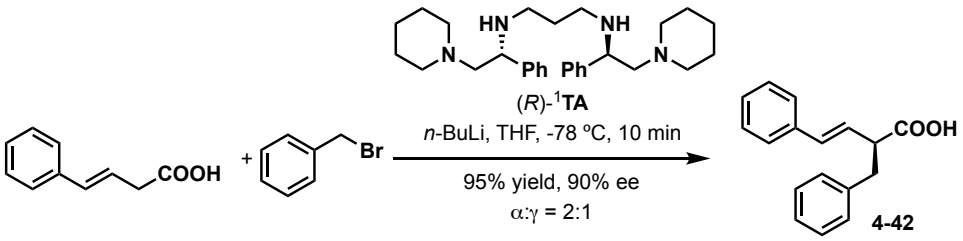
(*S*,*E*)-2-Cyanomethyl-4-phenyl-3-butenoic acid (4-40). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of 2-bromoacetonitrile (0.240 g, 2.00 mmol, 4.0 equiv) in THF (1.0 mL) at –78 °C over 10 min. The reaction was quenched immediately and crude product **4-40** was directly used for the next step.

Methyl (*S*,*E*)-2-(cyanomethyl)-4-phenylbut-3-enoate (4-40 methyl ester). The crude acid **5h** prepared as described in the preceding procedure was treated with $TMSCHN_2$ (0.34 mL, 2.96 M in hexanes, 1.00 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (2% methanol in dichloromethane) to afford product **4-40 methyl ester** (97.1 mg, 0.451 mmol, 90% yield over 2 steps). Ee 45% (Chiralcel® AD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 254 nm; t_1=26.1 min (major); t_2=30.1 min). $[\alpha]_D^{23}$ +72.8 (*c* 0.68, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.36 (m, 2H), 7.36 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 6.65 (d, J = 15.8 Hz, 1H), 6.16 (dd, J = 15.8, 8.6 Hz, 1H), 3.78 (s, 3H), 3.57 (virt. q, J = 7.5 Hz, 1H), 2.86 (dd, J = 16.8, 6.5 Hz, 1H), 2.75 (dd, J = 16.8, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.3, 135.6, 135.2, 128.7,

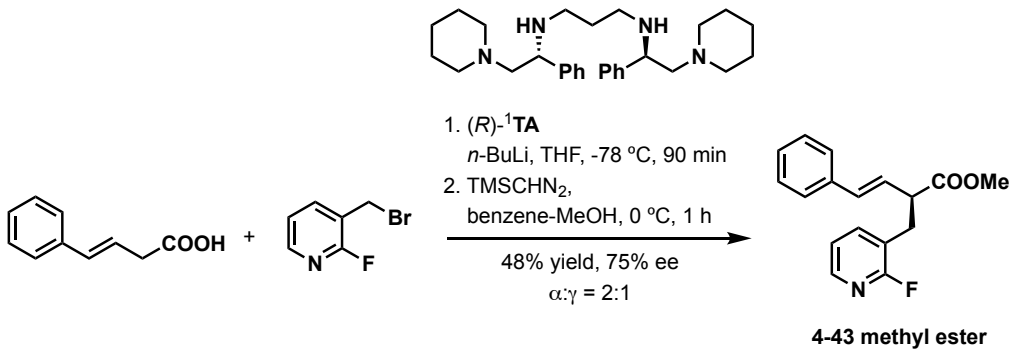
128.4, 126.6, 122.9, 117.3, 52.8, 45.3, 20.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{13}NO_2Na$, 238.0844; found, 238.0838.



(*S*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-styrylpentanoic acid (4-41). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of *tert*-butyl-(3-iodopropoxy)dimethylsilane (0.180 g, 0.600 mmol, 1.20 equiv) in THF (1.0 mL) at –78 °C over 10 min. The reaction was quenched after additional 18 h, and product **4-41** (92.1 mg, 0.275 mmol, 63% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 77% (Determined using methyl ester obtained from **4-41** and $TMSCHN_2$ in benzene-MeOH (4:1) at 0 °C for 1 h). (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 205 nm; t_2=5.9 min (major); t_1=5.3 min).) $[\alpha]_D^{23}$ +36.0 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.35 (m, 2H), 7.34 – 7.27 (m, 2H), 7.27 – 7.20 (m, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 8.9 Hz, 1H), 3.65 (t, J = 6.2 Hz, 2H), 3.21 (virt. q, J = 7.7 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.79 – 1.68 (m, 1H), 1.67 – 1.53 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.0, 136.6, 132.8, 128.6, 127.6, 126.9, 126.4, 62.7, 49.1, 30.1, 28.9, 25.9, 18.3, -5.3. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{19}H_{29}O_3Si$, 333.1886; found, 333.1875.



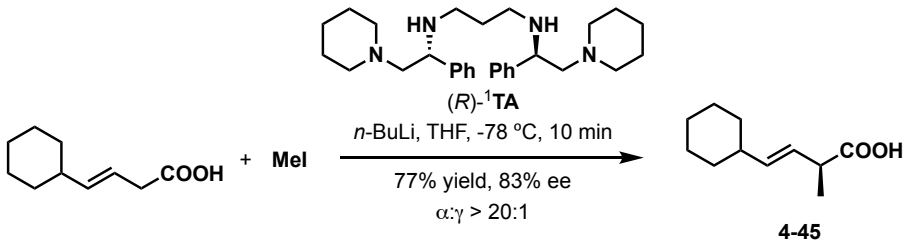
The mixture of **(*S*,*E*)-2-benzyl-4-phenyl-3-butenoic acid** and **(*E*)-4,5-diphenylpent-2-enoic acid** (**4-42**). The title mixture was prepared according to **general procedure VII** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of benzyl bromide (0.24 mL, 0.342 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched immediately, and the product was obtained as a mixture of α-isomer and γ-isomers, **4-42** (0.116 g, 0.459 mmol, 92% yield, α:γ=2:1) after purification by column chromatography on silica gel (3:1 hexanes/ethyl acetate). Er 90% (α-isomer); 40% (γ-isomer) (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; $t_1(\alpha)$=19.6 min; $t_2(\alpha)$=33.0 min; $t_1(\gamma)$=20.9 min; $t_2(\gamma)$=28.5 min). ^{1}H NMR (500 MHz, $CDCl_3$) (α-isomer) δ (ppm) 7.39 – 7.03 (m, 10H), 6.44 (d, J = 15.8 Hz, 1H), 6.23 (dd, J = 15.9, 8.7 Hz, 1H), 3.50 (virt. q, J = 7.8 Hz, 1H), 3.21 (dd, J = 13.8, 7.6 Hz, 1H), 2.97 (dd, J = 13.7, 7.4 Hz, 1H); (γ-isomer) δ (ppm) 7.39 – 7.03 (m, 11H), 5.70 (d, J = 15.6 Hz, 1H), 3.74 (virt. q, J = 7.6 Hz, 1H), 3.10 (d, J = 7.6 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm) 179.5, 171.7, 153.6, 141.1, 138.8, 138.2, 136.5, 133.3, 129.08, 129.05, 128.7, 128.5, 128.4, 128.3, 127.86, 127.7, 127.0, 126.6, 126.4, 126.3, 126.1, 120.6, 51.1, 50.4, 41.5, 38.6. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{17}H_{15}O_2$, 251.1072; found, 251.1062.



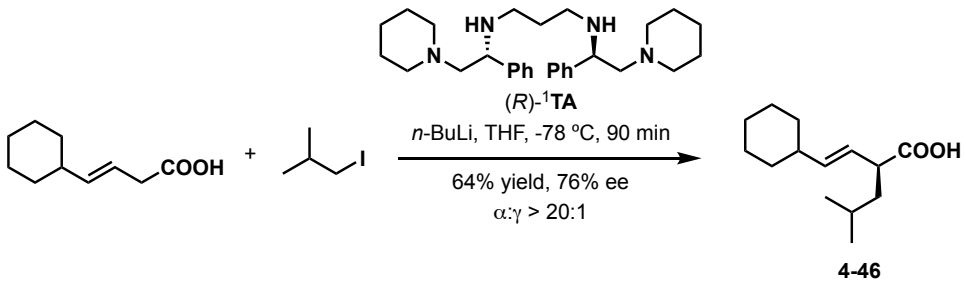
(*S*,*E*)-2-((2-Fluoropyridin-3-yl)methyl)-4-phenyl-3-butenoic acid (4-43). The title compound was prepared according to **general procedure VI** using (*E*)-4-phenyl-3-butenoic acid (81.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of a solution of 3-(bromomethyl)-2-fluoropyridine (0.114 g, 0.600 mmol, 1.20 equiv) in THF (1.0 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and crude product **4-43** (0.127 g) was directly used for the next step.

Methyl (*S*,*E*)-2-((2-fluoropyridin-3-yl)methyl)-4-phenylbut-3-enoate (4-43 methyl ester). The crude acid **5k** (0.127 g) prepared in the previous procedure was treated with $TMSCHN_2$ (0.34 mL, 2.96 M in hexanes, 1.00 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **4-43 methyl ester** (68.5 mg, 0.240 mmol, 48% yield over 2 steps). Ee 75% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=28.3 min (major), t_2=22.3 min). $[\alpha]_D^{23}$ +152.7 (*c* 1.10, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 4.7 Hz, 1H), 7.55 (t, J = 8.4 Hz, 2H), 7.31 – 7.15 (m, 3H), 7.04 (t, J = 5.8 Hz, 2H), 6.37 (d, J = 15.8 Hz, 1H), 6.14 (dd, J = 15.8, 8.9 Hz, 1H), 3.62 (s, 3H), 3.50 (virt. q, J = 7.9 Hz, 2H), 3.12 (dd, J = 13.9, 7.8 Hz, 1H), 2.93 (dd, J = 13.9, 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

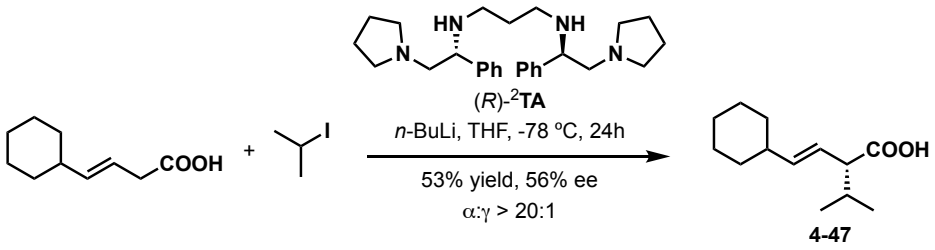
(ppm) 173.2, 162.1 (d, J = 238.5 Hz), 145.9 (d, J = 14.7 Hz), 141.9 (d, J = 5.6 Hz), 136.3, 133.5, 128.5, 127.8, 126.4, 125.7, 121.3 (d, J = 4.2 Hz), 120.5 (d, J = 30.7 Hz), 52.1, 49.2, 32.05 (d, J = 2.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -71.8 (d, J = 9.7 Hz). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{16}NO_2FNa$, 308.1063; found, 308.1068.



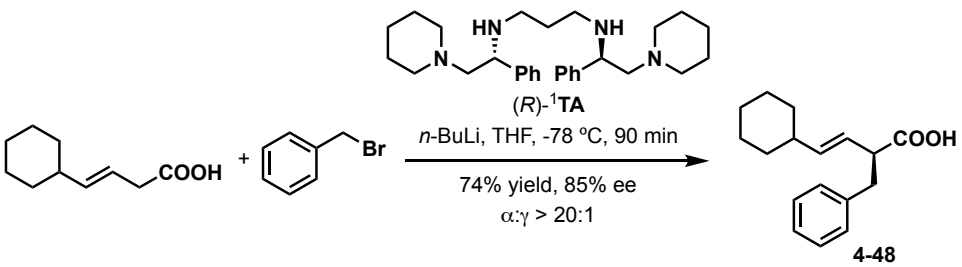
(*S*,*E*)-4-Cyclohexyl-2-methyl-3-butenoic acid (4-45). The title compound was prepared according to **general procedure VII** using (*E*)-4-cyclohexyl-3-butenoic acid (84.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of iodomethane (0.12 mL, 0.284 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched immediately, and product **4-45** (70.1 mg, 0.385 mmol, 77% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 83% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=5.6 min (major); t_1=5.3 min). $[\alpha]_D^{23}$ +25.2 (c 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.53 (dd, J = 15.6, 6.4 Hz, 1H), 5.45 (ddd, J = 15.5, 7.4, 1.0 Hz, 1H), 3.09 (dq, J = 7.2, 7.1 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.75 – 1.67 (m, 4H), 1.67 – 1.59 (m, 1H), 1.32 – 1.20 (m, 2H), 1.25 (d, J = 7.0 Hz, 3H), 1.20 – 1.10 (m, 1H), 1.12 – 1.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 181.6, 138.6, 125.7, 42.7, 40.5, 32.8, 26.1, 26.0, 17.3. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{11}H_{17}O_2$, 181.1228; found, 181.1225.



(*S*,*E*)-2-(2-Cyclohexylvinyl)-4-methylpentanoic acid (4-46). The title compound was prepared according to **general procedure VI** using (*E*)-4-cyclohexyl-3-butenoic acid (84.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of 1-iodo-2-methylpropane (0.23 mL, 0.368 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-46** (72.1 mg, 0.321 mmol, 64% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 76% (Chiralcel® OD-H; 0.3% *i*-PrOH in hexanes with 0.03% TFA; flow rate = 1.0 mL/min; detection at 190 nm; t_2=19.5 min (major); t_1=18.5 min). $[\alpha]_D^{19}$ +40.7 (*c* 1.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.52 (dd, J = 15.5, 6.6 Hz, 1H), 5.33 (dd, J = 15.5, 8.9 Hz, 1H), 3.02 (dt, J = 8.2, 8.0 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.75 – 1.67 (m, 4H), 1.63 – 1.57 (m, 2H), 1.44 – 1.36 (m, 1H), 1.32 – 1.01 (m, 6H), 0.91 (d, J = 6.1 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 181.3, 139.7, 124.7, 47.3, 41.4, 40.5, 32.83, 32.76, 26.1, 26.0, 25.5, 22.7, 22.0. LRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{14}H_{23}O_2$, 223.2; found, 223.4.



(*R*,*E*)-4-Cyclohexyl-2-isopropyl-3-butenoic acid (4-47). The title compound was prepared according **to general procedure VII** using (*E*)-4-cyclohexyl-3-butenoic acid (84.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.48 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of 2-iodopropane (0.20 mL, 0.340 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 24 h, and product **4-47** (55.4 mg, 0.263 mmol, 53% yield) was obtained after purification by column chromatography on silica gel (1-2% methanol in dichloromethane). Ee 56% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=5.1 min (major); t_1=4.8 min). $[\alpha]_D^{23}$ –28.4 (c 0.99, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 5.50 (dd, J = 15.5, 6.6 Hz, 1H), 5.36 (dd, J = 15.4, 9.5 Hz, 1H), 2.62 (virt. t, J = 8.9 Hz, 1H), 2.02 – 1.92 (m, 2H), 1.77 – 1.67 (m, 4H), 1.67 – 1.60 (m, 1H), 1.34 – 1.21 (m, 2H), 1.21 – 1.03 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.6, 140.9, 123.4, 56.9, 40.6, 32.9, 32.8, 30.7, 26.4, 26.0, 20.7, 19.5. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{13}H_{21}O_2$, 209.1542; found, 209.1541.



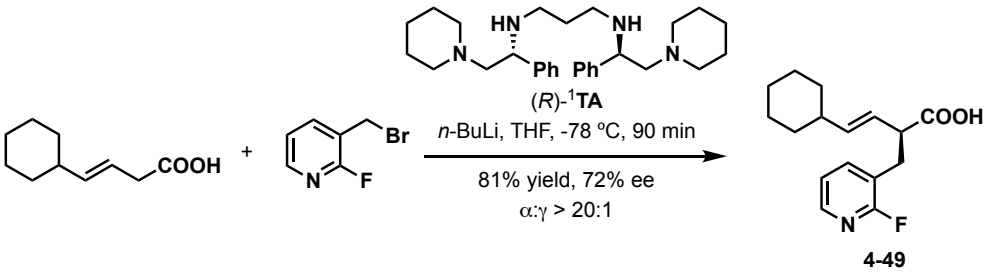
(*S*,*E*)-2-Benzyl-4-cyclohexyl-3-enoic acid (4-48). The title compound was prepared according to **general procedure VII** using (*E*)-4-cyclohexyl-3-butenoic acid (84.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of benzyl bromide (0.24 mL, 0.342 g, 2.00 mmol, 4.0 equiv) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-48** (95.6 mg, 0.370 mmol, 74% yield) was obtained after purification by column chromatography on silica gel (1% methanol in dichloromethane). Ee 85% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes with 0.2% TFA; flow rate = 1.0 mL/min; detection at 210 nm; t_2=14.5 min (major); t_1=9.5 min). $[\alpha]_D^{20}$ +39.9 (*c* 1.01, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.28 – 7.24 (m, 2H), 7.22 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 5.43 – 5.36 (m, 2H), 3.27 – 3.20 (m, 1H), 3.08 (dd, J = 13.6, 7.3 Hz, 1H), 2.79 (dd, J = 13.6, 7.7 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.71 – 1.59 (m, 5H), 1.28 – 1.17 (m, 2H), 1.17 – 1.09 (m, 1H), 1.03 – 0.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 180.0, 140.6, 138.6, 129.2, 128.2, 126.3, 123.7, 51.0, 40.5, 38.7, 32.63, 32.60, 26.1, 25.9. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{17}H_{21}O_2$, 257.1541; found, 257.1541.

Gram Scale Synthesis of 4-48 with Recovery of the Tetraamine (*R*)-[1]TA

A solution of *n*-BuLi (16.4 mL, 2.44 M in hexanes, 40.0 mmol, 4.0 equiv) was added dropwise to a solution of (*E*)-4-cyclohexyl-3-butenoic acid (1.68 g, 10.0 mmol) and (*R*)-**[1]TA** (4.62 g, 10.3 mmol, 1.03 equiv) in THF (80.0 mL) at 0 °C. The resulting mixture was warmed up to 23ºC and stirred at this temperature for 45 min. The reaction mixture was then cooled to –78 °C and stirred for an additional 5 min. Benzyl bromide (1.4 mL, 2.05 g, 12.0 mmol, 1.2 equiv) was added to the above reaction mixture dropwise over 10 min. The resultant mixture

was stirred for additional 80 min before a quench with a mixture of THF-MeOH (3:1, 12.8 mL) at –78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl to pH = 1 and extracted with ethyl acetate (3 x 150 mL). The combined organic phase was sequentially washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (1-2% methanol in dichloromethane) to afford product **4-48** (1.75 g, 6.77 mmol, 68% yield). Ee 85%.

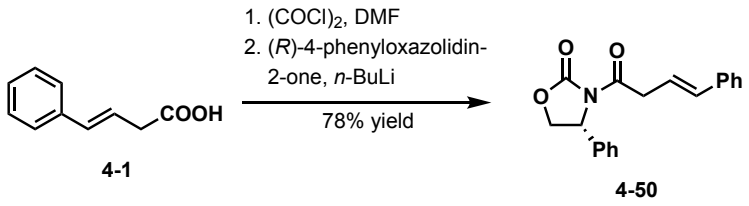
Recovery of (*R*)-^{1}TA: The combined aqueous layers were washed with diethyl ether and then basified with 3 M aqueous solution of sodium hydroxide to pH>12 at room temperature, and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to recover pure (*R*)-**^{1}TA**. Yield of recovered base: 4.51 g, (10.1 mmol, 98%).



(*S*,*E*)-4-Cyclohexyl-2-((2-fluoropyridin-3-yl)methyl)-3-butenoic acid (4-49). The title compound was prepared according to **general procedure VII** using (*E*)-4-cyclohexyl-3-butenoic acid (84.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (4.0 mL) followed by addition of the solution of 3-(bromomethyl)-2-fluoropyridine (0.114 g, 0.600 mmol, 1.20 equiv) in THF (1.0 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **4-49** (0.107 g, 0.385 mmol, 77% yield) was obtained after purification by column

chromatography on silica gel (3% methanol in dichloromethane). Ee 72% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 254 nm; t_2=68.8 min (major); t_1=62.5 min). $[\alpha]_D^{23}$ +62.5 (c 0.99, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.08 (dd, J = 5.1, 1.9 Hz, 1H), 7.58 (ddd, J = 9.5, 7.3, 1.9 Hz, 1H), 7.10 (ddd, J = 6.9, 4.9, 1.6 Hz, 1H), 5.44 – 5.32 (m, 2H), 3.29 (virt. q, J = 7.6 Hz, 1H), 3.09 (dd, J = 13.9, 7.0 Hz, 1H), 2.84 (dd, J = 13.9, 8.3 Hz, 1H), 1.94 – 1.83 (m, 1H), 1.73 – 1.57 (m, 4H), 1.27 – 1.06 (m, 4H), 1.02 – 0.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 178.7, 162.1 (d, J = 239.3 Hz), 145.7 (d, J = 14.4 Hz), 142.1 (d, J = 5.7 Hz), 141.5, 122.9, 121.2 (d, J = 4.2 Hz), 120.7 (d, J = 30.2 Hz), 48.9, 40.4, 32.6, 32.5, 31.7 (d, J = 2.7 Hz), 26.0, 25.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –71.9 (d, J = 9.6 Hz). HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{15}H_{19}NF$, 276.1400; found, 276.1398.

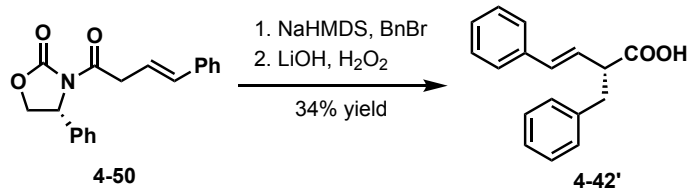
Determination of Absolute Configuration for 4-42 and 4-48



(*R*,*E*)-4-Phenyl-3-(4-phenylbut-3-enoyl)oxazolidin-2-one (4-50)

Oxalyl chloride (0.41 mL, 0.609 g, 4.80 mmol) was added to a solution of (*E*)-4-phenyl-3-butenoic acid (0.730 g, 4.50 mmol), dimethylformamide (10 μL) in dichloromethane (2.0 mL) at 0 °C. After 10 min, the solution was warmed up to 23 °C and stirred for 1h. The reaction mixture was then concentrated under vacuum. In a separate flask under argon, *n*-BuLi (1.31 mL, 2.40 M in hexanes, 3.15 mmol) was added to a solution of (*R*)-4-phenyloxazolidin-2-one (0.490 g, 3.0 mmol) in THF (9.0 mL) at -78 ºC. The resulting solution was stirred at -78 ºC for

30 min. A solution of the crude acyl chloride in THF (8.0 mL) was added dropwise at -78 ºC. After stirring at -78 ºC for 2h, the reaction mixture quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (x3). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate = 3:1) to afford **4-50** (0.722 g, 2.35 mmol, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.25 (m, 9H), 7.25 – 7.18 (m, 1H), 6.50 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.9 Hz, 1H), 5.45 (dd, J = 8.8, 3.6 Hz, 1H), 4.72 (t, J = 8.8 Hz, 1H), 4.31 (dd, J = 8.8, 3.6 Hz, 1H), 3.88 (d, J = 6.9 Hz, 2H).

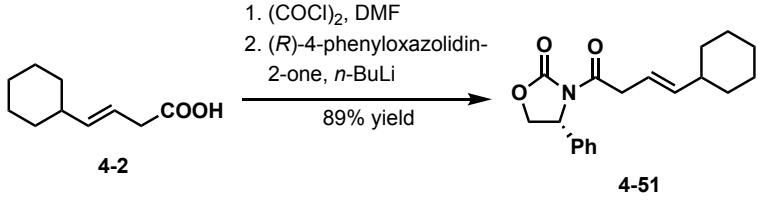


4-50 **4-42'**

(*R*,*E*)-2-Benzyl-4-phenyl-3-butenoic acid (4-42')

A solution of $NaN(SiMe_3)_2$ (0.60 M in toluene, 0.90 mL, 0.54 mmol) was added dropwise to a solution of **4-50** (0.100 g, 0.326 mmol) in THF (3.0 mL) at -78 ºC. After 1h stirring at -78 ºC, benzyl bromide (51 μL, 73.0 mg, 0.427 mmol) was added and the resultant solution was kept stirring at 0 ºC for 2h. The reaction mixture was then quenched with saturated NH_4Cl aqueous solution, extracted with dichloromethane (x3). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated. The residue was flashed through silica pad and then directly applied in the hydrolysis without further purification.

