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Lithium Enolates in the Enantioselective Construction of Tetrasubstituted Carbon Centers with Chiral Lithium Amides as Non-Covalent Stereodirecting Auxiliaries

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Abstract

Lithium enolates derived from carboxylic acids are ubiquitous intermediates in organic synthesis. Asymmetric transformations with these intermediates, a central goal of organic synthesis, are typically carried out with covalently attached chiral auxiliaries. An alternative approach is to utilize reagents that form discrete, well-defined aggregates with lithium enolates, providing a chiral environment conducive of asymmetric bond formation. These reagents effectively act as non-covalent, or traceless, chiral auxiliaries. Lithium amides are an obvious choice for such reagents as they are known to form mixed aggregates with lithium enolates. We demonstrate here that mixed aggregates can effect highly enantioselective transformations of lithium enolates in several types of reactions most notably in transformations forming tetrasubstituted and quaternary carbon centers. Easy recovery of the chiral reagent by aqueous extraction is another practical advantage of this one-step protocol. Crystallographic, spectroscopic, and computational studies of the central reactive aggregate, which provide insight into the origins of selectivity, are also reported.

The stereoselective construction of carbon-carbon bonds is a central goal of organic synthesis, and the generation of quaternary carbon centers is especially challenging.[1,2,3] 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[4,5] and self-regenerating stereocenters.[6] Classical methods developed during the early era of asymmetric synthesis have found broad application in both industry and academia on scales spanning nine orders of magnitude.[7,8] For example, oxazolidinone- and ephedrine-based auxiliaries have been used in large-scale stereoselective syntheses of pharmaceutical agents.[9,10,11]

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Methodologies based on covalent chiral auxiliaries require synthetic steps to attach, remove, and recycle a stereodirecting group, thereby extending the number of operations required for the installation of the requisite stereogenic center. In alkylations of enolates, high geometric selectivity in the formation of *E* or *Z* enolates is required to maximize enantioselectivity (Figure 1). Although enolizations of oxazolidinone- and *N*-alkylephedrine-based auxiliaries are highly stereoselective owing to allylic strain,[12] this same strain precludes the simple generation of the fully substituted enolates required for the formation of tetrasubstituted sp^3 carbon stereocenters.[13,14,15]

Non-covalently bound chiral auxiliaries offer considerable advantages for the enantioselective alkylation of lithium enolates. The stereodirecting auxiliary group is formed in situ, temporarily bound to the reactive intermediate, and removed for recycling by simply quenching the reaction.[16,17,18,19,20,21] The well-documented and structurally defined aggregates comprising lithium enolates and lithium amides translate this general concept into practice.[22,23] The enantioselective construction of tetrasubstituted carbon centers sets a high bar for validating this approach. Herein, we describe such a protocol that includes the facile and quantitative recovery of a tetramine auxiliary in nearly pure form through simple extraction. Carboxylic acids are used as abundant, inexpensive, and versatile enolate precursors. The free carboxy group in the resulting products can be readily converted to amines as well as a variety of heterocycles, alcohols, esters, amides, or nitriles. The requisite enediolates, produced by the double deprotonation of carboxylic acids, have been largely neglected as intermediates in organic synthesis[24,25] despite their high nucleophilicity and formal symmetry the eliminates the problem of stereoselective enolization. Enediolate dianions are also expected to form mixed aggregates with lithium amide-based stereodirecting auxiliaries.