$LiOH•H_2O$ (30.0 mg, 0.717 mmol) and H_2O_2 (30% aqueous solution, 0.10 mL) was added to a solution of crude benzylated imide in THF/H_2O (4:1, 5.0 mL) at 0 ºC. The reaction mixture was then warmed up to 23 ºC and stirred for 3h. The reaction mixture was then quenched with saturated sodium sulfite aqueous solution. After another 15 min stirring, the aqueous phase was acidified with 1M aqueous solution of HCl, and extracted with ethyl acetate (x3). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (1% methanol in dichloromethane) to afford **4-42'** (27.7 mg, 0.110 mmol, 34% yield). Ee 94%. $[\alpha]_D^{23}$ –130.3 (c 0.55, $CHCl_3$).

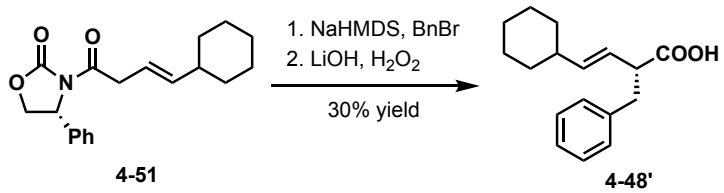


4-2 4-51

(*R*,*E*)-3-(4-Cyclohexylbut-3-enoyl)-4-phenyloxazolidin-2-one (4-51)

Oxalyl chloride (0.41 mL, 0.609 g, 4.80 mmol) was added to a solution of (*E*)-4-cyclohexyl-3-butenoic acid (0.757 g, 4.50 mmol), dimethylformamide (10 μL) in dichloromethane (2.0 mL) at 0 °C. After 10 min, the solution was warmed up to 23 °C and stirred for 1h. The reaction mixture was then concentrated under vacuum. In a separate flask under argon, *n*-BuLi (1.32 mL, 2.38 M in hexanes, 3.15 mmol) was added to a solution of (*R*)-4-phenyloxazolidin-2-one (0.490 g, 3.0 mmol) in THF (9.0 mL) at -78 ºC. The resulting solution was stirred at –78 ºC for 30 min. A solution of the crude acyl chloride in THF (8.0 mL) was added dropwise at -78 ºC. After stirring at –78 ºC for 2h, the reaction mixture quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (x3). The combined

organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate = 7:1) to afford **4-51** (0.834 g, 2.66 mmol, 89% yield). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.27 (m, 5H), 5.53 (dd, J = 15.6, 6.2 Hz, 1H), 5.47 (dt, J = 15.6, 5.8 Hz, 1H), 5.42 (dd, J = 8.7, 3.7 Hz, 1H), 4.69 (t, J = 8.8 Hz, 1H), 4.28 (dd, J = 8.9, 3.7 Hz, 1H), 3.70 – 3.59 (m, 2H), 1.97 – 1.89 (m, 1H), 1.73 – 1.60 (m, 5H), 1.30 – 1.18 (m, 2H), 1.18 – 1.09 (m, 1H), 1.09 – 0.98 (m, 2H).



4-51 4-48'

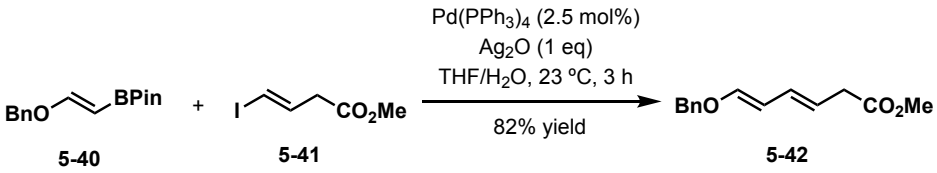
(*R*,*E*)-2-Benzyl-4-cyclohexyl-3-butenoic acid (4-48')

A solution of $NaN(SiMe_3)_2$ (0.60 M in toluene, 1.25 mL, 0.750 mmol) was added dropwise to a solution of **4-51** (0.157 g, 0.500 mmol) in THF (5.0 mL) at -78 ºC. After 1h stirring at -78 ºC, benzyl bromide (71 μL, 0.103 g, 0.600 mmol) was added and the resultant solution was kept stirring at 0 ºC for 2h. The reaction mixture was then quenched with saturated NH_4Cl aqueous solution, extracted with dichloromethane (x3). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated. The residue was flashed through silica pad and then directly applied in the hydrolysis without further purification.

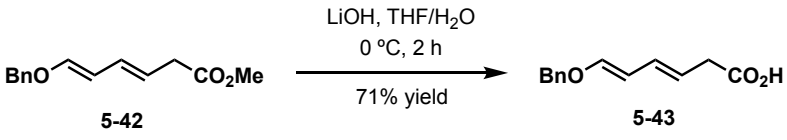
$LiOH•H_2O$ (52.3 mg, 1.25 mmol) and H_2O_2 (30% aqueous solution, 0.10 mL) was added to a solution of crude benzylated imide in THF/H_2O (4:1, 5.0 mL) at 0 ºC. The reaction mixture was then warmed up to 23 ºC and stirred for 3h. The reaction mixture was then quenched with saturated sodium sulfite aqueous solution. After another 15 min stirring, the aqueous phase

was acidified with 1M aqueous solution of HCl, and extracted with ethyl acetate (x3). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (1% methanol in dichloromethane) to afford **4-48'** (37.9 mg, 0.147 mmol, 30% yield). Ee 98%. $[\alpha]_D^{21}$ –50.4 (c 1.08, $CHCl_3$).

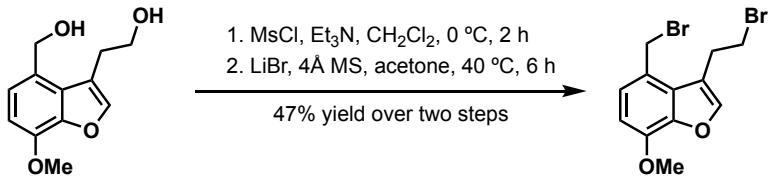
7.5 Concise Synthesis Towards (–)-Morphine



Methyl (3*E*,5*E*)-6-(benzyloxy)hexa-3,5-dienoate (5-42). Tetrakis(triphenylphosphine) palladium (0.578 g, 0.50 mmol) and silver(I) oxide (4.63 g, 20 mmol) was added to the solution of vinyl borate **5-40**[10] (5.20 g, 20 mmol) and vinyl iodide **5-41**[11] (4.52 g, 20 mmol) in THF-H_2O (10:1, v/v, 110 mL) under argon at 23 ºC. The reaction suspension was stirred for 3 h before filtered through celite. The filtrate was then concentrated, and the residue was purified by column chromatography on silica gel (17% ethyl acetate in hexanes) to afford **5-42** (3.81 g, 16.4 mmol, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.28 (m, 5H), 6.60 (d, *J* = 12.5 Hz, 1H), 6.00 (dd, *J* = 15.4, 10.9 Hz, 1H), 5.66 (dd, *J* = 12.4, 10.7 Hz, 1H), 5.54 (dt, *J* = 14.8, 7.2 Hz, 1H), 4.79 (s, 2H), 3.68 (s, 3H), 3.08 (d, *J* = 7.2 Hz, 2H).



(3*E*,5*E*)-6-(Benzyloxy)hexa-3,5-dienoic acid (5-43). $LiOH•H_2O$ (3.44 g, 82.0 mmol) was added to the solution of ester **5-42** (3.81 g, 16.4 mmol) in THF-H_2O (4:1, v/v, 100 mL) at 0 ºC. The resultant reaction mixture was stirred at this temperature for another 2 h. Water was then added. The aqueous layer was washed with diethyl ether, acidified by phosphate buffer (pH = 3) to pH 3~4, and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude yellow powdery solid was then recrystallized with hexanes and afforded acid **5-43** in pale yellow crystalline solid (2.54 g, 11.6 mmol, 71% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.29 (m, 5H), 6.62 (d, *J* = 12.5 Hz, 1H), 6.03 (dd, *J* = 15.2, 10.6 Hz, 1H), 5.70 – 5.62 (m, 1H), 5.53 (dt, *J* = 14.8, 7.2 Hz, 1H), 4.80 (s, 2H), 3.12 (d, *J* = 7.2 Hz, 2H).

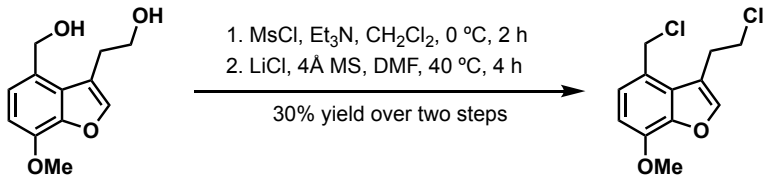


5-53 **5-35a**

3-(2-Bromoethyl)-4-(bromomethyl)-7-methoxybenzofuran (5-35a). Methanesulfonyl chloride (1.6 mL, 20.5 mmol) was added to the solution of diol **5-53**[12] (2.22 g, 10.0 mmol) and triethylamine (2.9 mL, 20.5 mmol) in CH_2Cl_2 (100 mL) at 0 ºC. The resultant solution was stirred at 0 ºC for 2 h, and quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford the crude of mesylate.

Lithium bromide (3.47 g, 40.0 mmol) and 4Å molecular sieve was added to the solution of the previous crude in acetone, and the reaction mixture was heated at 40 ºC for 6 h. The solution was then directly concentrated, and the residue was treated with water. The mixture was then

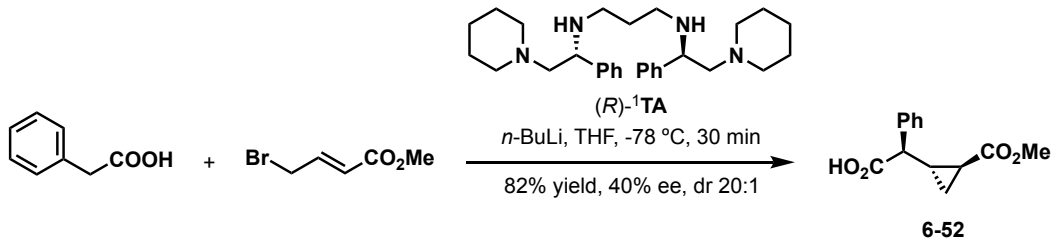
extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Trituration of the crude with cold hexanes afforded the dibromide **5-35a** as white solid (1.63 g, 4.68 mmol, 47% yield over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.59 (s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 4.84 (s, 2H), 4.00 (s, 3H), 3.71 (t, J = 7.2 Hz, 2H), 3.48 (t, J = 7.2 Hz, 2H).



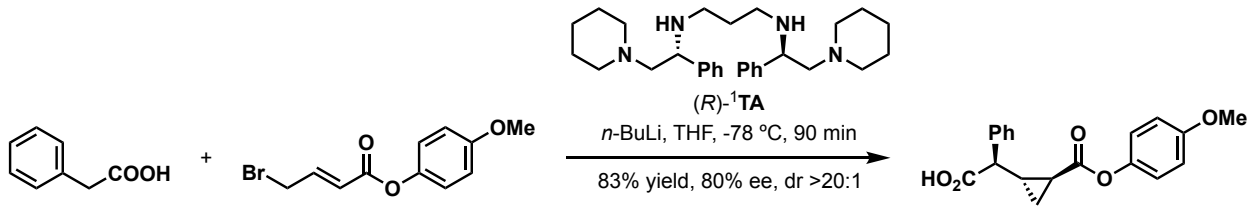
5-53 5-35b

3-(2-Chloroethyl)-4-(chloromethyl)-7-methoxybenzofuran (5-35b). The crude mesylate was prepared in the same procedure as the one above from the diol **5-53** (4.00 g, 18.0 mmol). Lithium chloride (3.05 g, 72.0 mmol) and 4Å molecular sieve was added to the solution of the previous crude in DMF, and the reaction mixture was heated at 40 ºC for 4 h before diluted with water. The mixture was then extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Trituration of the crude with cold hexanes afforded the dibromide **5-35b** as white solid (1.40 g, 5.42 mmol, 30% yield over two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.57 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 4.86 (s, 2H), 4.00 (s, 3H), 3.84 (t, J = 7.0 Hz, 2H), 3.36 (t, J = 7.2 Hz, 2H).

7.6 Enantioselective Michael-Initiated Ring Closure Reaction

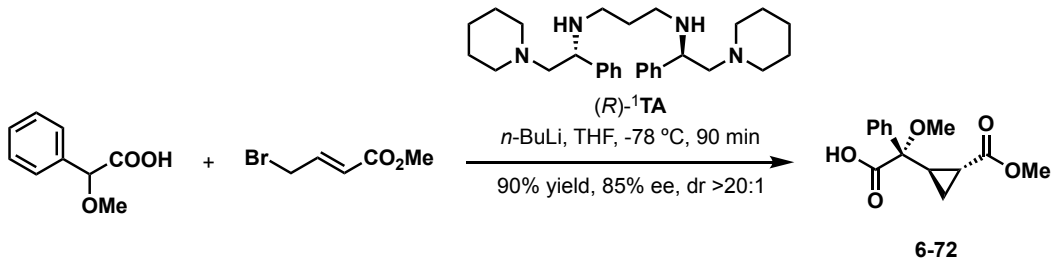


(*R*)-2-((1*S*,2*S*)-2-(Methoxycarbonyl)cyclopropyl)-2-phenylacetic acid (6-52). A solution of *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (68.1 mg, 0.500 mmol) and (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 ºC and the resulting mixture was stirred at this temperature for 15 min. The reaction mixture was then cooled to –78 ºC and stirred for an additional 5 min. Methyl (*E*)-4-bromo-2-butenoate (0.107 g, 0.600 mmol, 1.20 equiv) was added to the above reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 20 min before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at –78 ºC. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was washed brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (5% methanol in dichloromethane) to afford product **6-52** (95.7 mg, 0.409 mmol, 82% yield). Ee 40% (Chiralcel® AD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=10.1 min; t_2=15.2 min). $[\alpha]_D^{21}$ –11.7 (c 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38 – 7.26 (m, 5H), 3.62 (s, 3H), 3.06 (d, J = 9.6 Hz, 1H), 2.14 (dtd, J = 13.6, 6.2, 4.4 Hz, 1H), 1.50 (dt, J = 8.9, 4.6 Hz, 1H), 1.36 (dt, J = 9.2, 4.8 Hz, 1H), 0.99 (ddd, J = 8.5, 5.9, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 178.1, 173.8, 136.8, 128.8, 128.0, 127.8, 54.3, 51.9, 23.8, 19.2, 15.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{14}O_4Na$, 257.0784; found 257.0789.



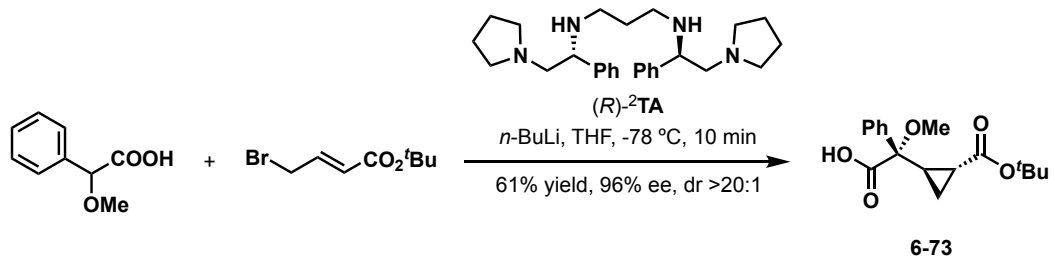
6-62

(*R*)-2-((1*S*,2*S*)-2-((4-Methoxyphenoxy)carbonyl)cyclopropyl)-2-phenylacetic acid (6-62). The title compound was prepared according to the procedure of **6-52** using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of 4-methoxyphenyl (*E*)-4-bromo-2-butenoate (0.163 g, 0.600 mmol, 1.20 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **6-62** (0.136 g, 0.416 mmol, 83% yield) was obtained after purification by column chromatography on silica gel (2-10% methanol in dichloromethane). Ee 80% (Chiralcel® AD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=18.7 min; t_2=23.4 min). $[\alpha]_D^{23}$ –93.2 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.28 (m, 5H), 6.92 (d, J = 9.1 Hz, 2H), 6.84 (d, J = 9.1 Hz, 2H), 3.77 (s, 3H), 3.14 (d, J = 9.5 Hz, 1H), 2.26 (tdd, J = 9.5, 6.2, 4.3 Hz, 1H), 1.69 (dt, J = 8.8, 4.6 Hz, 1H), 1.50 (dt, J = 9.3, 4.8 Hz, 1H), 1.16 – 1.08 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 177.9, 172.3, 157.2, 144.1, 136.8, 128.9, 128.0, 127.9, 122.2, 114.4, 55.6, 54.2, 24.6, 19.3, 15.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{18}O_5Na$, 349.1046; found 349.1038.



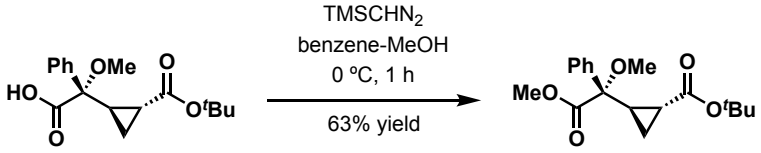
6-72

(*S*)-2-Methoxy-2-((1*R*,2*R*)-2-(methoxycarbonyl)cyclopropyl)-2-phenylacetic acid (6-72). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of methyl (*E*)-4-bromo-2-butenoate (0.107 g, 0.600 mmol, 1.20 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **6-72** (0.119 g, 0.451 mmol, 90% yield) was obtained after purification by column chromatography on silica gel (10% methanol in dichloromethane). Ee 85% (Chiralcel® AD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=7.4 min; t_2=8.1 min). $[\alpha]_D^{24}$ –18.5 (c 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, Methanol-d4) δ (ppm) 7.53 – 7.47 (m, 2H), 7.36 – 7.24 (m, 3H), 3.66 (s, 3H), 3.18 (s, 3H), 2.14 (ddd, J = 9.1, 6.7, 4.5 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.26 – 1.15 (m, 2H). ^{13}C NMR (101 MHz, Methanol-d4) δ (ppm) 177.3, 176.1, 140.4, 129.1, 129.1, 128.8, 85.1, 53.1, 52.4, 28.8, 18.1, 13.7. HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{14}H_{15}O$, 263.0925; found, 263.0937.



6-73

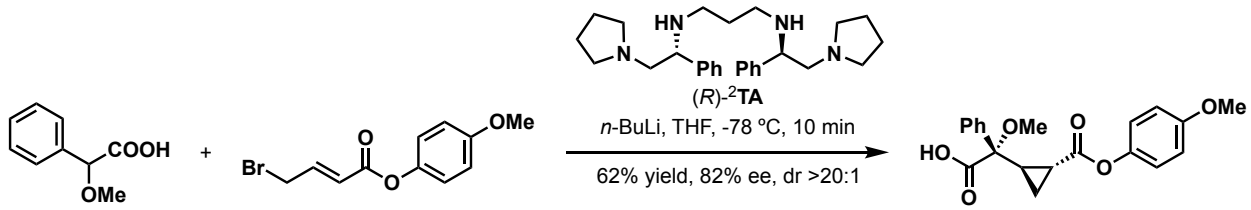
(*S*)-2-((1*R*,2*R*)-2-(*tert*-Butoxycarbonyl)cyclopropyl)-2-methoxy-2-phenylacetic acid (6-73). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of *tert*-butyl (*E*)-4-bromo-2-butenoate (0.133 g, 0.600 mmol, 1.20 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched immediately, and product **6-73** (93.0 mg, 0.303 mmol, 61% yield) was obtained after purification by column chromatography on silica gel (10% methanol in dichloromethane), and directly converted to methyl ester for measuring the enantiomeric excess.



6-73 **6-73 methyl ester**

***tert*-Butyl (1*R*,2*R*)-2-((*S*)-1,2-dimethoxy-2-oxo-1-phenylethyl)cyclopropane-1-carboxylate (6-73 methyl ester).** A solution of $TMSCHN_2$ was added dropwise to a solution of carboxylic acid **6-73** (93.0 mg, 0.303 mmol) in a mixture of benzene-MeOH (4:1, 5.0 mL) at 0 ºC. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the product **6-73 methyl ester** (59.0 mg, 0.184 mmol, 61% yield). Ee 96% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=7.4 min; t_2=9.8 min). $[\alpha]_D^{24}$ –58.6 (c 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.30 (m, 5H), 3.80 (s, 3H), 3.23 (s, 3H), 2.07 (ddd, J = 9.0,

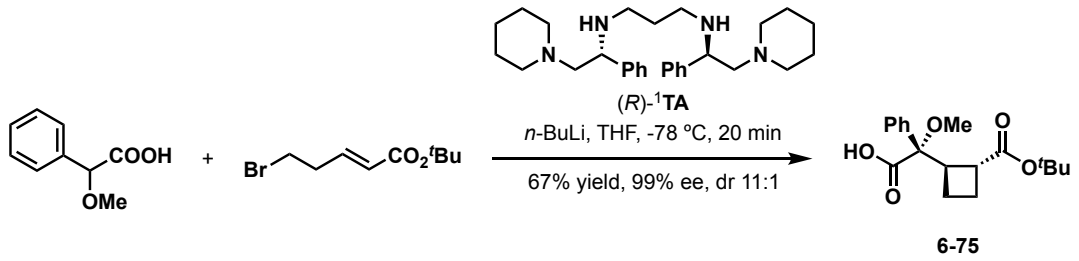
6.5, 4.6 Hz, 1H), 1.69 (dt, J = 8.4, 5.0 Hz, 1H), 1.43 (s, 9H), 1.26 (ddd, J = 9.2, 5.4, 4.3 Hz, 1H), 1.10 (ddd, J = 8.5, 6.5, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, Methanol-d4) δ (ppm) 174.6, 174.0, 139.0, 129.6, 129.3, 128.5, 83.7, 81.7, 53.6, 52.7, 30.1, 28.3, 18.4, 12.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{24}NaO_5$, 343.1516; found, 343.1513.



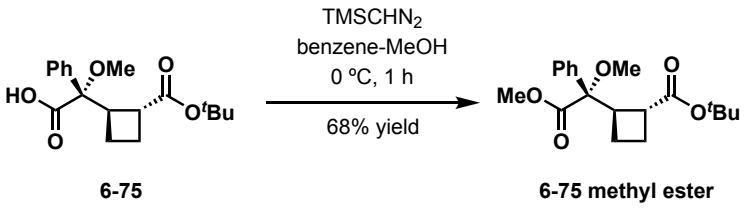
6-74

(*S*)-2-Methoxy-2-((1*R*,2*R*)-2-((4-methoxyphenoxy)carbonyl)cyclopropyl)-2-phenylacetic acid (6-74). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of 4-methoxyphenyl (*E*)-4-bromo-2-butenoate (0.163 g, 0.600 mmol, 1.20 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **6-74** (0.110 g, 0.309 mmol, 62% yield) was obtained after purification by column chromatography on silica gel (10% methanol in dichloromethane). Ee 82% (Chiralcel® AD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=26.6 min; t_2=35.9 min). $[\alpha]_D^{23}$ –42.1 (c 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, Methanol-d4) δ (ppm) 7.58 – 7.53 (m, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.35 – 7.30 (m, 1H), 6.97 (d, J = 9.1 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 3.78 (s, 3H), 3.23 (s, 3H), 2.26 (ddd, J = 9.1, 6.8, 4.5 Hz, 1H), 2.11 (dt, J = 9.2, 4.9 Hz, 1H), 1.41 (dt, J = 9.2, 4.7 Hz, 1H), 1.37 (ddd, J = 8.2, 6.8, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, Methanol-d4) δ (ppm) 172.6, 157.1,

144.2, 128.3, 127.2, 122.2, 114.3, 77.2, 60.4, 55.5, 21.0, 14.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{20}O_6Na$, 379.1158; found 379.1159.

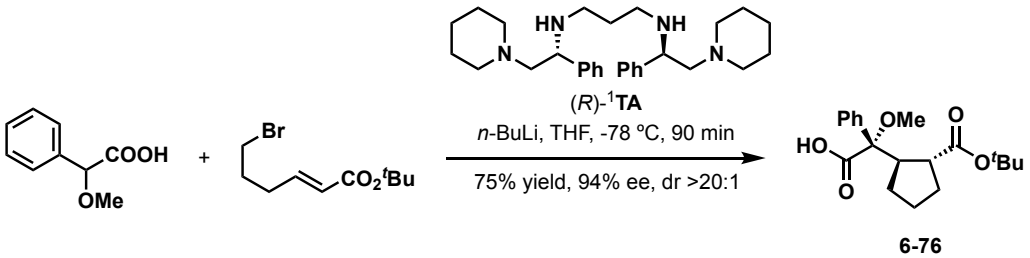


(*S*)-2-((1*R*,2*R*)-2-(*tert*-Butoxycarbonyl)cyclobutyl)-2-methoxy-2-phenylacetic acid (6-75). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of *tert*-butyl (*E*)-5-bromo-2-pentenoate (0.129 g, 0.550 mmol, 1.10 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 20 min, and product **6-75** (0.107 g, 0.334 mmol, 67% yield) was obtained after purification by column chromatography on silica gel (2-10% methanol in dichloromethane), and directly converted to methyl ester for measuring the enantiomeric excess.