Our initial studies focused on the alkylation of *O*-methyl mandelic acid (2-methoxy-2-phenylacetic acid) with allyl bromide. The screening of several chiral amines revealed clean, high-yielding allylations. C_2-symmetric tetramines ^{1}**TA** and ^{2}**TA**, shown in Figure 2, are optimal stereodirecting reagents. (See Supplementary Information for a full list of the chiral amines tested.) The temperature and time of enolization are critical parameters influencing enantiocontrol. For example, when (*S*)-*O*-methyl mandelic acid (**1a**), ^{2}**TA**, and *n*-butyllithium were maintained at 0 °C for 15 min to form the putative mixed lithium amide-enediolate complex before the addition of allyl bromide, the product was isolated in 78% enantiomeric excess (ee). If mixtures were aged at 0 °C for 2 hr before alkylation, the product formed with 89% ee. The time-dependent stereoselectivity correlates with the slow formation of mixed aggregates described below. Similar strong correlations for lithium enolate aging and stereoselectivity have been documented previously.[26]

With the optimal conditions for aggregate generation identified, a survey (Figure 2a) showed that chiral amines ^{1}**TA** and ^{2}**TA** promoted the alkylation of **1** with a variety of reactive alkyl halides in good yields and excellent enantioselectivity. The alkyl halides included iodomethane (**2b**, ^{1}**TA**, 97% ee; ^{2}**TA**, 93% ee), benzylic bromides (**2c**, ^{2}**TA**, 94% ee; **2d**, ^{2}**TA**, 84% ee), 1-(trimethylsilyl)-3-bromopropyne (**2e**, ^{2}**TA**, 89% ee), and cinnamyl bromide (**2f**, ^{2}**TA**, 85% ee). Less reactive haloalkanes such as 1-iodobutane required a slightly elevated temperature of –40 °C but still afforded good yields and selectivities (**2g**, ^{2}**TA**, 89%

ee). Remarkably, 3-bromocyclohexene with subsequent hydrogenation provided cyclohexyl-substituted **2h** in 91% ee using ^{2}**TA**.

We surveyed carboxylic acid substrates, choosing methylation with iodomethane emblematically—a transformation of significance because hydrogen-to-methyl substitution is valuable during drug discovery (Figure 2b).[27] Varying the position of the chloro substituent on the phenyl group had a measurable impact on enantioselectivity. Enantioselectivities of 90% and 82% ee were obtained for 4-chlorophenyl- and 3-chlorophenyl-substitited products **3a** and **3b**, respectively, with ^{1}**TA** as the chiral lithium amide auxiliary. By contrast, a notably lower 75% ee was observed for (*S*)-2-(2-chorophenyl)-2-methoxypropionic acid **3c**. The ee was enhanced to 84% by switching the chiral reagent to ^{2}**TA**. The heteroaromatic substrate 2-methoxy-2-(thiophen-2-yl)acetic acid afforded **3d** in 80% yield and 94% ee (with ^{2}**TA**). Importantly, aliphatic 2-methoxy carboxylic acids were also suitable substrates, affording **3e** in 83–91% ee and **3f** in 85% ee. For these compounds, *n*-butyllithium had to be replaced with *sec*-butyllithium to minimize side reactions stemming from the addition of the organolithium reagent to the carboxy group. These are the first highly enantioselective alkylations of aliphatic carboxylic acids. An unexpected reduction in enantioselectivity was observed during the methylation of *O*-methoxymethylmandelic acid (**3g**) with ^{1}**TA** as the stereodirecting reagent. The enantioselectivity could be restored to 88% ee with ^{2}**TA** as the chiral reagent. The methoxymethyl (MOM) protecting group was readily removed to access the free alcohol.

A significant attribute of this lithium enolate alkylation is illustrated by a direct enantioselective construction of all-carbon quaternary centers in **3h** and **3i** in 90% ee and 88% ee, respectively, under slightly modified reaction conditions with ^{1}**TA** as the stereodirecting reagent. Note that, despite the use of the same enantiomer of the lithium amide, ^{1}**TA** causes the facial selectivity to *reverse*, affording products with the opposite absolute to those derived from ^{2}**TA**.

Another key reaction of lithium enolates is conjugate addition to α,β-unsaturated esters, which can afford two or more stereogenic centers.21 We found that non-covalent lithium amide auxiliaries enable highly enantio- and diastereoselective conjugate additions affording products with adjacent tetrasubstituted and trisubstituted stereogenic carbon centers in good to excellent yields (Figure 3a). The use of tetramine (*R*)-^{1}**TA**, acid **1A**, and methyl cinnamate afforded adduct **4a** in 96% ee as a single diastereomer. Similarly, functionalized products **4b**–**4d** were prepared in 93–97% ee from methyl (*E*)-crotonate, methyl (*E*)-4,4,4-trifluoro-2-butenoate, and *tert*-butyl (*E*)-3-cyclopropylacrlylate, respectively. Heteroaryl-substituted acrylates such as 3-indolyl, 2-furyl, and 3-pyridinyl acrylates afforded the corresponding products **4e**–**4g**, respectively, in high selectivity (diastereomeric ratio [dr] > 30:1, 92–98% ee).

Substituted 2-methoxy-2-arylacetic acids were surveyed (Figure 3b). As in the alkylation reaction, enantioselectivity deteriorated with 2-(2-chlorophenyl)-2-methoxyacetic acid (**5c**, 78% ee) when compared with 4-cholophenyl (**5a**, 93% ee) and 3-chlorophenyl (**5b**, 86% ee) congeners. Once again, high selectivity (91% ee) was restored with (*R*)-^{2}**TA** as the stereodirecting reagent. The conjugate addition of 2-methoxy-2-(thiophen-2-yl)acetic acid to methyl (*E*)-crotonate afforded **5d** with high diastereo- and enantioselectivity (dr > 30:1, 97% ee) in 66% yield. More strikingly, a range of aliphatic 2-methoxy carboxylic acids delivered the corresponding adducts with methyl (*E*)-crotonate in high diastereoselectivity and excellent enantioselectivity under slightly modified conditions. A combination of *i*-Pr_2NLi and (*R*)-$Li_2{}^1TA$ afforded good yields of **5e**–**5g** in 89–98% ee with a 7–10:1 dr. Similarly, a reaction of tetrahydropyran-2-carboxylic acid and benzyl crotonate afforded product **5h** in 74% yield and 98% ee as a single diastereomer. Addition of the more versatile methoxymethyl derivative (**5i**) also occurred with only slightly reduced enantio- and diastereocontrol. Underscoring the simplicity of tetramine auxiliary recycling, (*R*)-**^{1}TA** was recovered in 98% yield after a 4 g scale conversion of racemic **1a** to **4b** (84% yield, dr > 30:1, 94% ee) via acid-base extraction.

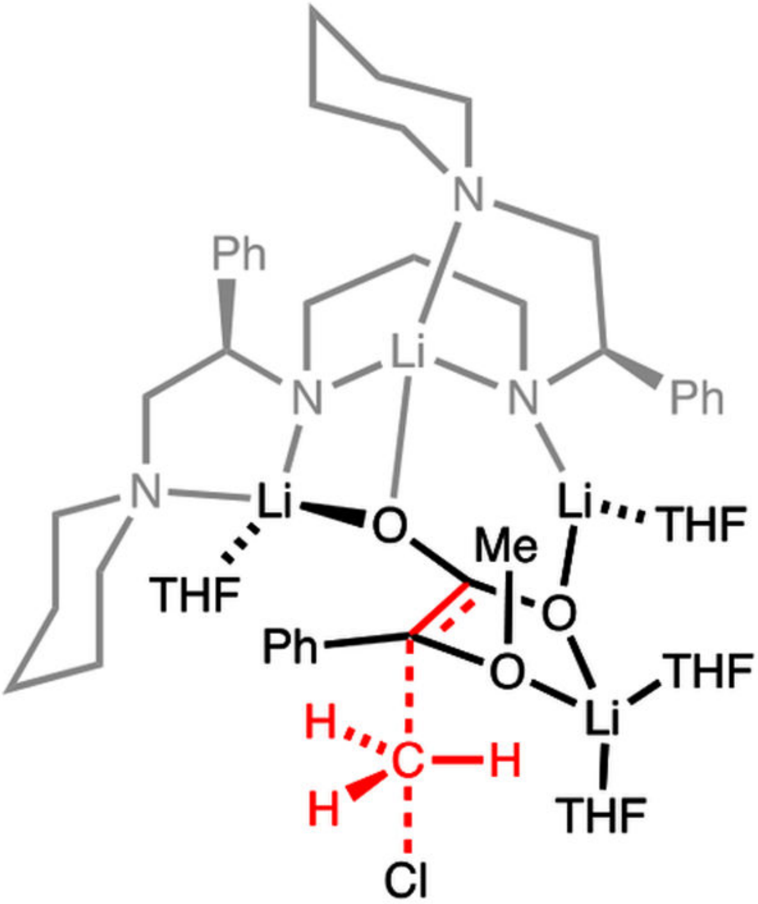
A survey of aldol additions—the third important class of enolate reactions examined in this study—revealed that the non-covalent lithium amide auxiliaries induce high selectivities (see Figure 3b). Aldol addition of **1a** to pivalaldehyde with (*R*)-**^{2}TA** as the stereodirecting reagent furnished **6a** in 89% ee, 13:1 dr, and 64% yield. Lower enantio- and diastereoselectivity was observed with (*R*)-**^{1}TA** (dr = 10:1, 50% ee). Remarkably, the readily enolizable 3-phenylpropanal proved a suitable substrate and afforded a 3:2 mixture of diastereomers *syn*-**6b** and *anti*-**6b** in 52% yield and 80% ee with (*R*)-**^{1}TA**. [(*R*)-**^{2}TA** gave comparable results.] Cyclohexanone afforded the adduct **6c** in good yields (68–84%) and enantioselectivities (77–80% ee) with three auxiliaries.