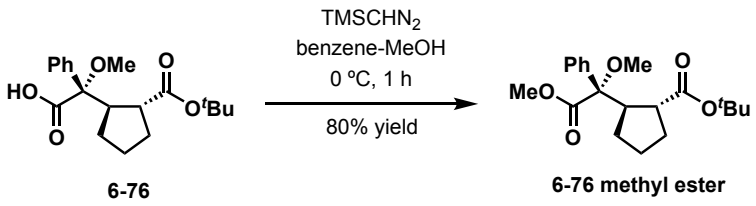
***tert*-Butyl (1*R*,2*R*)-2-((*S*)-1,2-dimethoxy-2-oxo-1-phenylethyl)cyclobutane-1-carboxylate (6-75 methyl ester).** A solution of $TMSCHN_2$ was added dropwise to a solution of carboxylic acid **6-75** (44.0 mg, 0.137 mmol) in a mixture of benzene-MeOH (4:1, 5.0 mL)

at 0 ºC. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (7% ethyl acetate in hexanes) to afford the product **6-75 methyl ester** (30.0 mg, 89.7 μmol, 68% yield). Ee 99% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=8.5 min; t_2=9.2 min). $[\alpha]_D^{24}$ –54.9 (c 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.36 (m, 2H), 7.34 (ddd, J = 7.6, 6.7, 1.2 Hz, 2H), 7.31 – 7.27 (m, 1H), 3.85 (s, 0.27H), 3.78 (s, 2.89H), 3.30 (s, 2.92H), 3.24 (dtd, J = 9.6, 8.7, 0.8 Hz, 1H), 3.16 (s, 0.27H), 3.12 (qd, J = 9.1, 1.0 Hz, 1H), 2.08 – 1.83 (m, 3H), 1.73 – 1.66 (m, 1H), 1.42 (s, 8.50H), 1.40 (s, 0.89H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 173.78, 172.0, 137.3, 128.0, 127.7, 127.1, 85.3, 79.7, 54.0, 51.9, 45.5, 40.2, 28.1, 21.5, 19.9. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{26}O_5Na$, 357.1678; found 357.1669.



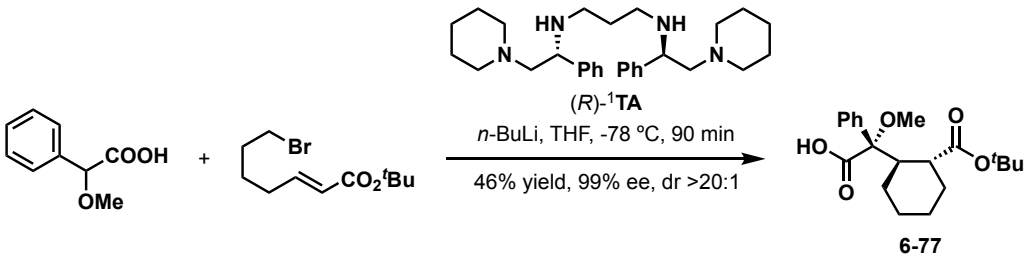
(*S*)-2-((1*R*,2*R*)-2-(*tert*-Butoxycarbonyl)cyclopentyl)-2-methoxy-2-phenylacetic acid (6-76). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of *tert*-butyl (*E*)-6-bromo-2-henxenoate (0.137 g, 0.550 mmol, 1.10 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **6-76** (0.126 g, 0.377 mmol, 75% yield) was obtained after purification by

column chromatography on silica gel (2-10% methanol in dichloromethane), and directly converted to methyl ester for measuring the enantiomeric excess. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{26}O_5Na$, 357.1678; found 357.1677.

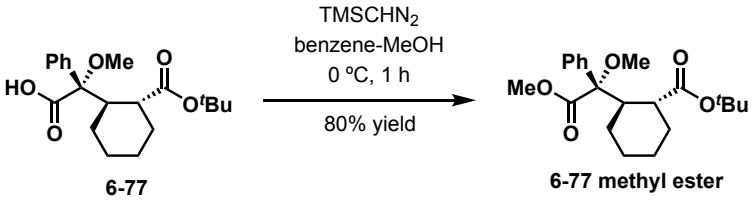


6-76 6-76 methyl ester

***tert*-Butyl (1*R*,2*R*)-2-((*S*)-1,2-dimethoxy-2-oxo-1-phenylethyl)cyclopentane-1-carboxylate (6-76 methyl ester).** A solution of $TMSCHN_2$ was added dropwise to a solution of carboxylic acid **6-76** (40.0 mg, 0.120 mmol) in a mixture of benzene-MeOH (4:1, 5.0 mL) at 0 ºC. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford the product **6-76 methyl ester** (32.0 mg, 92.0 μmol, 80% yield). Ee 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=6.0 min; t_2=6.5 min). $[\alpha]_D^{25}$ –67.3 (c 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.46 – 7.41 (m, 2H), 7.38 – 7.27 (m, 3H), 3.80 (s, 3H), 3.25 (s, 3H), 3.21 – 3.14 (m, 1H), 2.70 (ddd, J = 9.3, 7.2, 5.8 Hz, 1H), 1.87 – 1.41 (m, 6H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.0, 172.4, 137.4, 127.8, 127.8, 127.7, 87.6, 79.5, 54.0, 51.9, 50.7, 46.0, 32.2, 28.9, 28.0, 25.5. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{28}O_5Na$, 371.2; found 371.2.

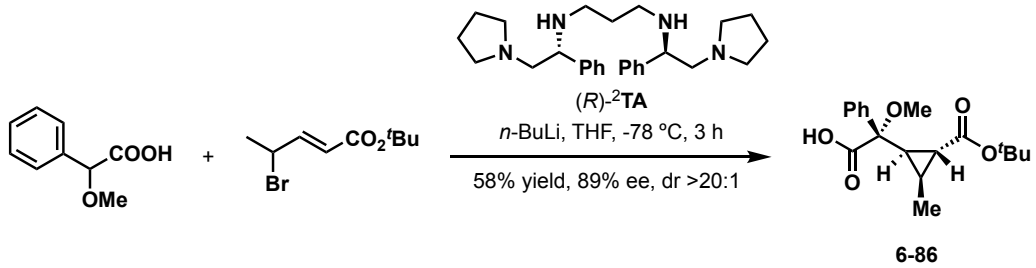


(*S*)-2-((1*R*,2*R*)-2-(*tert*-Butoxycarbonyl)cyclohexyl)-2-methoxy-2-phenylacetic acid (6-77). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of *tert*-butyl (*E*)-7-bromo-2-heptenoate (0.145 g, 0.550 mmol, 1.10 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 80 min, and product **6-77** (80.0 mg, 0.230 mmol, 46% yield) was obtained after purification by column chromatography on silica gel (2-10% methanol in dichloromethane), and directly converted to methyl ester for measuring the enantiomeric excess.



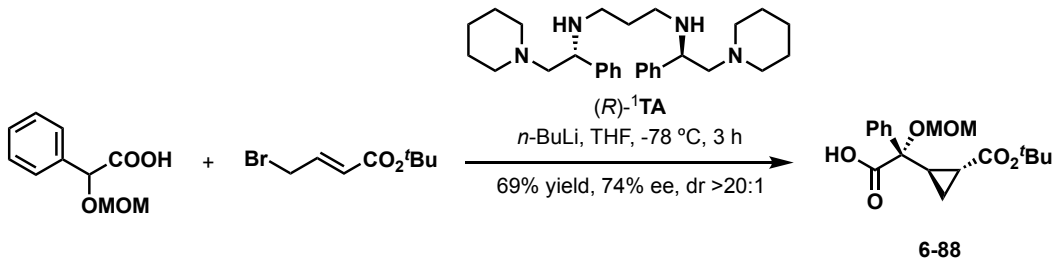
***tert*-Butyl (1*R*,2*R*)-2-((*S*)-1,2-dimethoxy-2-oxo-1-phenylethyl)cyclohexane-1-carboxylate (6-77 methyl ester).** A solution of $TMSCHN_2$ was added dropwise to a solution of carboxylic acid **6-77** (80.0 mg, 0.230 mmol) in a mixture of benzene-MeOH (4:1, 5.0 mL) at 0 ºC. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford the product **6-77 methyl ester** (72.4 mg, 0.200

mol, 87% yield). Ee 99% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=10.6 min; t_2=16.4 min). $[\alpha]_D^{25}$ –26.0 (c 1.80, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.48 (dt, J = 6.3, 1.4 Hz, 2H), 7.38 – 7.29 (m, 3H), 3.80 (s, 3H), 3.14 (s, 3H), 2.77 (ddd, J = 12.3, 10.7, 3.3 Hz, 1H), 1.79 – 1.68 (m, 3H), 1.66 – 1.54 (m, 3H), 1.52 (s, 9H), 1.50 – 1.42 (m, 1H), 1.28 (qt, J = 12.4, 3.1 Hz, 1H), 0.85 (qt, J = 13.2, 3.3 Hz, 1H), 0.70 (qd, J = 12.8, 3.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 175.5, 171.6, 135.2, 129.1, 127.5, 126.9, 89.2, 79.1, 53.3, 52.1, 44.8, 44.6, 31.1, 28.1, 27.6, 25.2, 25.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{30}O_5Na$, 385.1990; found 385.1991.



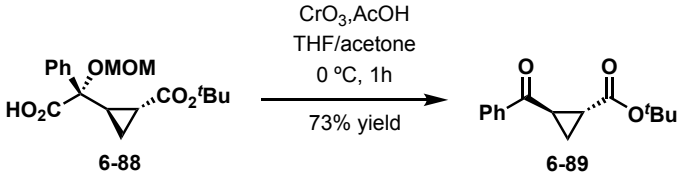
(*S*)-2-((1*R*,2*R*,3*S*)-2-(*tert*-Butoxycarbonyl)-3-methylcyclopropyl)-2-methoxy-2-phenylacetic acid (6-86). The title compound was prepared according to **general procedure II** using (±)-2-methoxy-2-phenylacetic acid (83.1 mg, 0.500 mmol), (*R*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (3.5 mL) followed by addition of the solution of *tert*-butyl (*E*)-4-bromo-2-pentenoate (0.129 g, 0.550 mmol, 1.10 equiv) in THF (0.50 mL) at –78 °C over 10 min. The reaction was quenched after additional 3 h, and product **6-86** (92.0 mg, 0.287 mmol, 58% yield) was obtained after purification by column chromatography on silica gel (2-10% methanol in dichloromethane), and directly converted to methyl ester for measuring the enantiomeric excess.

***tert*-Butyl (1*R*,2*R*,3*S*)-2-((*S*)-1,2-dimethoxy-2-oxo-1-phenylethyl)-3-methylcyclopropane-1-carboxylate (6-86 methyl ester).** A solution of $TMSCHN_2$ was added dropwise to a solution of carboxylic acid **6-86** (32.0 mg, 0.100 mmol) in a mixture of benzene-MeOH (4:1, 5.0 mL) at 0 ºC. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (14% ethyl acetate in hexanes) to afford the product **6-86 methyl ester** (28.0 mg, 83.8 µmol, 84% yield). Ee 89% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=6.3 min; t_2=7.5min). $[\alpha]_D^{25}$ –17.8 (c 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39 – 7.29 (m, 5H), 3.78 (s, 3H), 3.26 (s, 3H), 2.00 (dd, J = 6.6, 5.4 Hz, 1H), 1.72 (dd, J = 9.5, 5.4 Hz, 1H), 1.46 – 1.39 (m, 10H), 1.24 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 172.7, 170.9, 138.0, 128.25, 128.19, 127.1, 83.4, 80.4, 52.9, 52.3, 33.1, 28.2, 22.9, 20.2, 11.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{26}O_5Na$, 357.1678; found 357.1687.



(*S*)-2-((1*R*,2*R*)-2-(*tert*-Butoxycarbonyl)cyclopropyl)-2-(methoxymethoxy)-2-phenylacetic acid (6-88). The title compound was prepared according to **general procedure II** using 2-methoxymethoxy-2-phenylacetic acid (0.589 g, 3.00 mmol), (*R*)-**1TA** (1.39 g, 3.09 mmol, 1.03 equiv), *n*-BuLi (4.8 mL, 2.51 M in hexanes, 12.0 mmol, 4.0 equiv) in THF (20 mL) followed by addition of the solution of methyl (*E*)-4-bromo-2-butenoate (0.730 g, 3.30

mmol, 1.10 equiv) in THF (4.0 mL) at –78 °C over 20 min. The reaction was quenched after additional 3 h, and product **6-88** (0.697 g, 2.07 mmol, 69% yield) was obtained after purification by column chromatography on silica gel (10% methanol in dichloromethane). Ee 74% (Chiralcel® OJ-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=9.3 min; t_2=11.5 min). $[\alpha]_D^{25}$ –27.3 (c 0.97, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.54 – 7.41 (m, 2H), 7.38 – 7.28 (m, 3H), 4.71 (s, 2H), 3.35 (s, 3H), 2.22 – 2.13 (m, 1H), 1.86 – 1.76 (m, 1H), 1.43 (s, 9H), 1.31 – 1.22 (m, 1H), 1.11 – 1.02 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 174.8, 172.7, 136.9, 128.8, 128.4, 127.3, 93.0, 83.2, 80.6, 56.4, 28.0, 27.4, 17.9, 12.3. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{24}O_6Na$, 359.1465; found 359.1470.



6-88 6-89

***tert*-Butyl (1*R*,2*R*)-2-benzoylcyclopropane-1-carboxylate (6-89).** To a solution of **6-88** (67.0 mg, 0.200 mmol) in a mixture of THF-acetone (5:1, 3.0 mL) was added a solution of CrO_3 (25.0 mg, 0.250 mmol, 1.25 equiv) in acetic acid (0.25 mL) at 0 ºC. The resultant reaction mixture was stirred at the same temperature for another 1 h, then diluted with dichloromethane, and quenched with saturated Na_2SO_3 aqueous solution. The aqueous layer was extracted with dichloromethane for two more times. The combined organic phase was washed with water and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **6-89** (36.0 mg, 0.146 mmol, 73% yield). $[\alpha]_D^{22}$ –90.7 (c 0.50, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) δ 8.05 – 7.95 (m, 2H), 7.59 (ddt, J = 8.7, 7.0, 1.3 Hz, 1H), 7.53 – 7.46 (m, 2H), 3.12 (ddd, J = 8.6, 5.7,

3.8 Hz, 1H), 2.30 (ddd, J = 8.7, 5.9, 3.8 Hz, 1H), 1.57 (ddd, J = 8.8, 5.7, 3.4 Hz, 1H), 1.53 (ddd, J = 8.6, 5.9, 3.4 Hz, 1H), 1.47 (s, 9H).[13]

7.7 References

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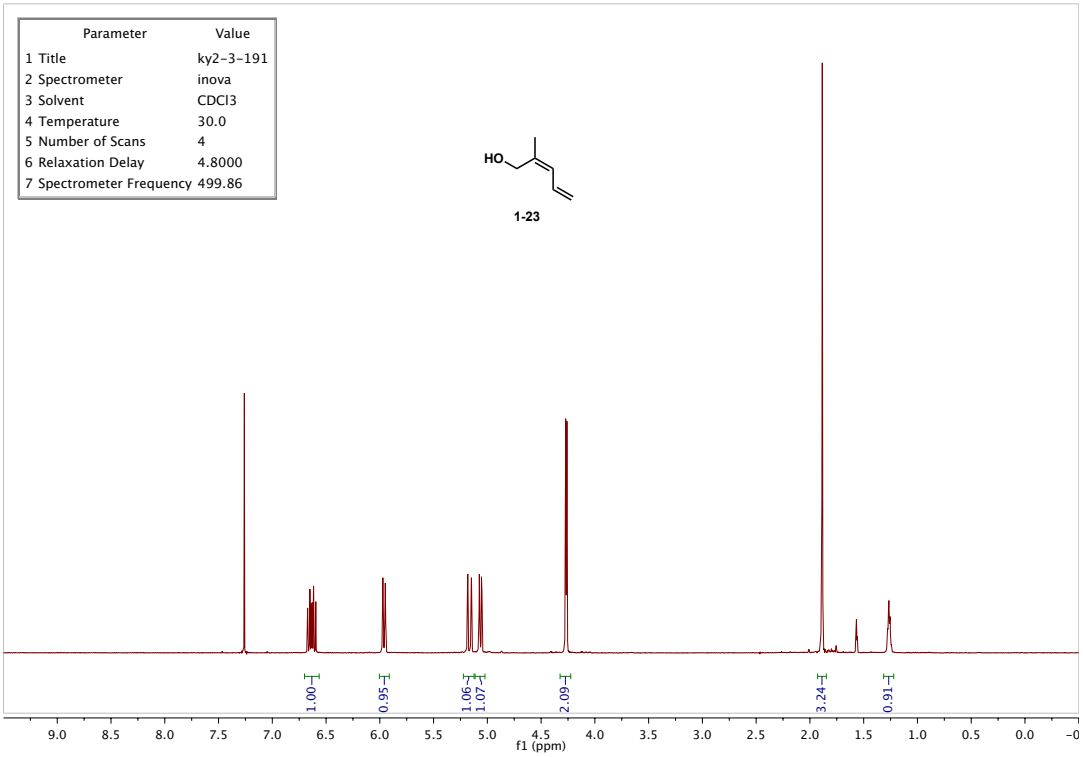
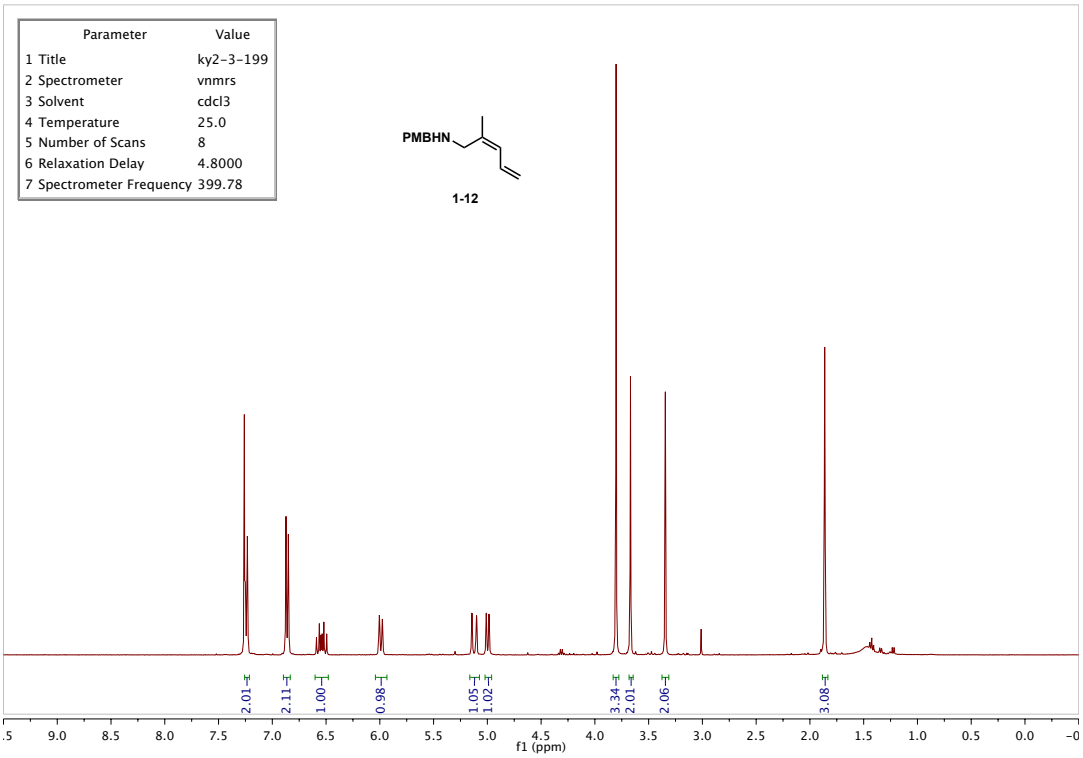
(13) The spectra data matched the reported: *J. Am. Chem. Soc.* **2010**, *132*, 7626-7630.

Chapter 8. Appendix: Selected NMR Spectra and HPLC Traces





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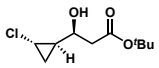

1-31

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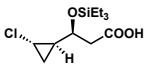

1-33

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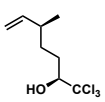

1-35

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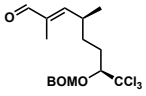