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,[28,29,30] and we found evidence of such aggregates in an X-ray crystal structure. The crystal was prepared from a mixture of 1.0 equiv each of racemic 2-methoxy-2-phenylacetic acid and (*R*)-**^{1}TA** and 4.0 equiv of *n*-butyllithium in tetrahydrofuran at 0 °C (Figure 4). The binding mode of the chiral lithium amide continues to display a remarkable capacity to form mixed aggregates with a range of lithium salts.[20]

Given results of previous spectroscopic studies,[23] 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 cosolvent). 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[31] with single-point MP2 corrections revealed the putative isomers **6a**–**6d** (Figure 5). The *relative* energies are noted in parentheses. Notable features include: (1) the lowest energy form, **6c**, corresponds to that found crystallographically; (2) the apparent distortion of the methoxy-derived oxygen from the preferred trigonal geometry[32] 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 **6a**–**6c** structural isomeric pair to be preferred relative to the **6b**–**6d** by approximately 4:1, which would nicely coincide with the ^{6}Li NMR spectroscopy.

The results of transition state calculations are also summarized in Figure 5. 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 (**6a)**. 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 **6a**, 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 **6a**–**6c** and **6b**–**6d** are *not* equilibrating on the timescales of the reaction, a loss in selectivity from minor structural isomer **6b**–**6d** 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 **7**. We examined two additional models, which were relegated to the Supplementary Information. The first involved dissociation of a THF ligand, and the second involved attack of the methyl chloride from the face opposite the pucker of the enolate lithium (syn to the red methyl moiety, Figure 5). In both cases, the barriers were found to be higher than those in Figure 5, and both models predicted the wrong stereochemistry. We hasten to add that this is a model basedon a single substrate; substrate-dependent mechanisms and relative stereochemistries are a certainty.



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In closing, 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 enantioselectivities, 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 tetramines such as ^{1}**TA** to form discrete and stable aggregates, we anticipate that other such enantioselective transformations are possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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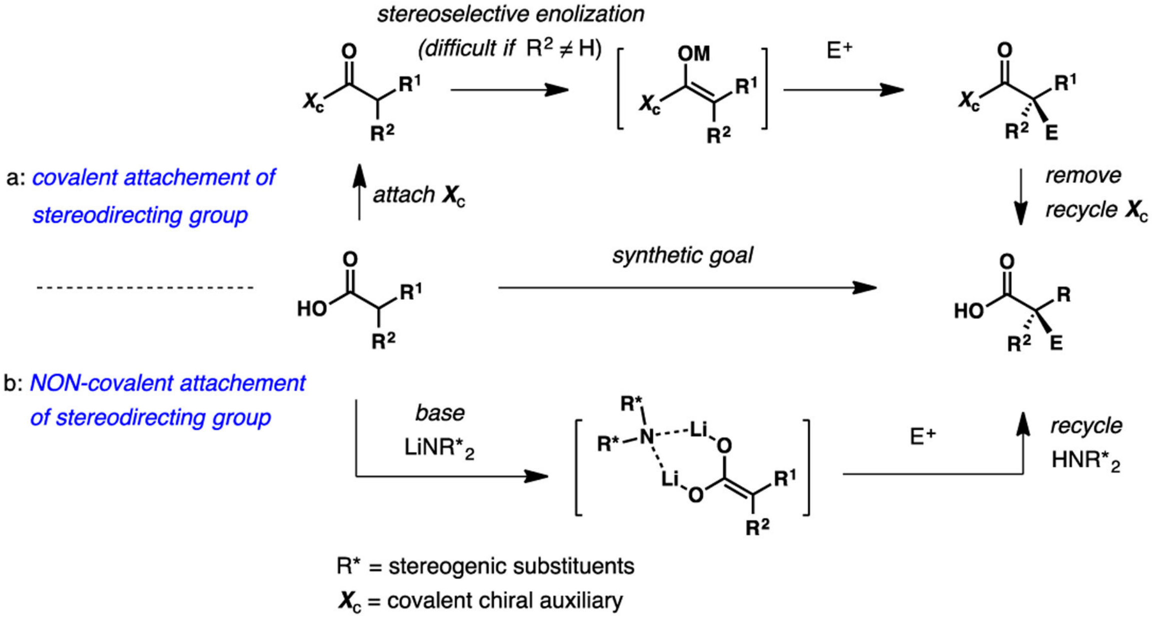

Figure 1 |. Strategies for forming quaternary stereocenters.

a, Auxiliary-directed stereoselective transformation of a lithium enolate. **b,** Chiral lithium amide-based (traceless) auxiliary.