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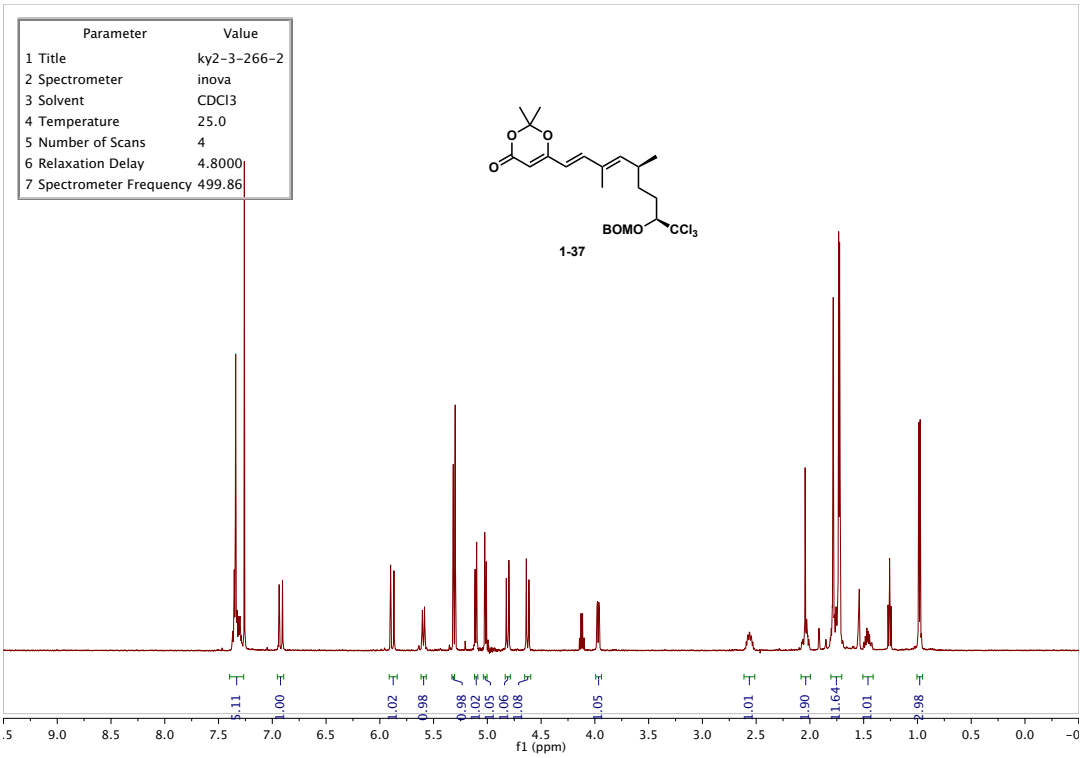
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BOMO
CCl3
1-37
5.11
1.00
1.02
0.98
0.98
1.02
1.05
1.06
1.08
1.05
1.01
1.90
11.64
1.01
2.98
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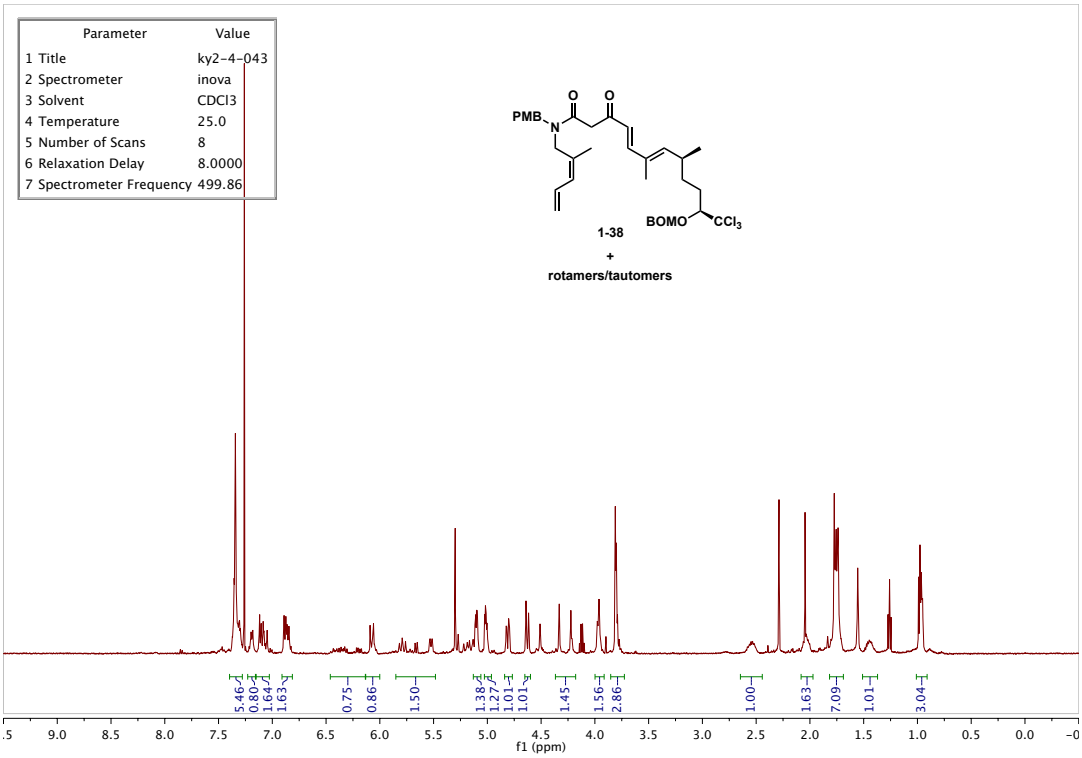
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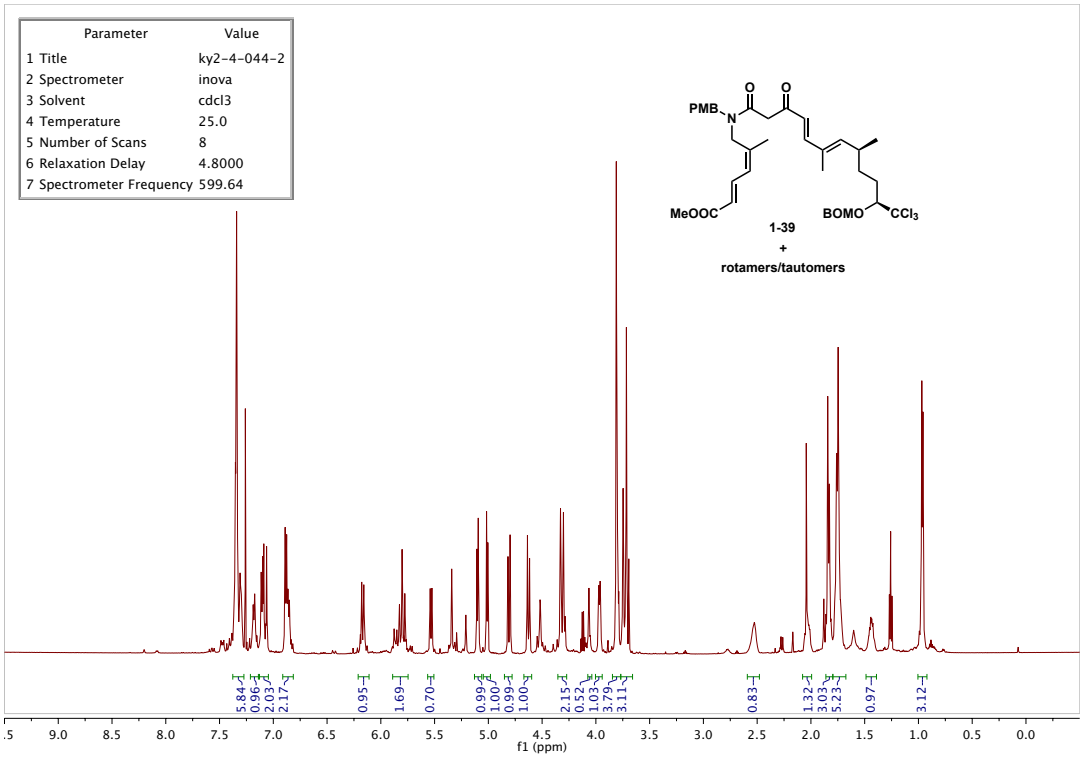
PMB
BOMO
CCl3
1-38
+
rotamers/tautomers
5.46
0.80
1.64
1.63
0.75
0.86
1.50
1.38
1.27
1.01
1.01
1.45
1.56
2.86
1.00
1.63
7.09
1.01
3.04
f1 (ppm)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N
O
O
MeOOC
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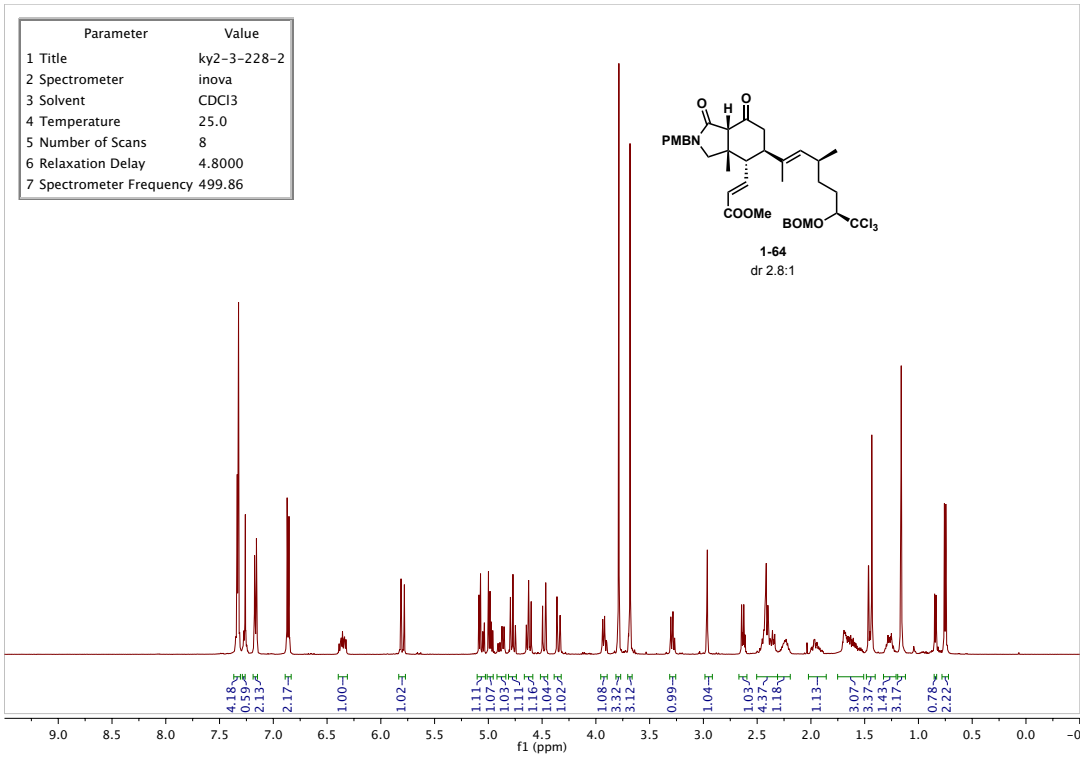
CCl3
1-39
+
rotamers/tautomers
f1 (ppm)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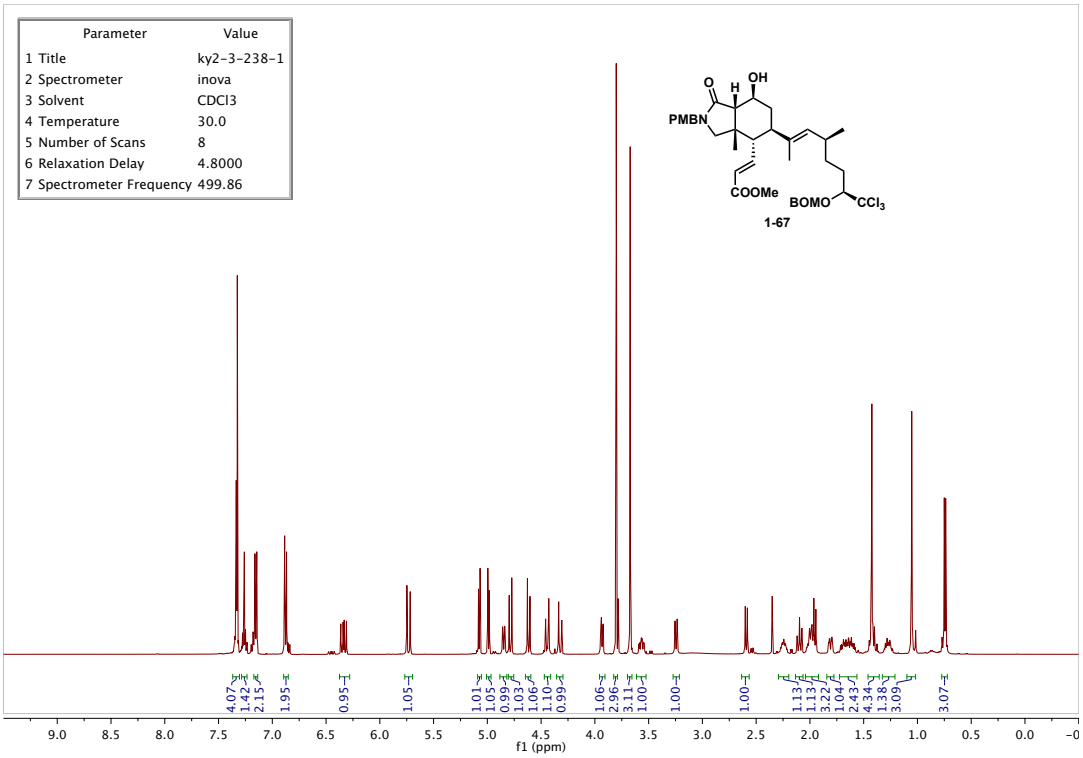
O
H
O
PMBN
COOMe
BOMO
CCl3
1-64
dr 2.8:1
f1 (ppm)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CCl3
1-67
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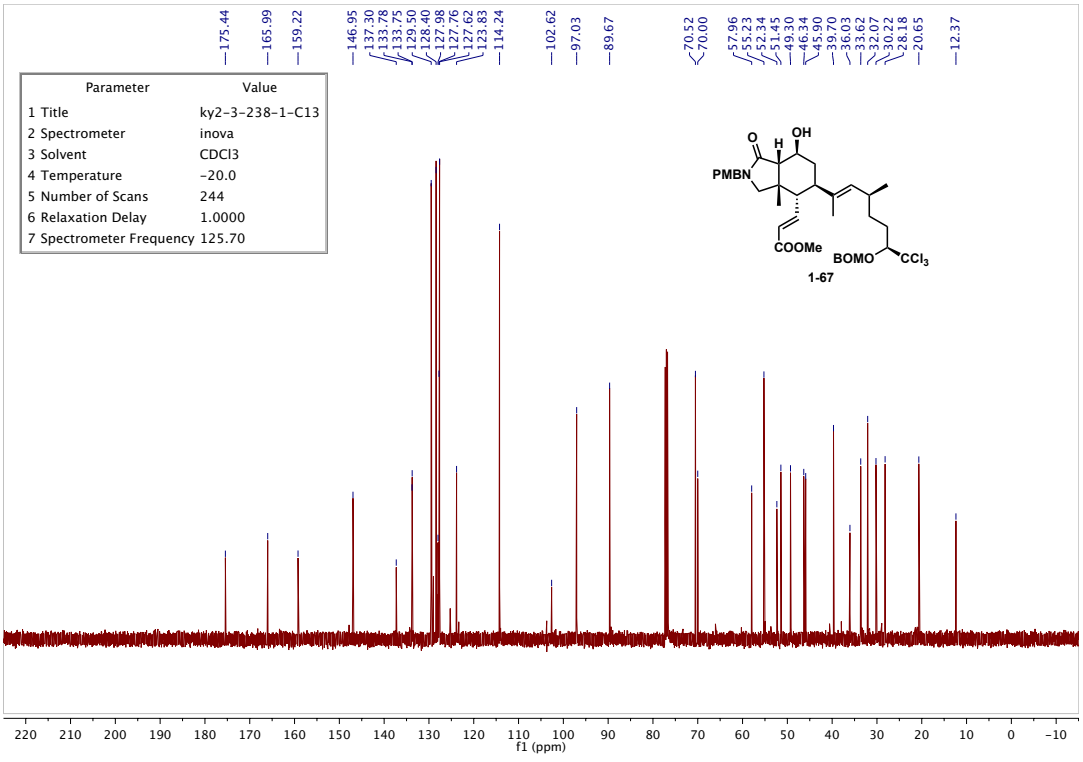
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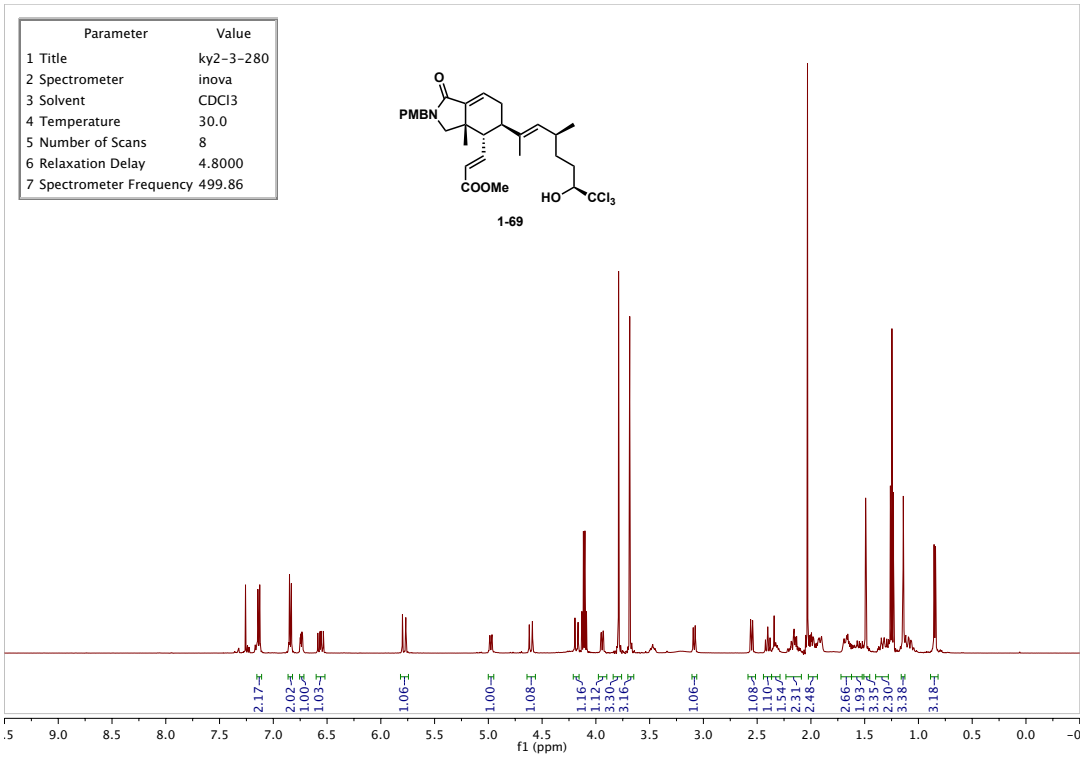
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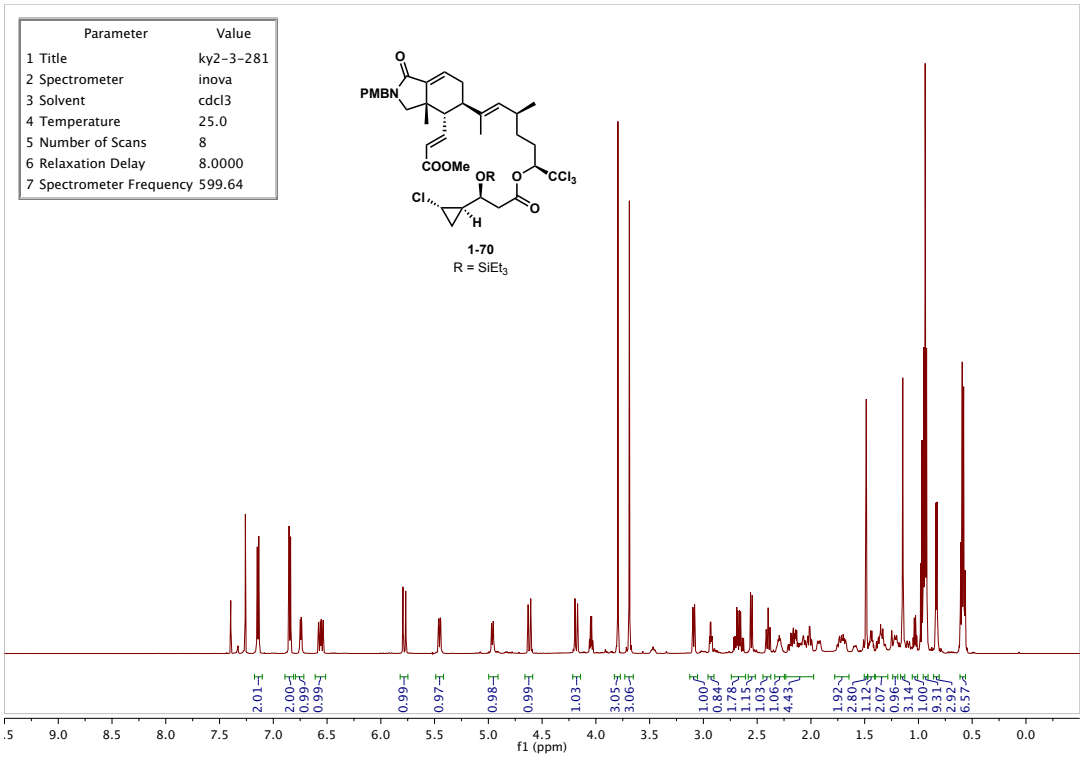
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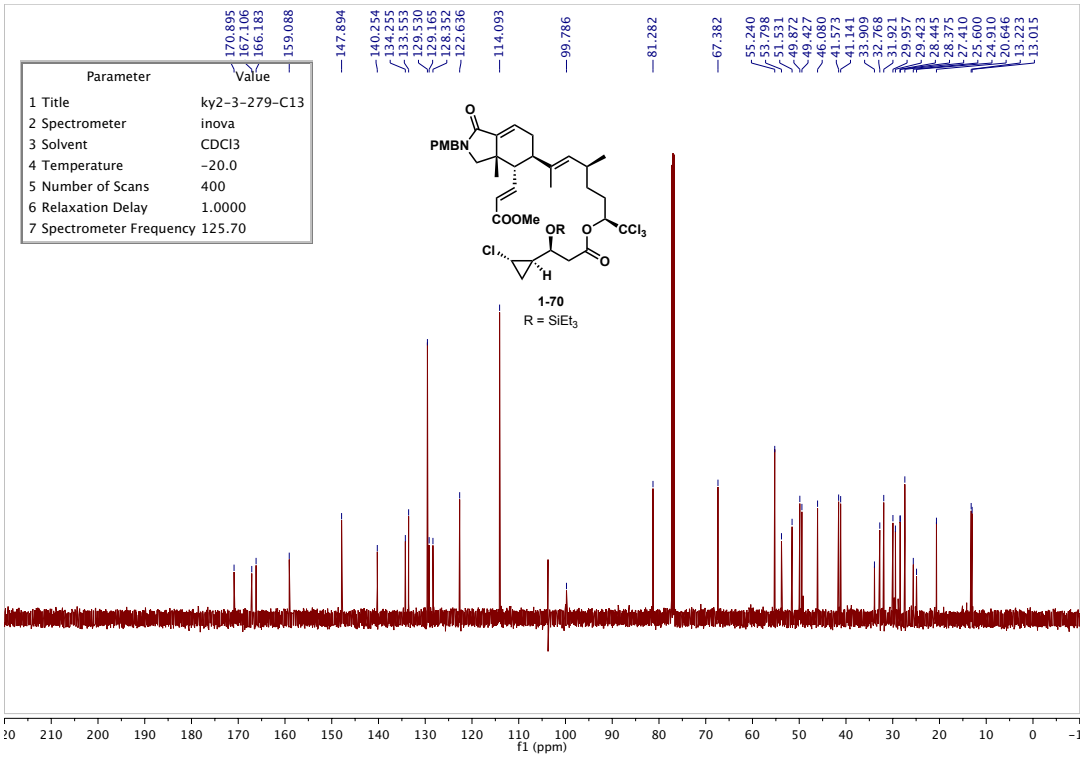
OR
CCl3
Cl
H
1-70
R = SiEt3
f1 (ppm)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133.553
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129.165
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114.093
99.786
81.282
67.382
55.240
53.798
51.531
49.872
49.427
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41.141
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20.646
13.223
13.015
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COOMe
OR
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Cl
H
1-70
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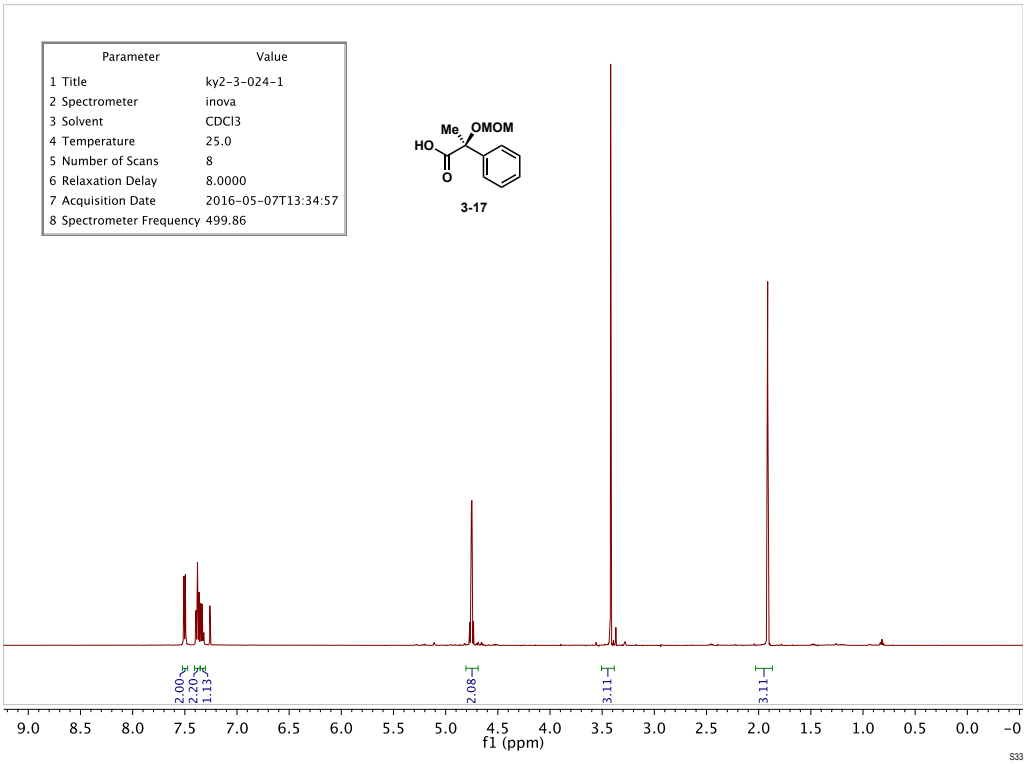
f1 (ppm)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OMOM
HO
3-17
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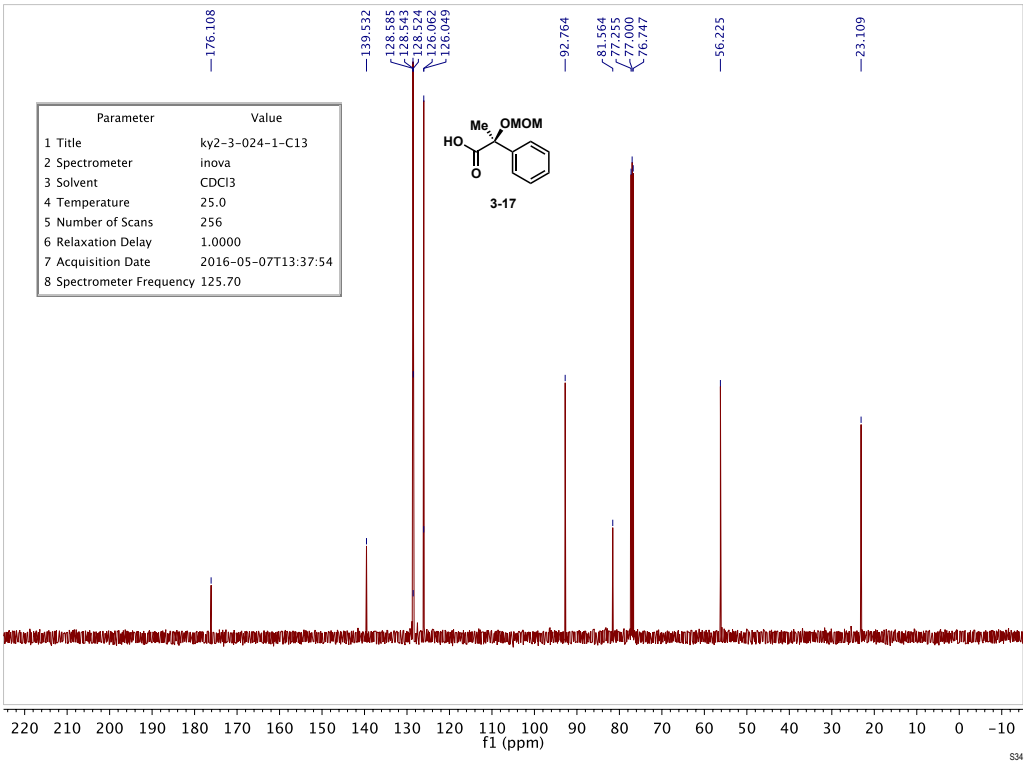
2.20
1.13
2.08
3.11
3.11
f1 (ppm)
S33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77.255
77.000
76.747
56.225
23.109
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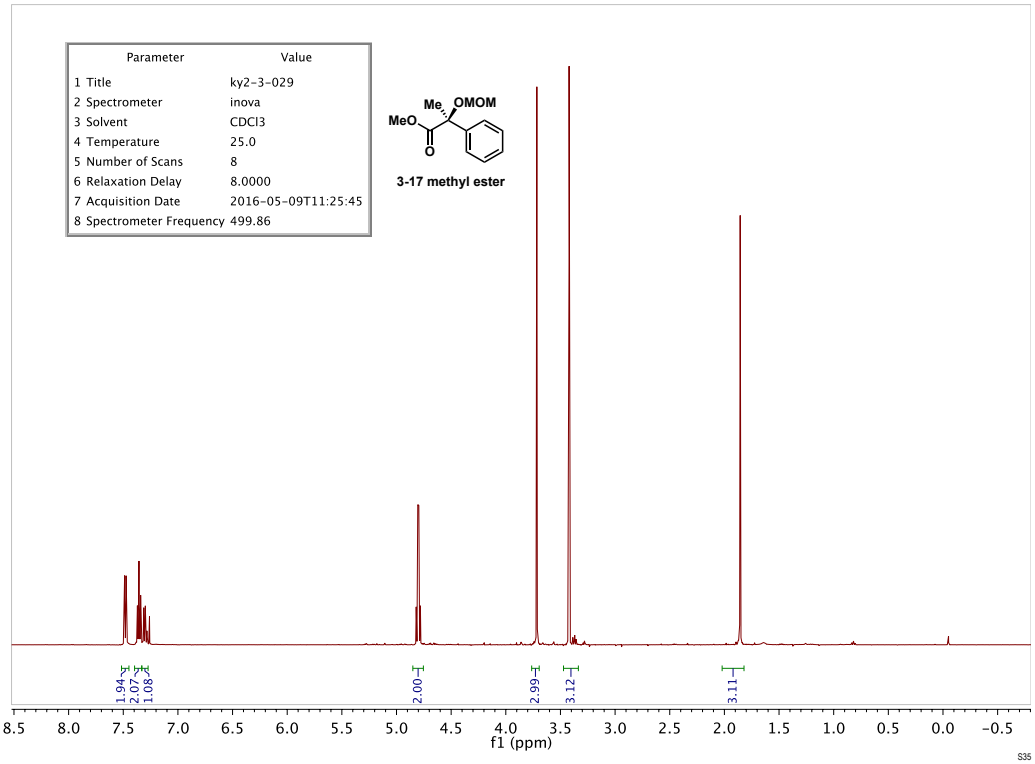
OMOM
HO
O
3-17
f1 (ppm)
S34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OMOM
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O
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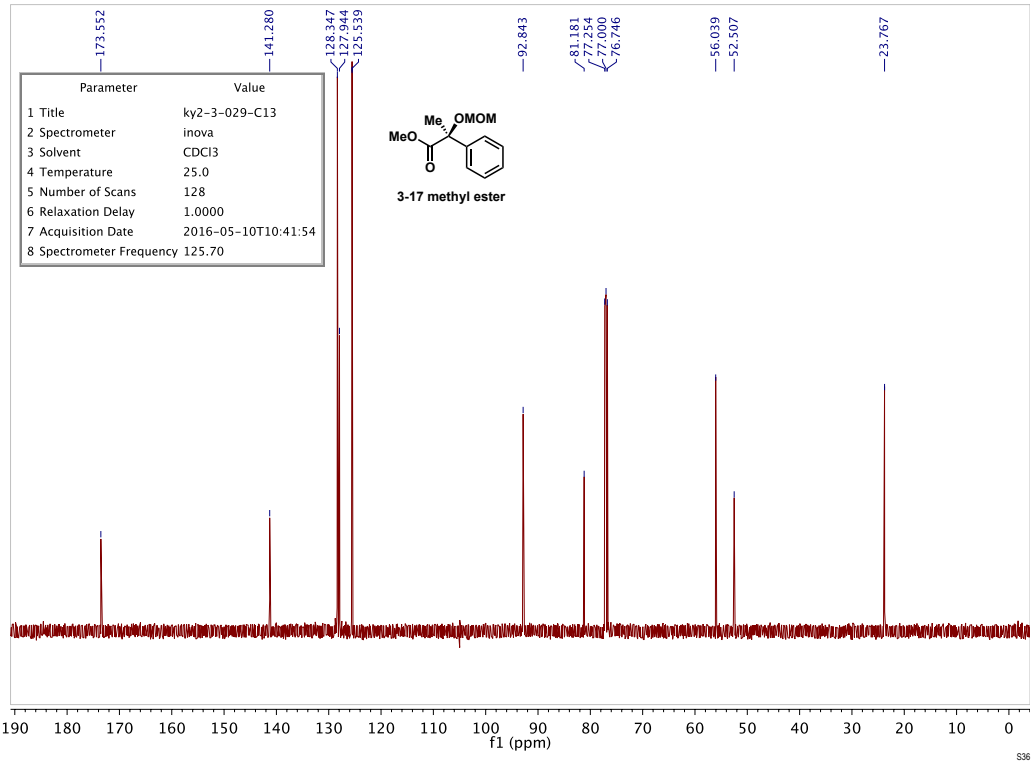
3.11
f1 (ppm)
S35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OMOM
MeO
O
3-17 methyl ester
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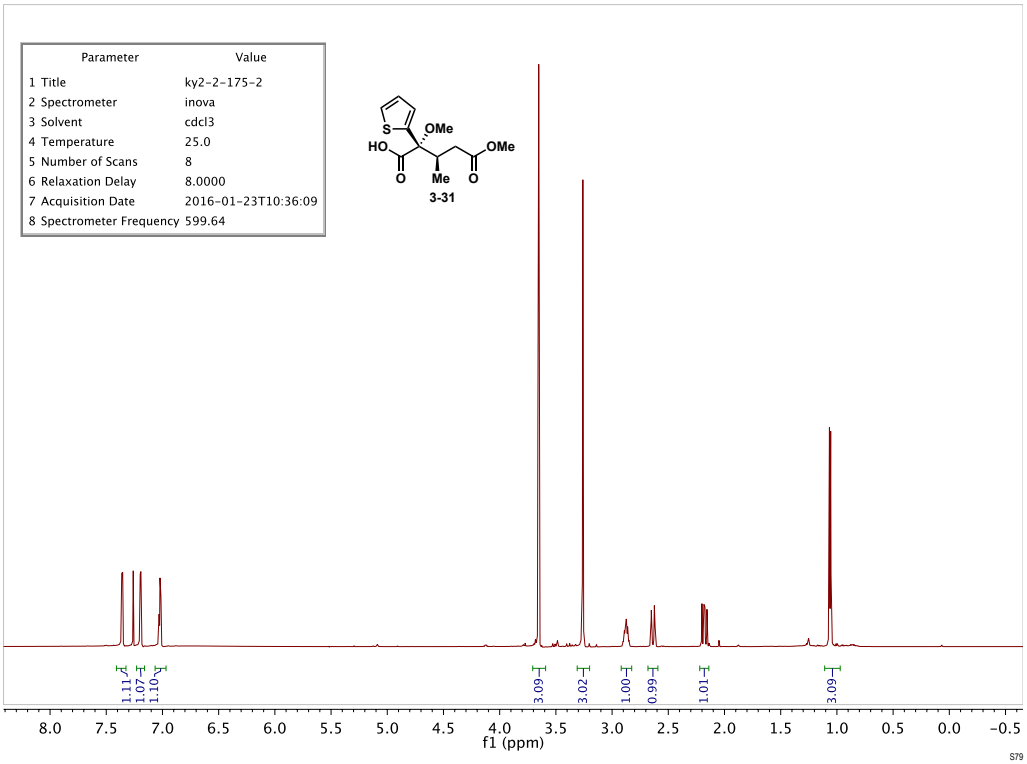
f1 (ppm)
S36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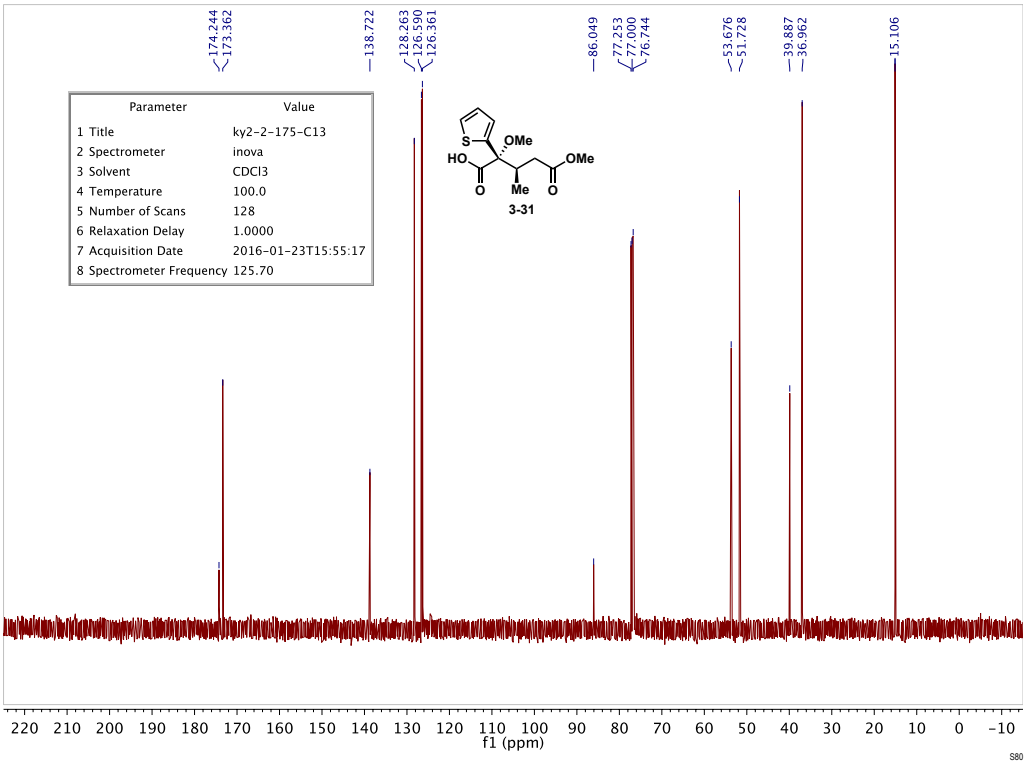
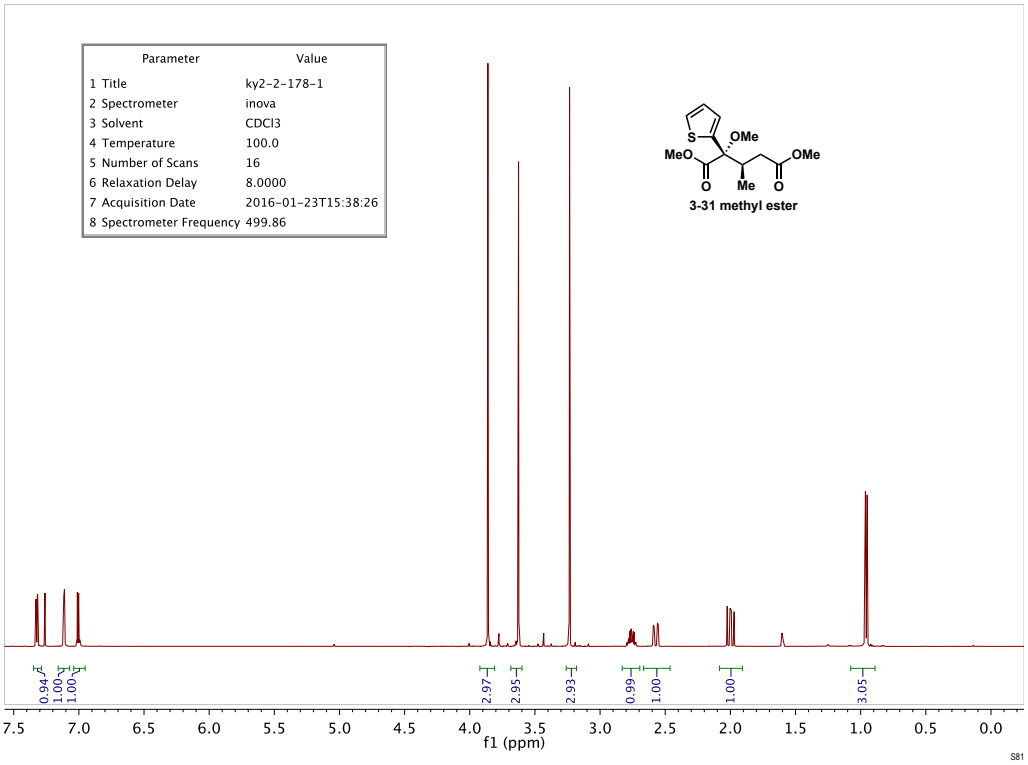
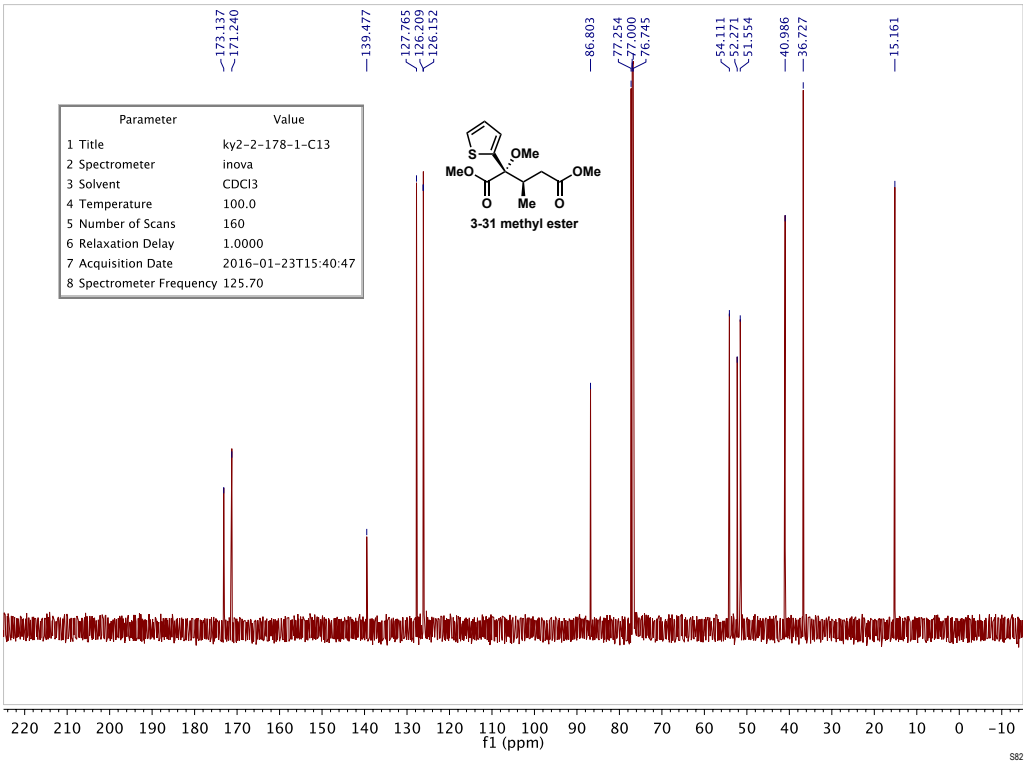
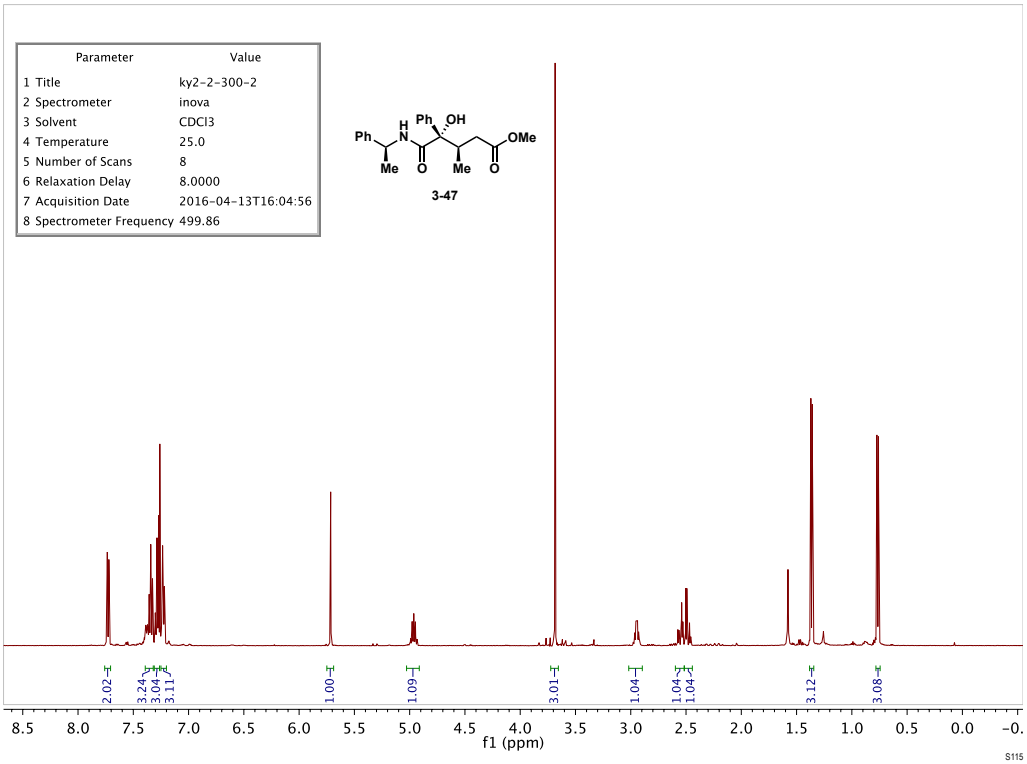
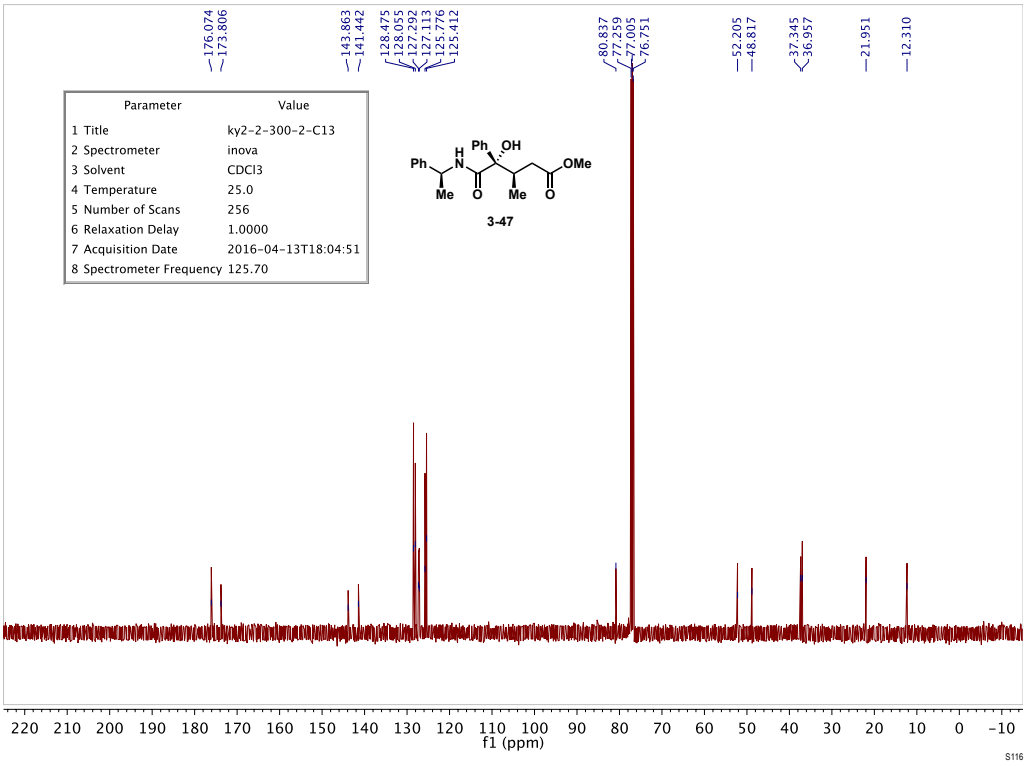
S
OMe
HO
OMe
O
O
Me
3-31
1.11
1.07
1.10
3.09
3.02
1.00
0.99
1.01
3.09
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
S79

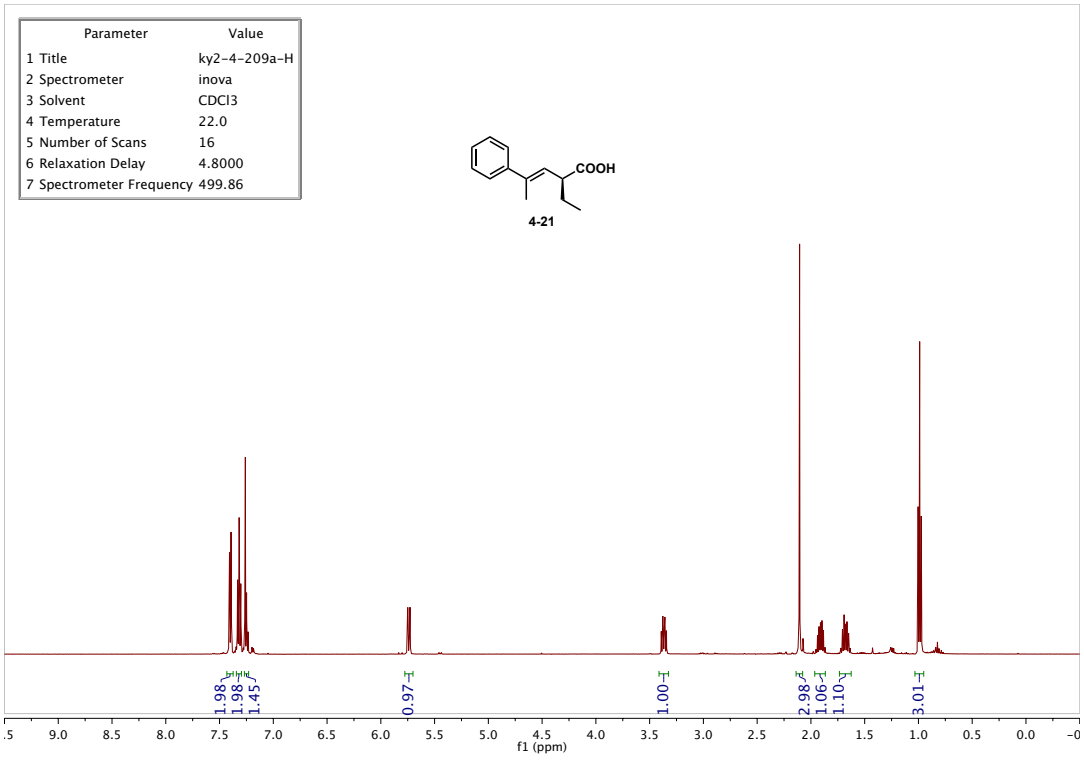

174.244
173.362
138.722
128.263
126.590
126.361
86.049
77.253
77.000
76.744
53.676
51.728
39.887
36.962
15.106
Parameter Value
1 Title ky2-2-175-C13
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 100.0
5 Number of Scans 128
6 Relaxation Delay 1.0000
7 Acquisition Date 2016-01-23T15:55:17
8 Spectrometer Frequency 125.70
OMe
HO
OMe
O
Me
O
3-31
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
S80