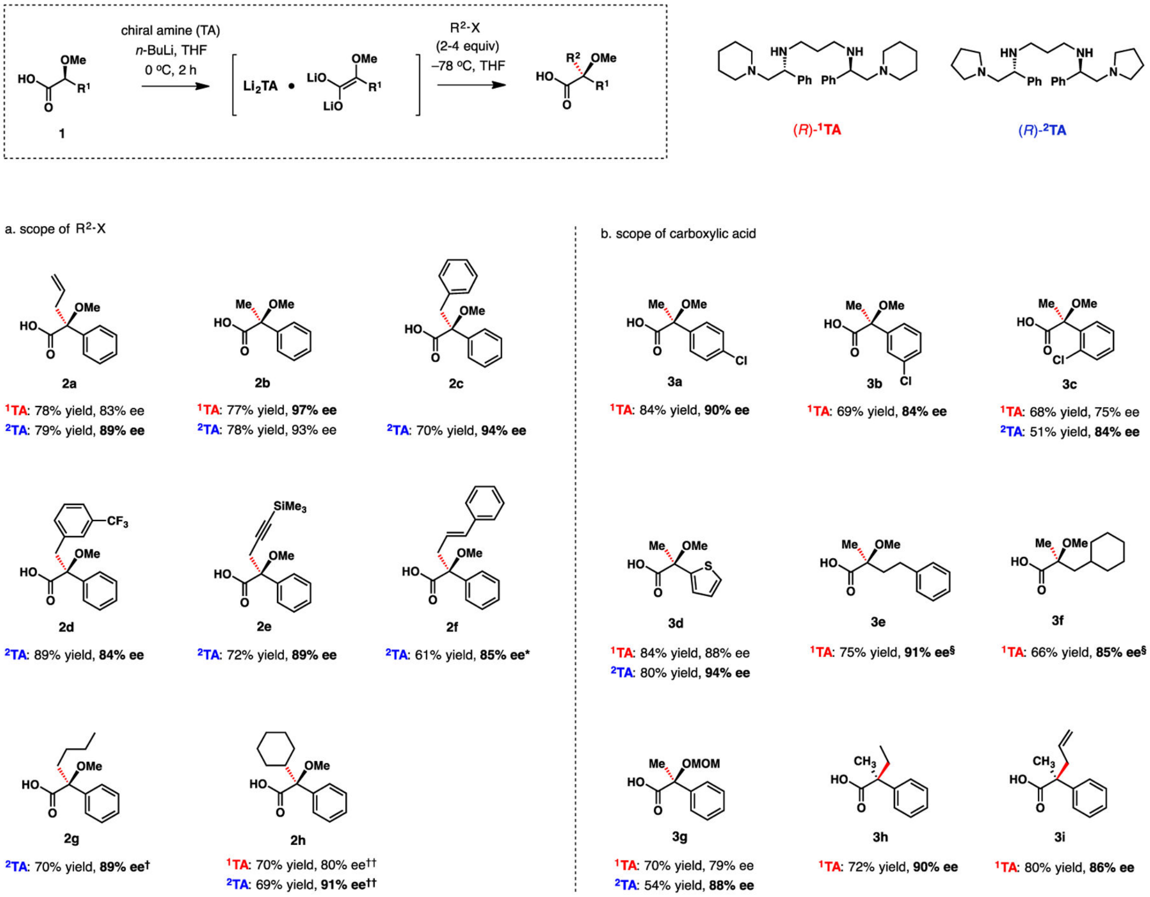

Figure 2 |. Enantioselective construction of tetrasubstituted and quaternary carbon centers via lithium enediolate alkylation with chiral lithium amides as non-covalent stereodirecting auxiliaries.

The reactive aggregate was generated by incubating the carboxylic acid, the tetramine reagent (1:1 molar ratio), and 4.0 equiv of alkyllithium reagent in tetrahydrofuran (THF) at 0 °C for 2 h. Alkylations were carried out at –78 °C unless noted otherwise. Enantiomeric excess (ee) was determined with high-performance liquid chromatography; all have been corrected to bases with the *R* configuration as shown. **a,** Alkylation reagent was varied. **b,** Carboxylic acid was varied. *Isolated yield after methyl ester formation. †Alkylation was conducted at –40 °C. ‡3-Bromocyclohexene was used as the reagent. §*sec*-butyllithium was used instead of *n*-butyllithium (*n*-BuLi).