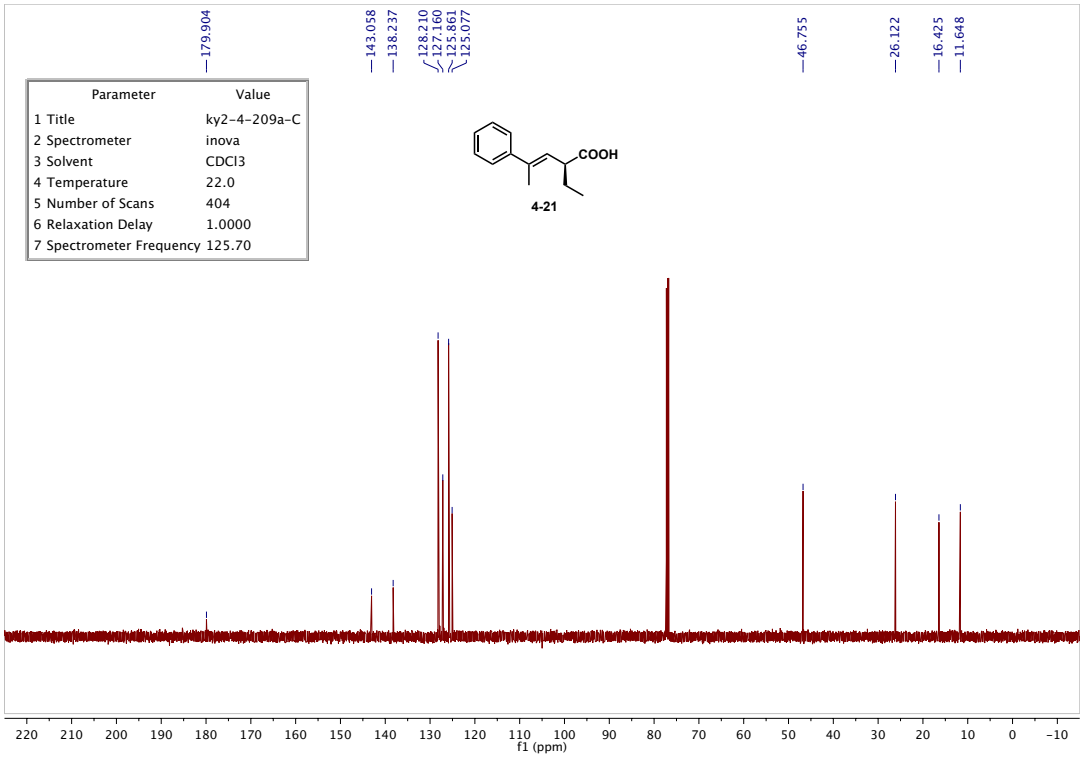

Parameter Value
1 Title ky2-2-178-1
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 100.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-01-23T15:38:26
8 Spectrometer Frequency 499.86
OMe
MeO
OMe
O
Me
O
3-31 methyl ester
0.94
1.00
1.00
2.97
2.95
2.93
0.99
1.00
1.00
3.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
S81

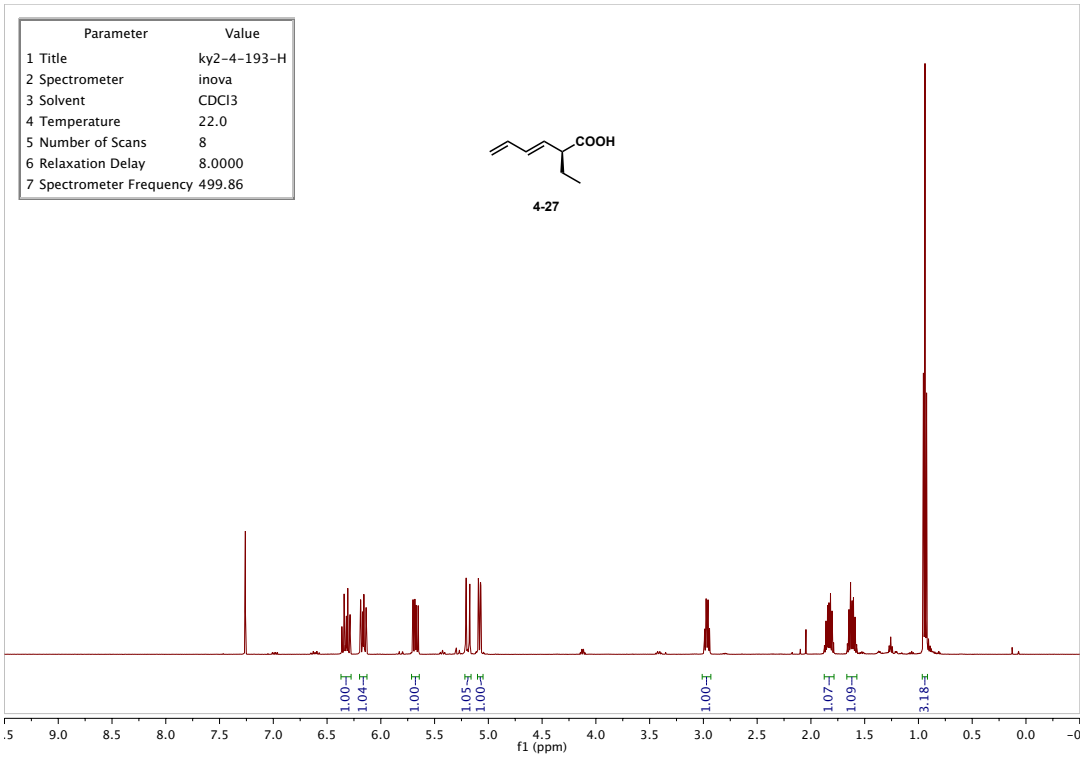

173.137
171.240
139.477
127.765
126.209
126.152
86.803
77.254
77.000
76.745
54.111
52.271
51.554
40.986
36.727
15.161
Parameter Value
1 Title ky2-2-178-1-C13
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 100.0
5 Number of Scans 160
6 Relaxation Delay 1.0000
7 Acquisition Date 2016-01-23T15:40:47
8 Spectrometer Frequency 125.70
S
OMe
MeO
O
Me
O
OMe
3-31 methyl ester
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
S82

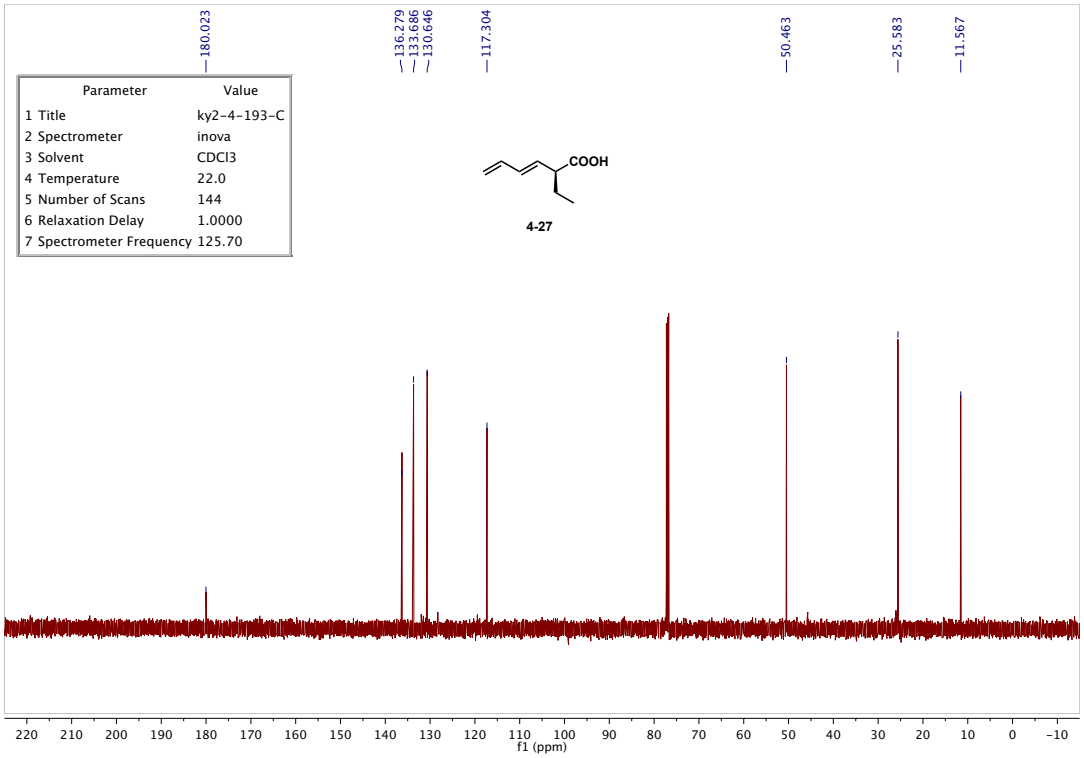

Parameter Value
1 Title ky2-2-300-2
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Acquisition Date 2016-04-13T16:04:56
8 Spectrometer Frequency 499.86
Ph
H
N
Ph
OH
OMe
Me
O
Me
O
3-47
2.02
3.24
3.04
3.11
1.00
1.09
3.01
1.04
1.04
1.04
3.12
3.08
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)
S115

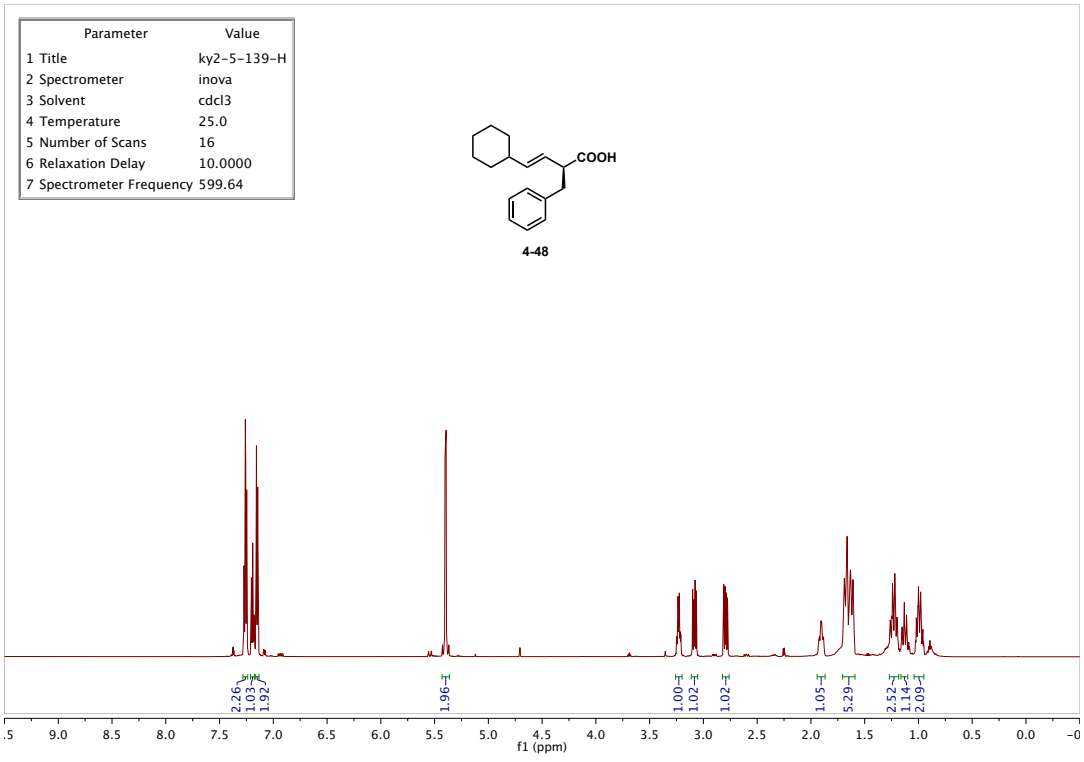

176.074
173.806
143.863
141.442
128.475
128.055
127.292
127.113
125.776
125.412
80.837
77.259
77.005
76.751
52.205
48.817
37.345
36.957
21.951
12.310
Parameter Value
1 Title ky2-2-300-2-C13
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 256
6 Relaxation Delay 1.0000
7 Acquisition Date 2016-04-13T18:04:51
8 Spectrometer Frequency 125.70
Ph
H
N
Ph
OH
OMe
Me
O
Me
O
3-47
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
S116

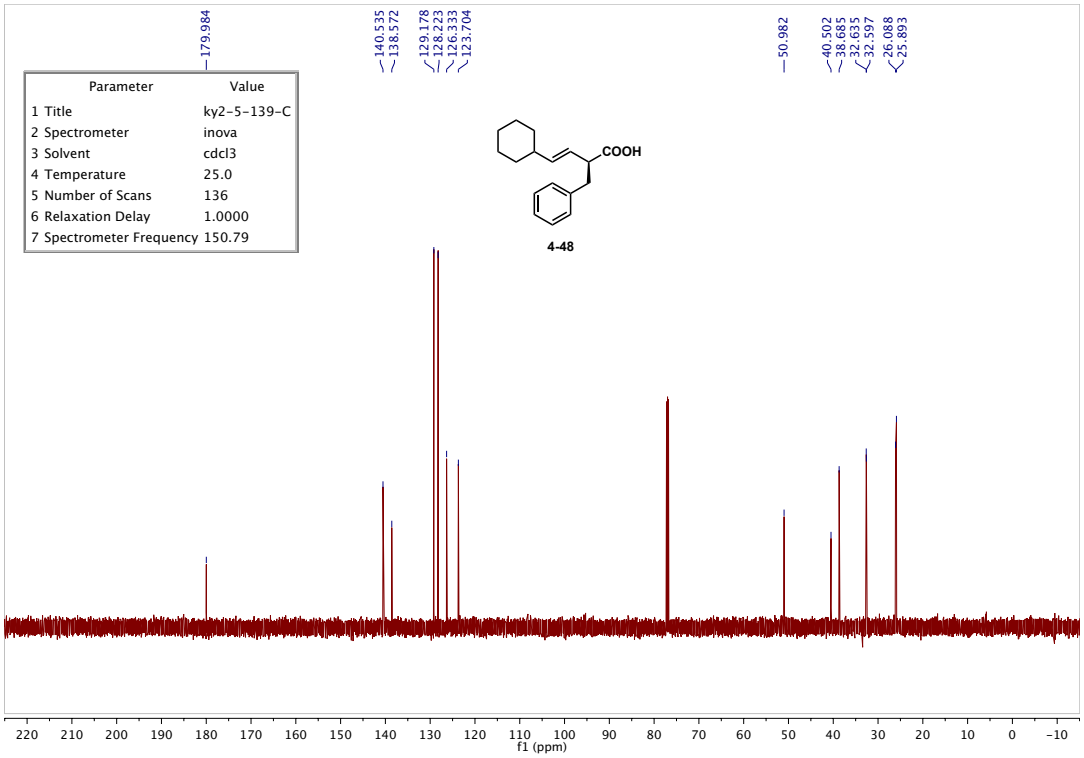

Parameter Value
1 Title ky2-4-209a-H
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 22.0
5 Number of Scans 16
6 Relaxation Delay 4.8000
7 Spectrometer Frequency 499.86
COOH
4-21
1.98
1.98
1.45
0.97
1.00
2.98
1.06
1.10
3.01
.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

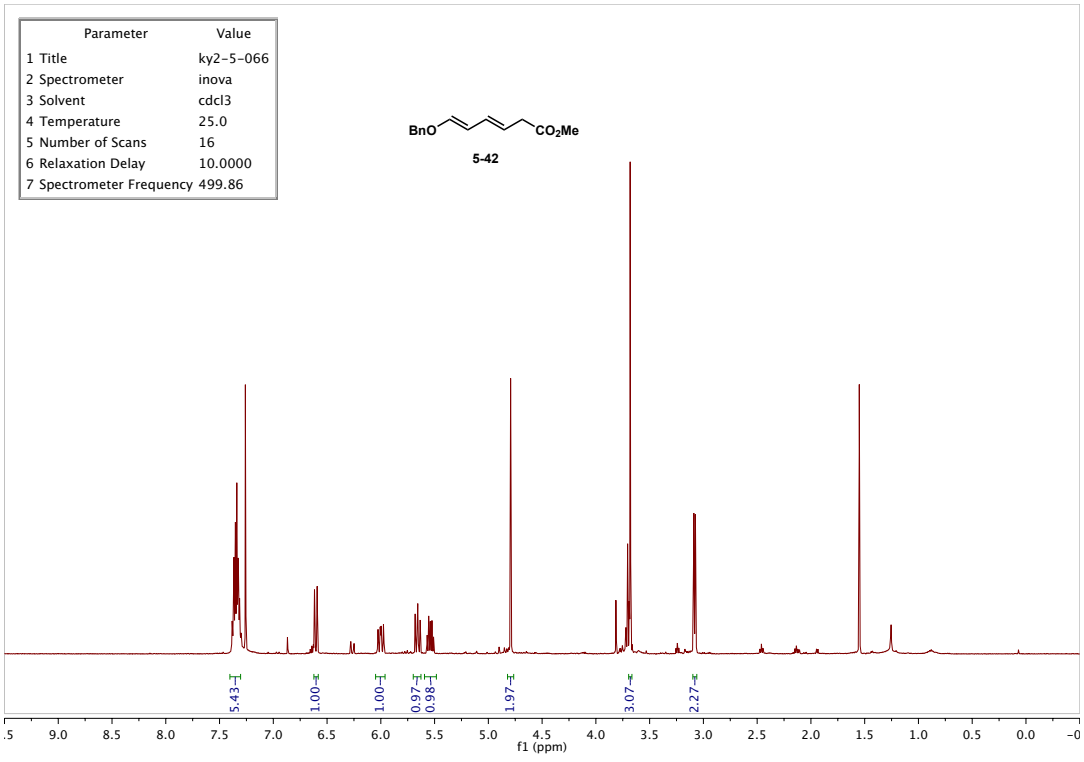

179.904
143.058
138.237
128.210
127.160
125.861
125.077
46.755
26.122
16.425
11.648
Parameter Value
1 Title ky2-4-209a-C
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 22.0
5 Number of Scans 404
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 125.70
COOH
4-21
f1 (ppm)

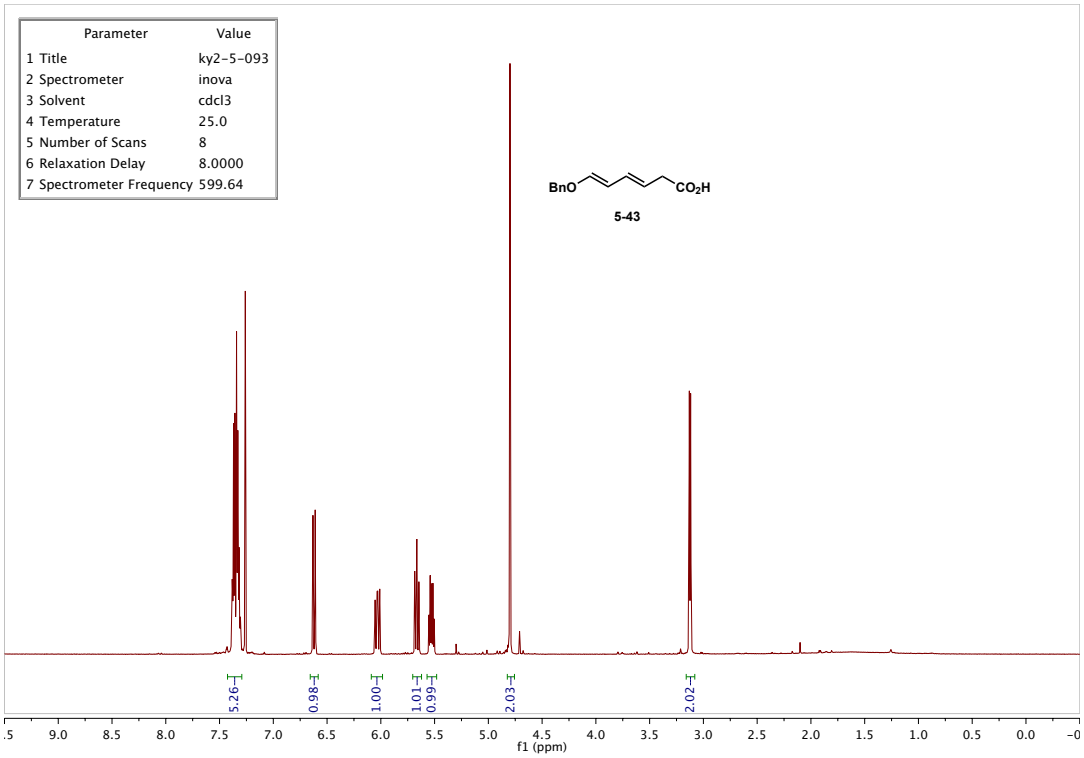

Parameter Value
1 Title ky2-4-193-H
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 22.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Spectrometer Frequency 499.86
COOH
4-27
1.00
1.04
1.00
1.05
1.00
1.00
1.07
1.09
3.18
f1 (ppm)

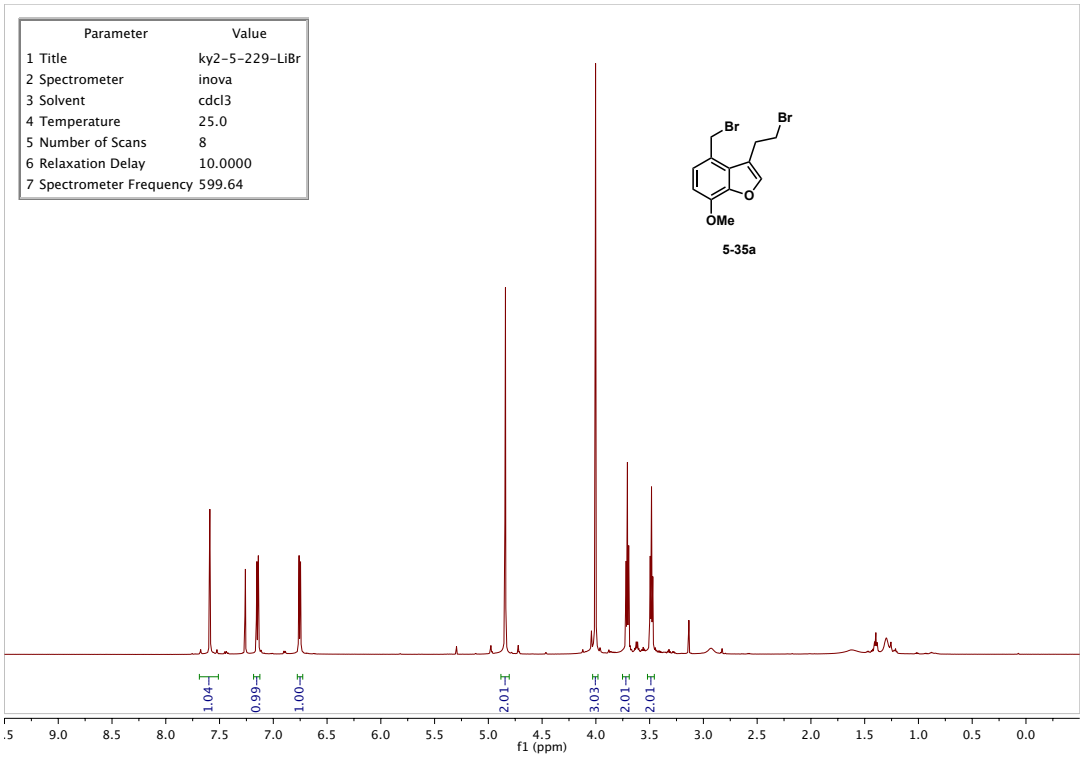

180.023
136.279
133.686
130.646
117.304
50.463
25.583
11.567
Parameter Value
1 Title ky2-4-193-C
2 Spectrometer inova
3 Solvent CDCl3
4 Temperature 22.0
5 Number of Scans 144
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 125.70
COOH
4-27
f1 (ppm)


Parameter Value
1 Title ky2-5-139-H
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 10.0000
7 Spectrometer Frequency 599.64
COOH
4-48
2.26
1.03
1.92
1.96
1.00
1.02
1.02
1.05
5.29
2.52
1.14
2.09
f1 (ppm)

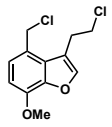

179.984
140.535
138.572
129.178
128.223
126.333
123.704
50.982
40.502
38.685
32.635
32.597
26.088
25.893
Parameter Value
1 Title ky2-5-139-C
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 136
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 150.79
COOH
4-48
f1 (ppm)


Parameter Value
1 Title ky2-5-066
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 10.0000
7 Spectrometer Frequency 499.86
BnO
CO2Me
5-42
5.43
1.00
1.00
0.97
0.98
1.97
3.07
2.27
f1 (ppm)


Parameter Value
1 Title ky2-5-093
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Spectrometer Frequency 599.64
BnO
CO2H
5-43
5.26
0.98
1.00
1.01
0.99
2.03
2.02
f1 (ppm)

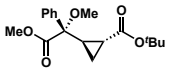

Parameter Value
1 Title ky2-5-229-LiBr
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 10.0000
7 Spectrometer Frequency 599.64
Br
Br
O
OMe
5-35a
1.04
0.99
1.00
2.01
3.03
2.01
2.01
f1 (ppm)

Parameter	Value
1 Title	ky2-5-281-a
2 Spectrometer	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	16
6 Relaxation Delay	10.0000
7 Spectrometer Frequency	599.64

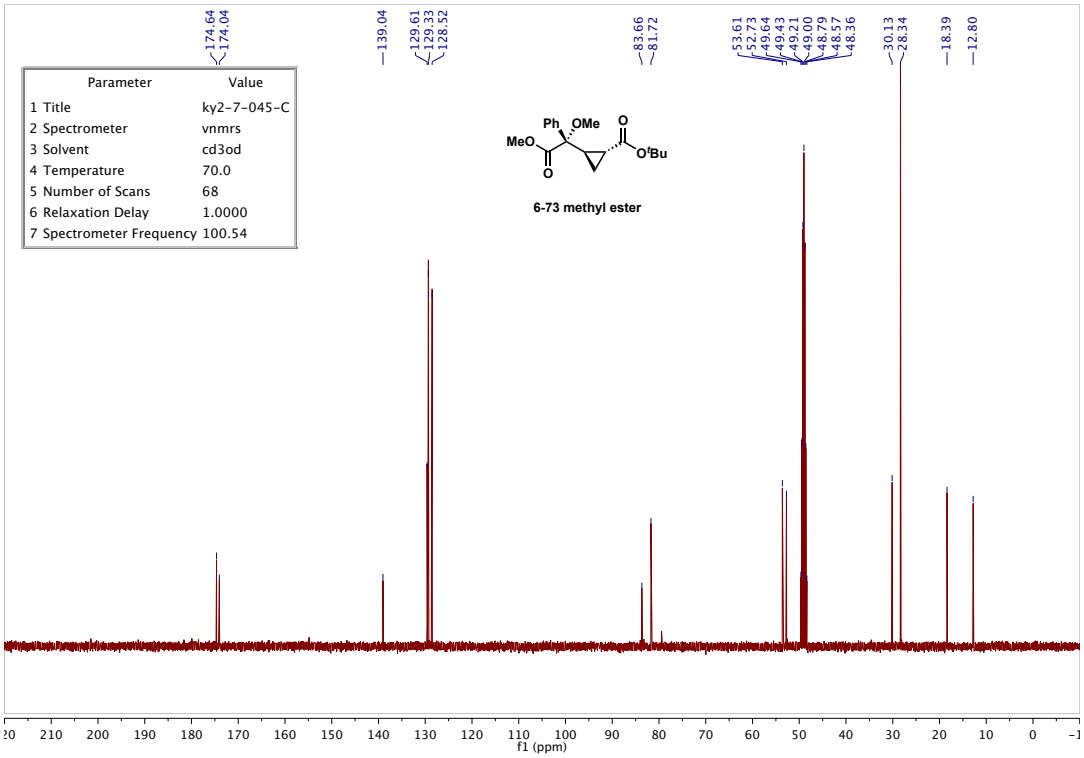


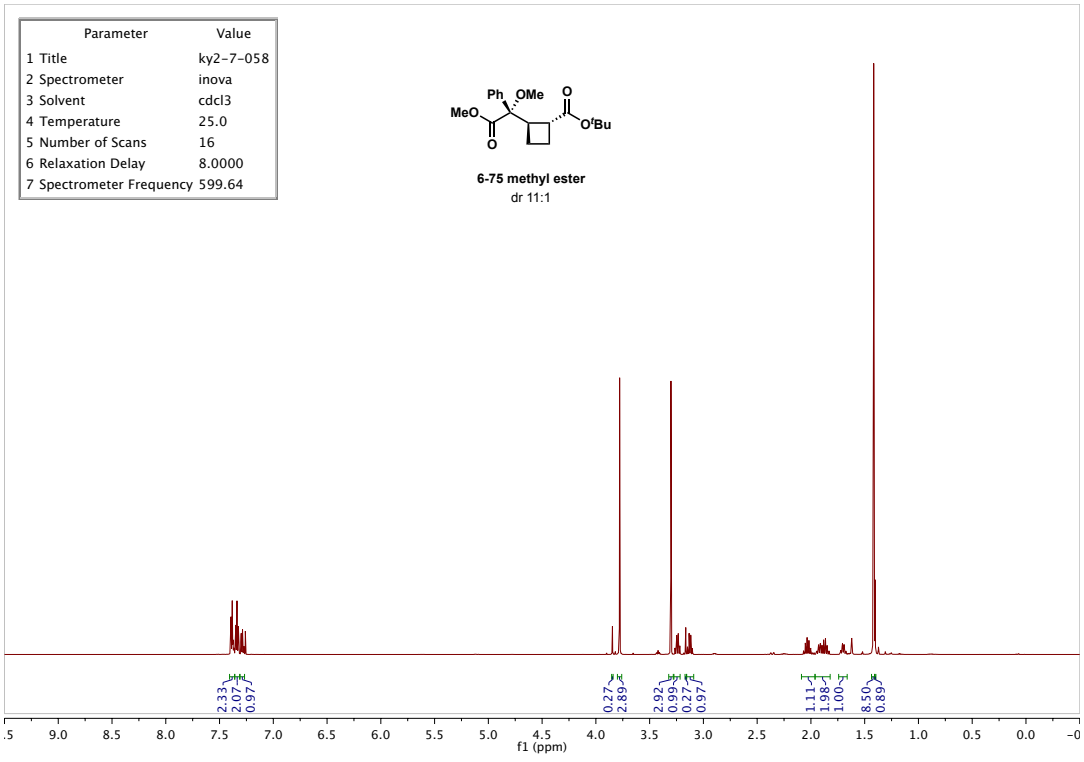
5-35b

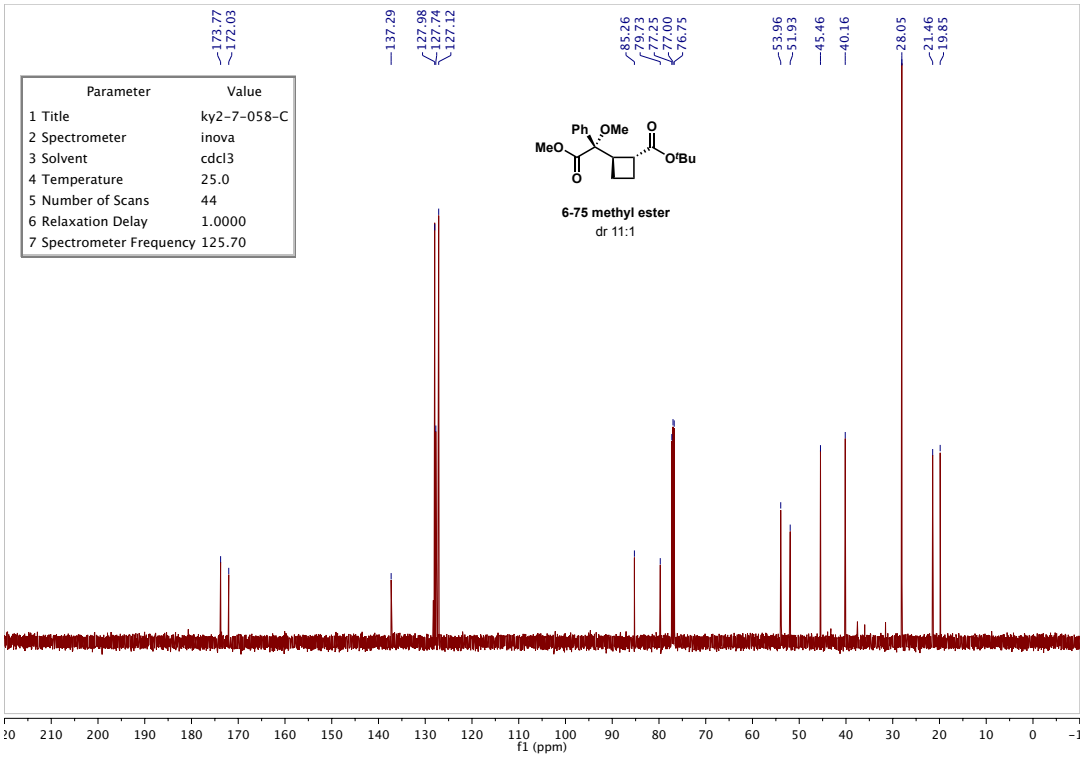
Parameter	Value
1 Title	ky2-7-045
2 Spectrometer	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Spectrometer Frequency	499.85

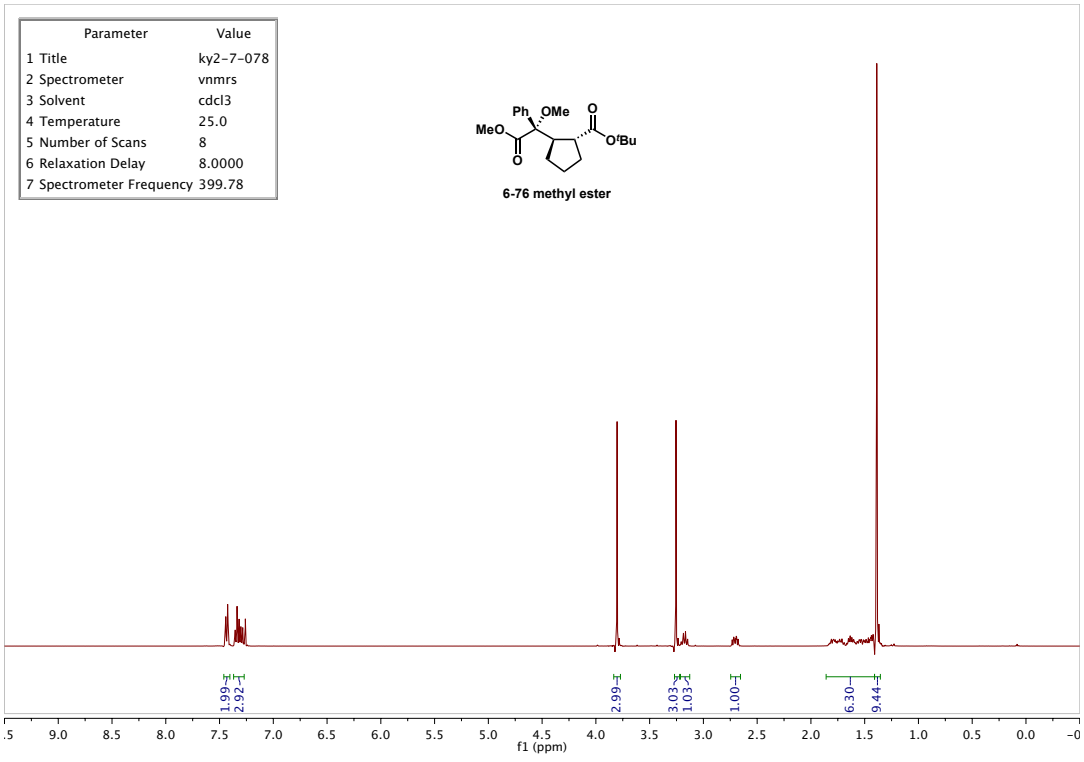


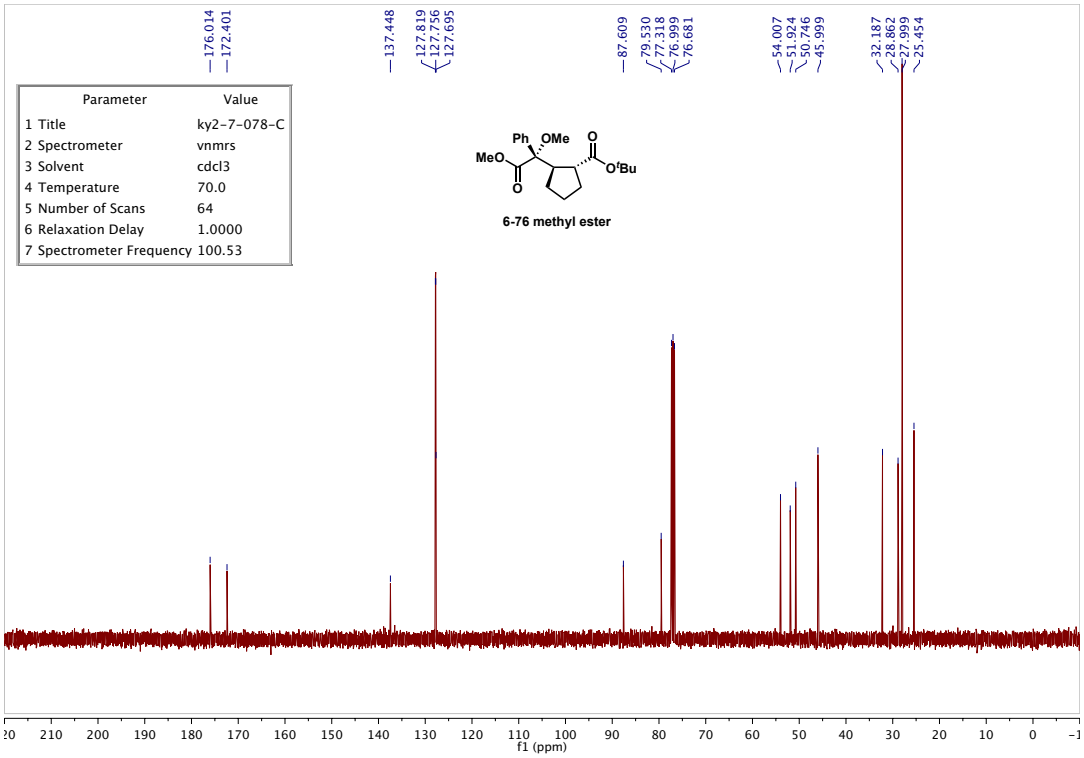
6-73 methyl ester

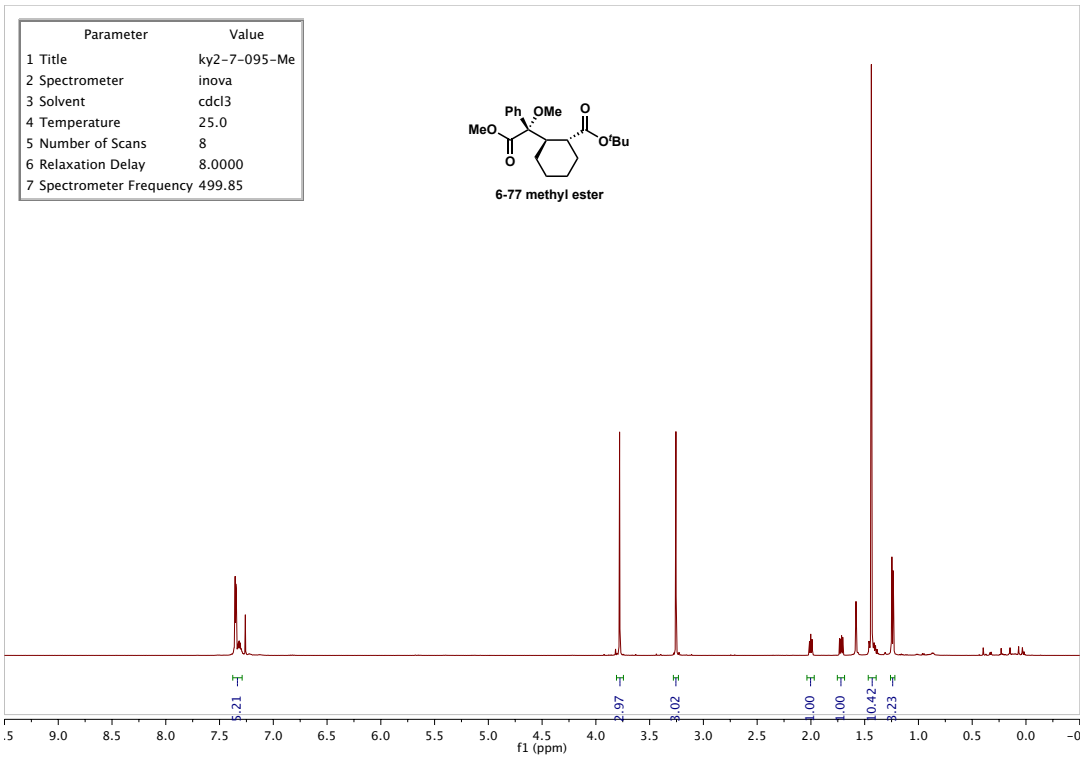

174.64
174.04
139.04
129.61
129.33
128.52
83.66
81.72
53.61
52.73
49.64
49.43
49.21
49.00
48.79
48.57
48.36
30.13
28.34
18.39
12.80
Parameter Value
1 Title ky2-7-045-C
2 Spectrometer vnmrs
3 Solvent cd3od
4 Temperature 70.0
5 Number of Scans 68
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 100.54
Ph OMe
MeO
O
O
O
O
tBu
6-73 methyl ester
f1 (ppm)

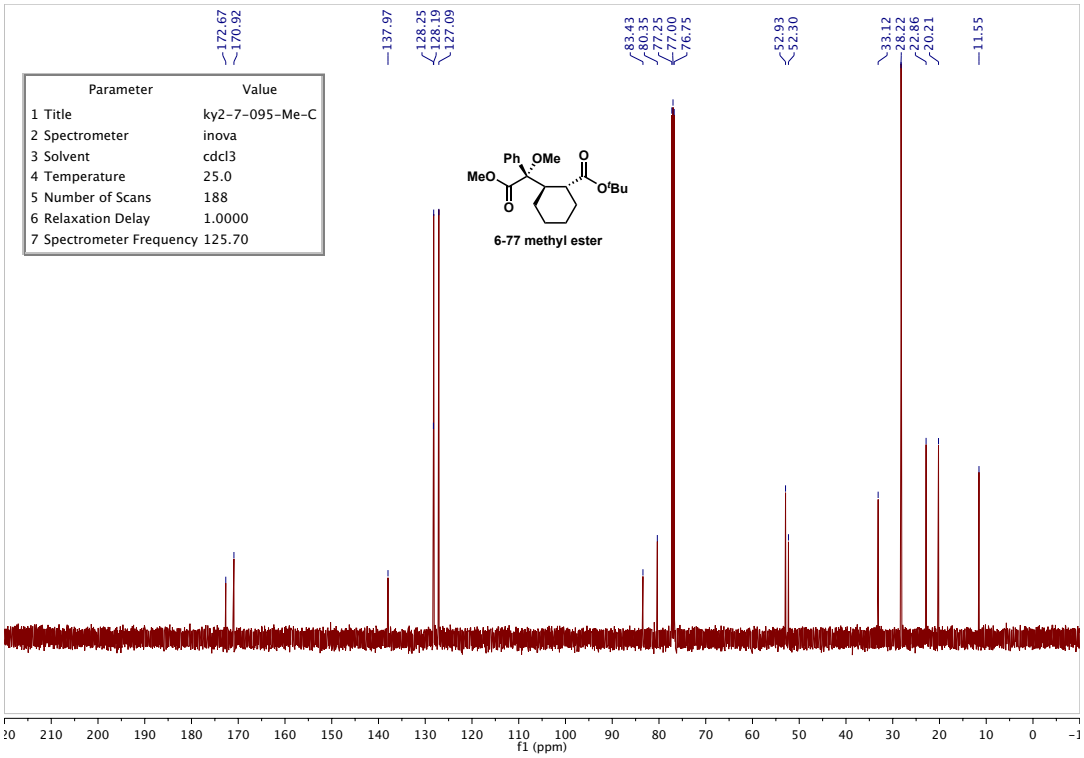

Parameter Value
1 Title ky2-7-058
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Spectrometer Frequency 599.64
Ph OMe
MeO
O
O
O
O
tBu
6-75 methyl ester
dr 11:1
2.33
2.07
0.97
0.27
2.89
2.92
0.99
0.27
0.97
1.11
1.98
1.00
8.50
0.89
f1 (ppm)


173.77
172.03
137.29
127.98
127.74
127.12
85.26
79.73
77.25
77.00
76.75
53.96
51.93
45.46
40.16
28.05
21.46
19.85
Parameter Value
1 Title ky2-7-058-C
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 44
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 125.70
Ph OMe
MeO
O
O
O
O
tBu
6-75 methyl ester
dr 11:1
f1 (ppm)


Parameter Value
1 Title ky2-7-078
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Spectrometer Frequency 399.78
Ph OMe
MeO
O
O
O
O
tBu
6-76 methyl ester
1.99
2.92
2.99
3.03
1.03
1.00
6.30
9.44
f1 (ppm)


176.014
172.401
137.448
127.819
127.756
127.695
87.609
79.530
77.318
76.999
76.681
54.007
51.924
50.746
45.999
32.187
28.862
27.999
25.454
Parameter Value
1 Title ky2-7-078-C
2 Spectrometer vnmrs
3 Solvent cdcl3
4 Temperature 70.0
5 Number of Scans 64
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 100.53
Ph OMe
MeO
O
O
O
O
tBu
6-76 methyl ester
f1 (ppm)

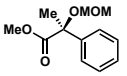

Parameter Value
1 Title ky2-7-095-Me
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Spectrometer Frequency 499.85
Ph OMe
MeO
O
O
O
O
tBu
6-77 methyl ester
5.21
2.97
3.02
1.00
1.00
10.42
3.23
f1 (ppm)


172.67
170.92
137.97
128.25
128.19
127.09
83.43
80.35
77.25
77.00
76.75
52.93
52.30
33.12
28.22
22.86
20.21
11.55
Parameter Value
1 Title ky2-7-095-Me-C
2 Spectrometer inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 188
6 Relaxation Delay 1.0000
7 Spectrometer Frequency 125.70
Ph OMe
MeO
O
O
O
O^{t}Bu
6-77 methyl ester
f1 (ppm)

==== Shimadzu LCsolution Analysis Report ====

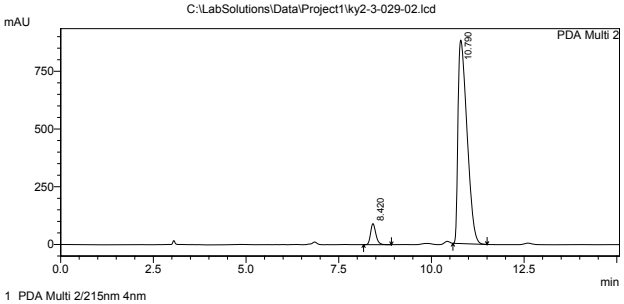
C:\LabSolutions\Data\Project1\ky2-3-029-02.lcd

Acquired by : Admin
Sample Name : ky2-3-029
Sample ID : ky2-3-029
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-3-029-02.lcd
Method File Name : ATH-OD-J-analytical-hplc.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 5/13/2016 10:30:52 AM
Data Processed : 5/13/2016 10:45:55 AM



3-17 methyl ester

<Chromatogram>



1 PDA Multi 2/215nm 4nm

PeakTable

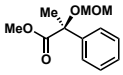
PDA Ch2 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.420	901213	91083	5.685	9.366
2	10.790	14950598	881395	94.315	90.634
Total		15851811	972477	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

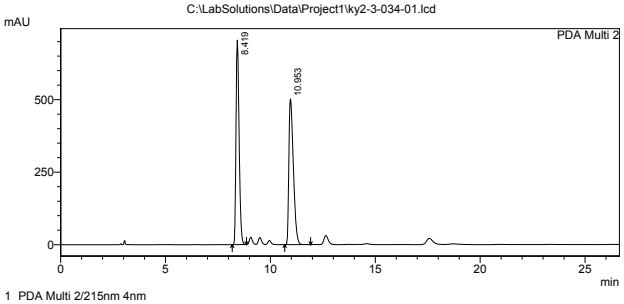
C:\LabSolutions\Data\Project1\ky2-3-034-01.lcd

Acquired by : Admin
Sample Name : ky2-3-034
Sample ID : ky2-3-034
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-3-034-01.lcd
Method File Name : ATH-OD-J-analytical-hplc.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 5/13/2016 9:44:16 AM
Data Processed : 5/13/2016 10:10:57 AM