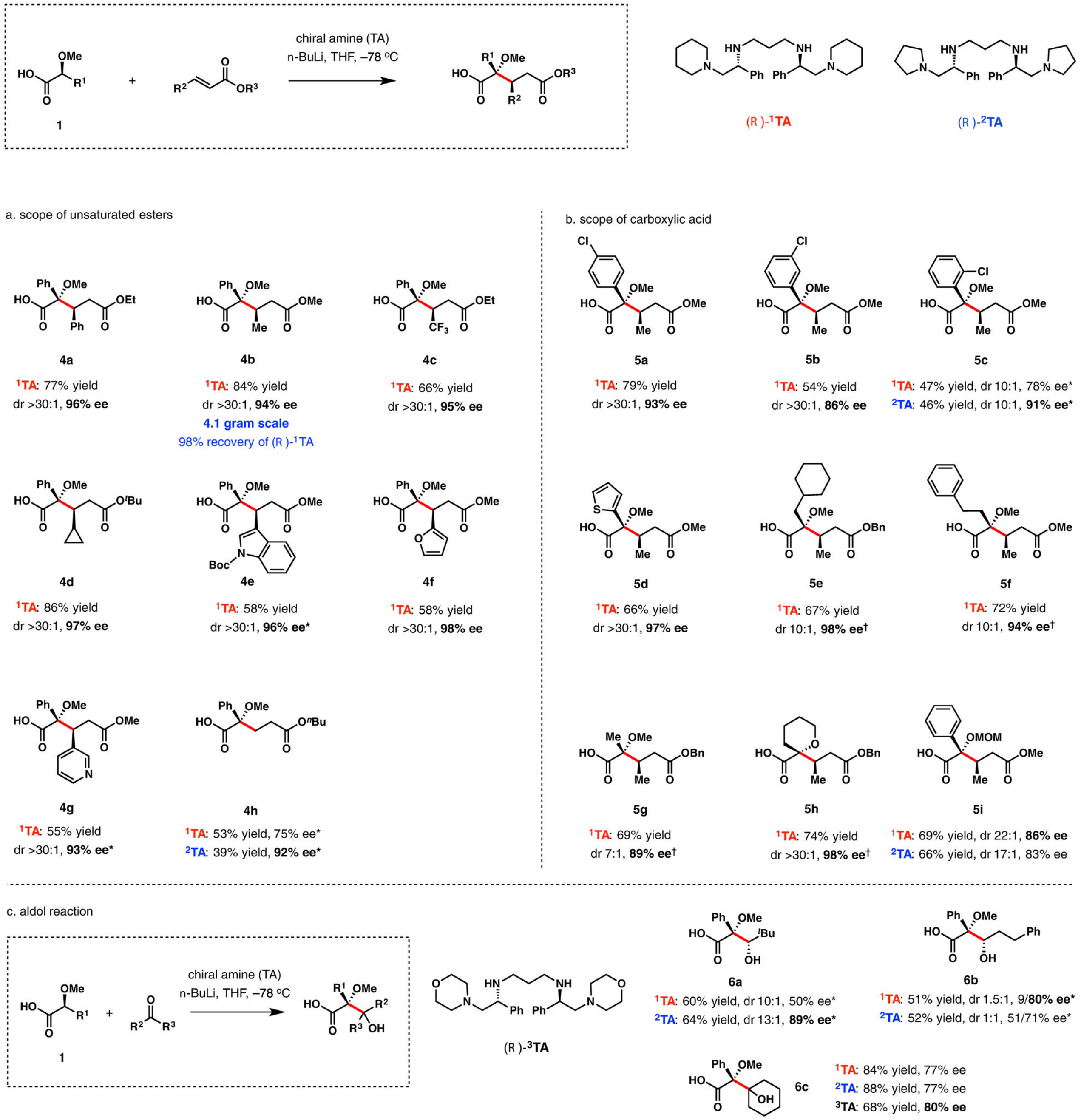

Figure 3 |. Enantioselective construction of tetrasubstituted and quaternary carbon centers via lithium enediolate conjugate addition or aldol reaction with chiral lithium amides as non-covalent stereodirecting auxiliaries.

The reactive aggregate was generated by incubating the carboxylic acid, the tetramine reagent (1:1 molar ratio), and 4.0 equiv of alkyllithium reagent in tetrahydrofuran (THF) at 0 °C for 2 h. Reactions were carried out at –78 °C unless noted otherwise. Enantiomeric excess (ee) was determined with high-performance liquid chromatography; all results shown have been corrected to bases with the *R* configuration as shown. a, Unsaturated ester (Michael acceptor) was varied in the enantioselective conjugate addition. Synthesis of 4b was performed on a 4.1 g scale with a 98% recovery of the tetramine reagent (*R*)-^{1}TA via simple aqueous extraction. b, Carboxylic acid was varied in the enantioselective conjugate addition. c, Preliminary observations for the enantioselective aldol reaction with chiral lithium amides as non-covalent stereodirecting auxiliaries. *Isolated yield after methyl ester formation. *i*-Pr_2NLi (2.0 equiv) was used for enediolate formation. dr, diastereomeric ratio; *n*-BuLi, *n*-butyllithium.