(±)-3-17 methyl ester

<Chromatogram>



1 PDA Multi 2/215nm 4nm

PeakTable

PDA Ch2 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.419	7278073	705107	49.269	58.392
2	10.953	7493902	502426	50.731	41.608
Total		14771975	1207533	100.000	100.000

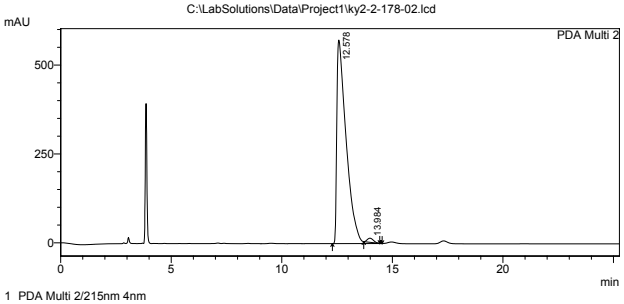
(±)-

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-2-178-02.lcd

Acquired by : Admin
Sample Name : ky2-2-178
Sample ID : ky2-2-178
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-2-178-02.lcd
Method File Name : ATH-OD-J-analytical-hplc.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 1/27/2016 4:21:22 PM
Data Processed : 1/27/2016 4:46:40 PM

<Chromatogram>

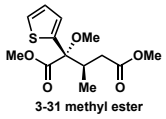


1 PDA Multi 2/215nm 4nm

PeakTable

PDA Ch2 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.578	16797629	572443	98.694	98.011
2	13.984	222242	11614	1.306	1.989
Total		17019870	584057	100.000	100.000



3-31 methyl ester

C:\LabSolutions\Data\Project1\ky2-2-178-02.lcd

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-2-187-01.lcd

Acquired by : Admin
Sample Name : ky2-2-187
Sample ID : ky2-2-187
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-2-187-01.lcd
Method File Name : ATH-OD-J-analytical-hplc.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 1/27/2016 3:35:18 PM
Data Processed : 1/27/2016 4:11:08 PM

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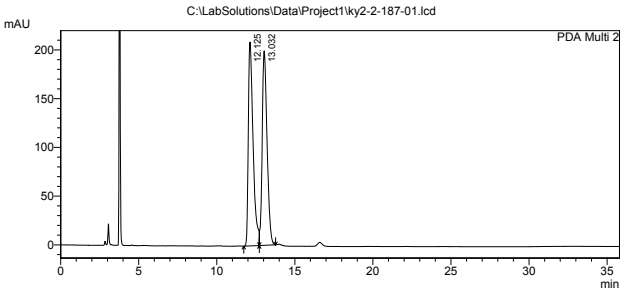
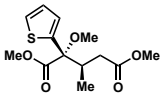


1 PDA Multi 2/215nm 4nm

PeakTable

PDA Ch2 215nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.125	4444051	209136	50.646	51.174
2	13.032	4330649	199542	49.354	48.826
Total		8774700	408679	100.000	100.000



(±)-3-31 methyl ester

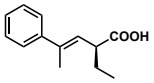
(±)-

C:\LabSolutions\Data\Project1\ky2-2-187-01.lcd

==== Shimadzu LCsolution Analysis Report ====

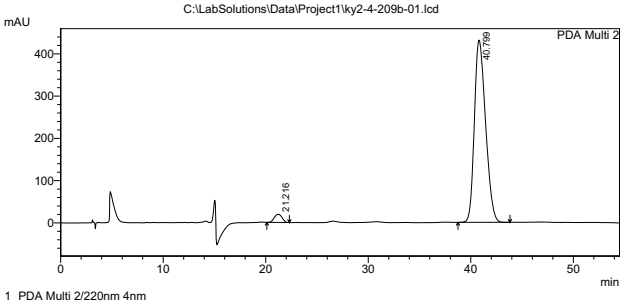
C:\LabSolutions\Data\Project1\ky2-4-209b-01.lcd

Acquired by : Kai Yu
Sample Name : ky2-4-209b
Sample ID : ky2-4-209b
Vail # : 0
Injection Volume : 1 uL
Data File Name : ky2-4-209b-01.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 8/14/2017 11:44:56 AM
Data Processed : 8/14/2017 12:39:27 PM



4-21

<Chromatogram>



1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

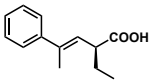
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.216	1009184	19133	2.992	4.247
2	40.799	32721040	431413	97.008	95.753
Total		33730223	450547	100.000	100.000

C:\LabSolutions\Data\Project1\ky2-4-209b-01.lcd

==== Shimadzu LCsolution Analysis Report ====

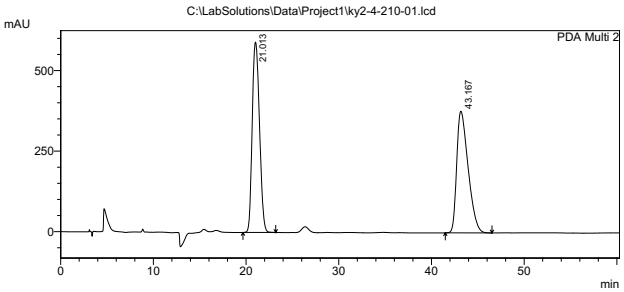
C:\LabSolutions\Data\Project1\ky2-4-210-01.lcd

Acquired by : Kai Yu
Sample Name : ky2-4-210
Sample ID : ky2-4-210
Vail # : 0
Injection Volume : 1 uL
Data File Name : ky2-4-210-01.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 8/14/2017 9:34:17 AM
Data Processed : 8/14/2017 10:34:36 AM



(±)-4-21

<Chromatogram>



1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.013	32297786	590983	50.050	61.014
2	43.167	32233653	377612	49.950	38.986
Total		64531439	968595	100.000	100.000

C:\LabSolutions\Data\Project1\ky2-4-210-01.lcd

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-4-193-03.lcd

Acquired by	: Kai Yu
Sample Name	: ky2-4-193
Sample ID	: ky2-4-193
Vail #	: 0
Injection Volume	: 1 uL
Data File Name	: ky2-4-193-03.lcd
Method File Name	: brad.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 8/2/2017 12:13:51 PM
Data Processed	: 8/2/2017 12:52:34 PM

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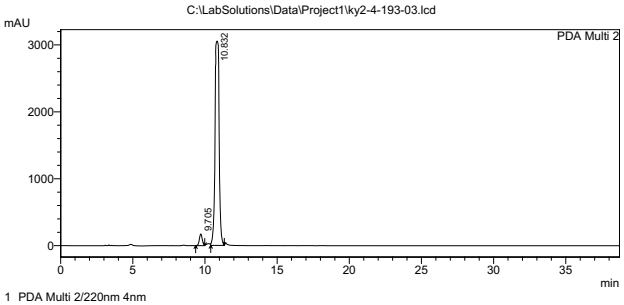

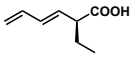

4-27

1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.705	2500175	174413	3.941	5.402
2	10.832	60941377	3053967	96.059	94.598
Total		63441552	3228380	100.000	100.000

C:\LabSolutions\Data\Project1\ky2-4-193-03.lcd

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-4-194-04.lcd

Acquired by	: Kai Yu
Sample Name	: ky2-4-194
Sample ID	: ky2-4-194
Vail #	: 0
Injection Volume	: 1 uL
Data File Name	: ky2-4-194-04.lcd
Method File Name	: brad.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 8/2/2017 10:56:08 AM
Data Processed	: 8/2/2017 11:54:08 AM

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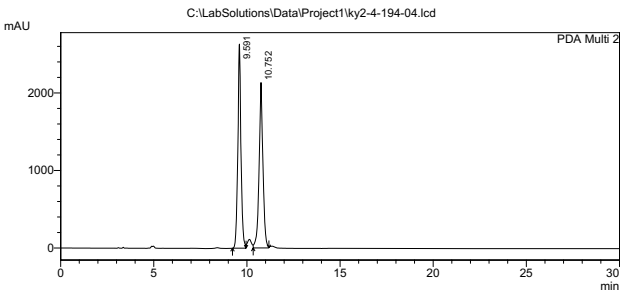
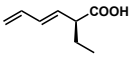




(±)-4-27

1 PDA Multi 2/220nm 4nm

PeakTable

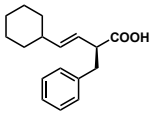
PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.591	30699804	2631996	50.106	55.247
2	10.752	30569564	2132019	49.894	44.753
Total		61269368	4764014	100.000	100.000

C:\LabSolutions\Data\Project1\ky2-4-194-04.lcd

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-4-074b-01.lcd
OD-H, 2% iPrOH/Hex, 0.2% TFA, 1 mg/mL, 1 mL/min, 10 uLAcquired by : Kai Yu
Sample Name : ky2-4-074b
Sample ID : ky2-4-074b
Vail # :
Injection Volume : 1 uL
Data File Name : ky2-4-074b-01.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 4/17/2017 12:46:48 PM
Data Processed : 4/17/2017 2:10:49 PM



4-48

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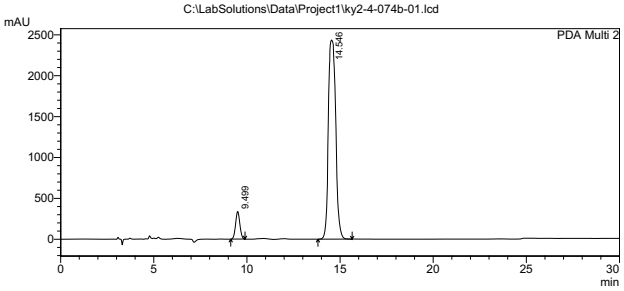

1 PDA Multi 2/210nm 4nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.499	5365538	337661	7.449	12.177
2	14.546	66666232	2435218	92.551	87.823
Total		72031770	2772880	100.000	100.000

C:\LabSolutions\Data\Project1\ky2-4-074b-01.lcd

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-5-139-01.lcd
Acquired by : Kai Yu
Sample Name : ky2-5-139
Sample ID : ky2-5-139
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-5-139-01.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 3/20/2018 4:30:39 PM
Data Processed : 3/20/2018 5:09:46 PM

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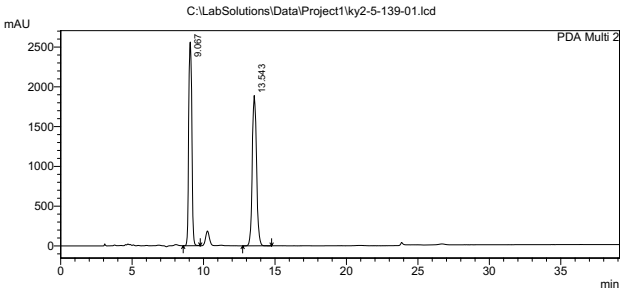

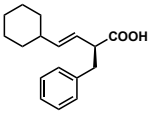

(±)-4-48

1 PDA Multi 2/210nm 4nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.067	39299447	2558703	49.921	57.536
2	13.543	39423383	1888449	50.079	42.464
Total		78722830	4447153	100.000	100.000

C:\LabSolutions\Data\Project1\ky2-5-139-01.lcd

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-7-045-01.lcd
OJ-H, 5% iPrOH/Hex, 1 mg/mL, 1 mL/min, 10 uLAcquired by : Kai Yu
Sample Name : ky2-7-045
Sample ID : ky2-7-045
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-7-045-01.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name :
Data Acquired : 4/26/2019 1:43:10 PM
Data Processed : 4/26/2019 2:39:32 PM

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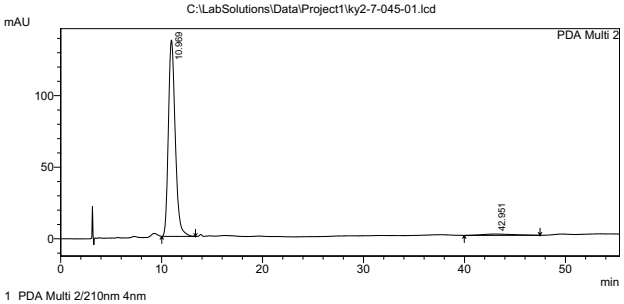

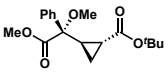

6-73 methyl ester

1 PDA Multi 2/210nm 4nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.969	6458406	137180	96.955	99.337
2	42.951	202804	916	3.045	0.663
Total		6661210	138096	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-7-045-rac-03.lcd
OD-H, 5% iPrOH/Hex, 1 mg/mL, 1 mL/min, 10 uLAcquired by : Kai Yu
Sample Name : ky2-7-045-rac
Sample ID : ky2-7-045-rac
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-7-045-rac-03.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 4/26/2019 3:24:03 PM
Data Processed : 4/26/2019 3:40:08 PM

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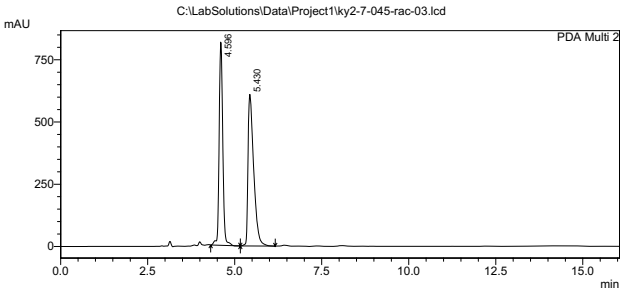

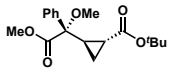

(±)-6-73 methyl ester

1 PDA Multi 2/210nm 4nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.596	5905337	816416	46.087	57.306
2	5.430	6908064	608248	53.913	42.694
Total		12813401	1424664	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-7-060-01.lcd
AD-H, 1% iPrOH/Hex, 1 mg/mL, 1 mL/min, 10 uLAcquired by : Kai Yu
Sample Name : ky2-7-060
Sample ID : ky2-7-060
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-7-060-01.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 5/7/2019 2:52:34 PM
Data Processed : 5/7/2019 3:06:39 PM

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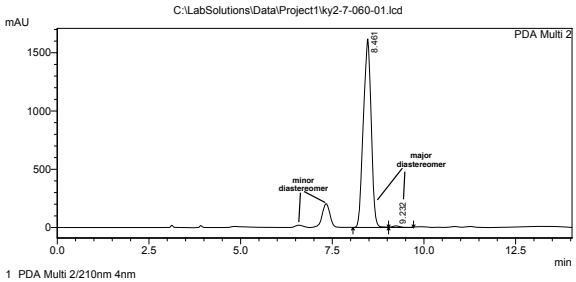
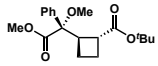


1 PDA Multi 2/210nm 4nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.461	23935610	1618227	99.239	99.181
2	9.232	183451	13357	0.761	0.819
Total		24119061	1631584	100.000	100.000

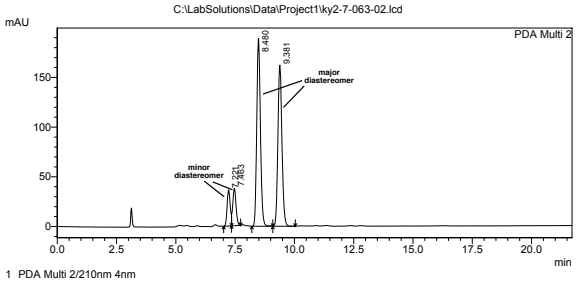


6-75 methyl ester
dr 11:1

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\ky2-7-063-02.lcd
AD-H, 1% iPrOH/Hex, 1 mg/mL, 1 mL/min, 10 uLAcquired by : Kai Yu
Sample Name : ky2-7-063
Sample ID : ky2-7-063
Vail # :
Injection Volume : 10 uL
Data File Name : ky2-7-063-02.lcd
Method File Name : brad.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 5/7/2019 2:29:59 PM
Data Processed : 5/7/2019 2:51:45 PM

<Chromatogram>

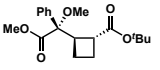


1 PDA Multi 2/210nm 4nm

PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.221	334369	36309	7.183	8.551
2	7.463	360759	37531	7.750	8.838
3	8.480	2038910	188727	43.802	44.444
4	9.381	1920842	162069	41.265	38.167
Total		4654880	424635	100.000	100.000



(±)-6-75 methyl ester

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\LCsolution\ky2-7-078-01.lcd

Acquired by	: Admin
Sample Name	: ky2-7-078
Sample ID	: ky2-7-078
Tray#	: 1
Vail #	: 94
Injection Volume	: 10 uL
Data File Name	: ky2-7-078-01.lcd
Method File Name	: 1ml_min_pumpBonly_premade_90-10_solvent.lcm
Batch File Name	:
Report File Name	: Default.lcr
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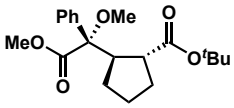
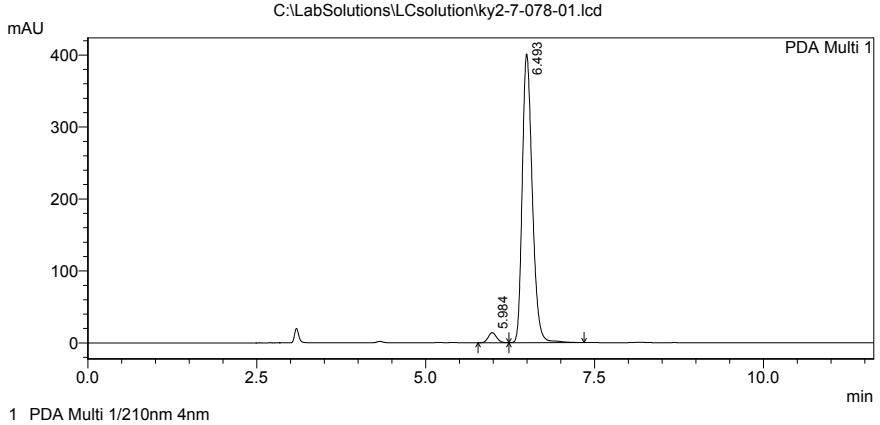


6-76 methyl ester

<Chromatogram>

C:\LabSolutions\LCsolution\ky2-7-078-01.lcd



1 PDA Multi 1/210nm 4nm

PeakTable

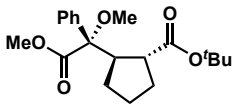
PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.984	122233	13975	2.867	3.368
2	6.493	4141771	400900	97.133	96.632
Total		4264004	414875	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\LCsolution\ky2-7-079-02.lcd

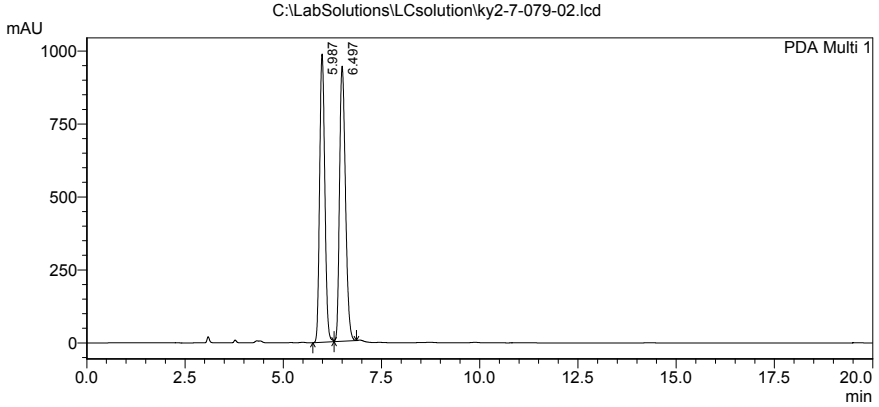
Acquired by	: Admin
Sample Name	: ky2-7-079
Sample ID	: ky2-7-079
Tray#	: 1
Vail #	: 93
Injection Volume	: 10 uL
Data File Name	: ky2-7-079-02.lcd
Method File Name	: 1ml_min_pumpBonly_premade_90-10_solvent.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 5/20/2019 4:04:34 PM
Data Processed	: 5/20/2019 4:34:41 PM



(±)-6-76 methyl ester

<Chromatogram>

C:\LabSolutions\LCsolution\ky2-7-079-02.lcd



1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.987	9090673	987100	47.867	51.185
2	6.497	9901039	941399	52.133	48.815
Total		18991712	1928499	100.000	100.000

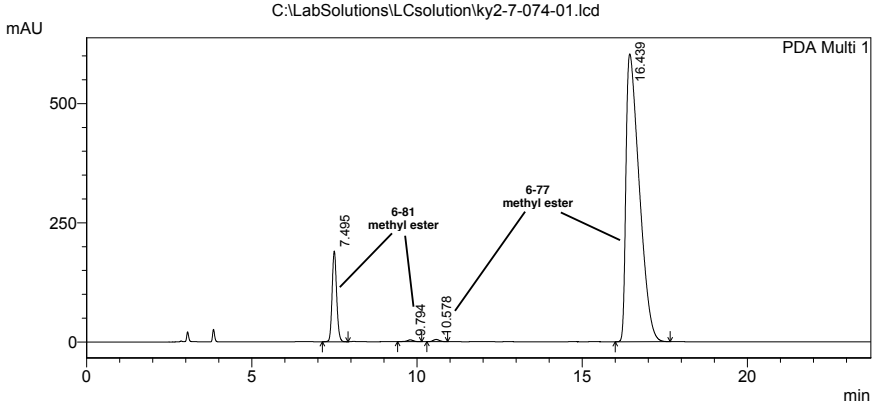
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\LCsolution\ky2-7-074-01.lcd

Acquired by	: Admin
Sample Name	: ky2-7-074
Sample ID	: ky2-7-074
Tray#	: 1
Vail #	: 94
Injection Volume	: 10 uL
Data File Name	: ky2-7-074-01.lcd
Method File Name	: 1ml_min_pumpBonly_premade_90-10_solvent.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 5/16/2019 2:53:43 PM
Data Processed	: 5/16/2019 3:17:37 PM

<Chromatogram>

C:\LabSolutions\LCsolution\ky2-7-074-01.lcd

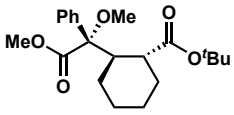


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.495	1804327	189981	9.587	23.685
2	9.794	54071	3886	0.287	0.484
3	10.578	62970	4740	0.335	0.591
4	16.439	16898483	603493	89.791	75.239
Total		18819851	802100	100.000	100.000



6-77 methyl ester

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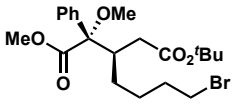


6-81 methyl ester

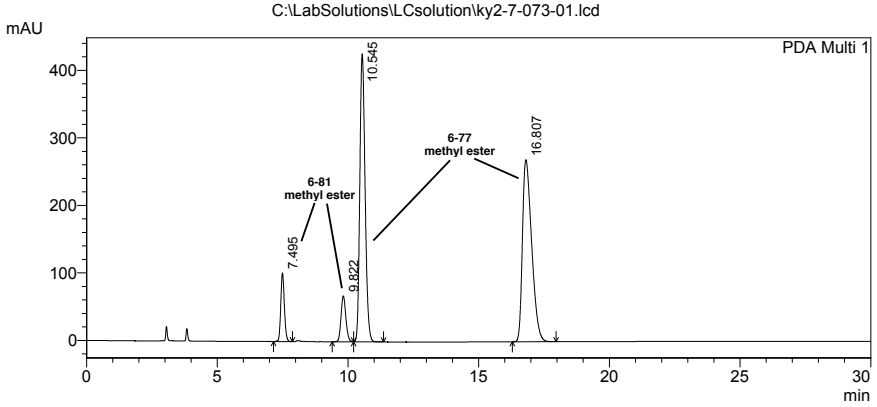
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\LCsolution\ky2-7-073-01.lcd

Acquired by	: Admin
Sample Name	: ky2-7-073
Sample ID	: ky2-7-073
Tray#	: 1
Vail #	: 93
Injection Volume	: 10 uL
Data File Name	: ky2-7-073-01.lcd
Method File Name	: 1ml_min_pumpBonly_premade_90-10_solvent.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 5/16/2019 1:50:24 PM
Data Processed	: 5/16/2019 2:52:51 PM

<Chromatogram>

C:\LabSolutions\LCsolution\ky2-7-073-01.lcd

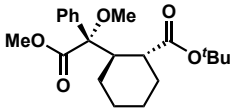


1 PDA Multi 1/210nm 4nm

PeakTable

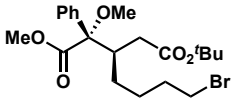
PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.495	970043	101598	6.707	11.742
2	9.822	876805	67909	6.062	7.849
3	10.545	5993856	426066	41.443	49.244
4	16.807	6622335	269644	45.788	31.165
Total		14463040	865217	100.000	100.000



(±)-6-77 methyl ester

+



(±)-6-81 methyl ester