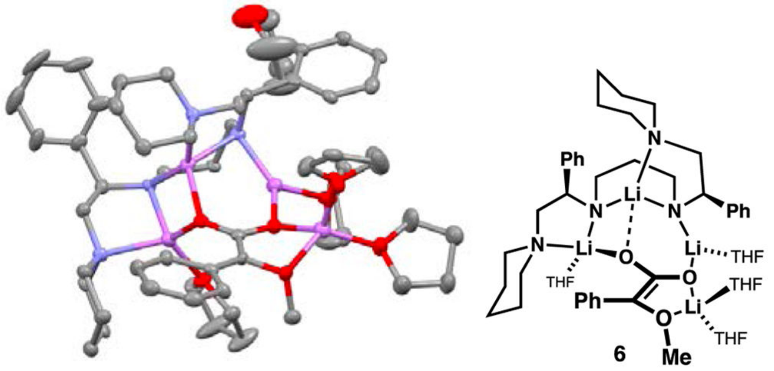

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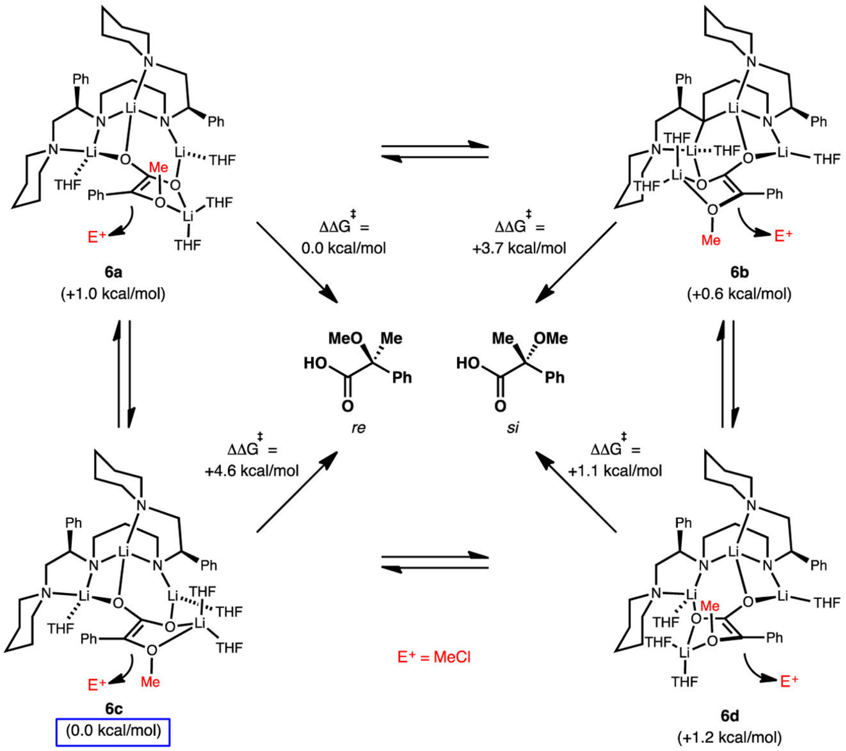
Figure 4.

a) a drawing of the lithium amide-lithium enediolate aggregate from (*R*)-^{1}**TA** and **1a** obtained by X-ray crystallographic analysis.



*Reactant energies are scaled to the lowest energy isomer (blue box)

*Activation energies are all scaled to the lowest energy barrier

Figure 5.

Four conformational isomers of structure **6** determined by DFT computations with MP2 corrections. Conformer **6c** corresponds to that seen crystallographically. Energies below the structures correspond to relative ground state energies. Energies on the arrows correspond to the relative energies of methylation by MeCl of each isomer via transition structures requiring no dissociation of a THF ligand from the geminally disolvated enolate lithium. The $\Delta\Delta G^{\ddagger}$ values are referenced to each respective isomer. The preferences for facial attack are obtained by referencing all to a single ground state (**6c**) and obtained by summing the relative conformer energies and the relative activation energies.