Title

New Methods for the Synthesis of alpha-Amino Acid Derivatives From N-tert-Butanesulfinyl Imines AND The Synthesis and Application of Novel Amino Acid Based N-tert-Butanesulfinyl Amide Organocatalysts

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The Synthesis and Application of Novel Amino Acid Based *N*-*tert*-Butanesulfinyl Amide Organocatalysts

by

Melissa Ann Herbage

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Committee in Charge:

Professor Jonathan A. Ellman, Chair
Professor Richmond Sarpong
Professor Douglas S. Clark

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Abstract

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Melissa Ann Herbage

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Professor Jonathan A. Ellman, Chair

Chapter 1. Methods for the synthesis of α-amino acid derivatives prepared from *N*-*tert*-butanesulfinyl imines are reviewed.

Chapter 2. The rhodium-catalyzed addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters is described. This chemistry is compatible with a variety of electronically and sterically diverse arylboronic acids providing the *N*-*tert*-butanesulfinyl protected α-arylglycine products in good yields and high diastereoselectivities. In addition, the utility of this method is demonstrated by subjecting the enantiomerically enriched *N*-*tert*-butanesulfinyl protected products to

selective synthetic manipulations with little to no racemization. The synthesis of an *N-tert*-butanesulfinyl isatin imine and its use in the rhodium-catalyzed addition of arylboronic acids reaction is also described.

Chapter 3. The copper-catalyzed addition of bis(pinacolato)diboron to *N-tert*-butanesulfinyl imines is described. This chemistry is amenable to a variety of alkyl and aryl *N-tert*-butanesulfinyl imines and provides rapid access to use of a number of chiral α-amino boronate esters, a biologically relevant scaffold that is difficult to access by other means. The utility of this methodology was demonstrated by the efficient synthesis of bortezomib (Velcade®), the first FDA approved proteasome inhibitor drug. The further functionalization of the α-amino boronate products is also described. This includes the homologation of the α-amino boronate ester products as well as the conversion of the boronate ester to the potassium trifluoroborate salt. The application of this methodology for the enantioselective synthesis of α-amino boronate esters is also addressed.

Chapter 4. The synthesis of new *N-tert*-butanesulfinyl amide organocatalysts and their application to the intermolecular aldol reaction is described. A number of catalysts were prepared in one step from commercially available amino acid precursors and were tested for their activity in the intermolecular aldol reaction. However, preliminary results indicate that the primary amine catalysts are not competitive with other amino acid derived catalysts reported in the literature. Further optimization is necessary to fully evaluate the potential for this new class of catalysts.

Approved:

Chair Date

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Acknowledgements

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Graduate school has been a once in a lifetime experience. In many respects I feel that I have learned much more than I expected in such a (relatively) short amount of time and made better friends than I could have imagined. Ellen and David Beaulieu kept the gang together by hosting movie nights, wine trips, and one memorable dinner at Fondue Fred's. The four founding Saprongs, Eric Bunnelle, Eric Simmons, Kimberly Larson, and Andrew Marcus, were not only fantastic classmates and sources of chemistry advice, but also guitar heroes, wine buddies, and hammer dancers. I would like to thank Kimberly Larson (my best country music loving friend and partner in singing "Strawberry Wine" and Andrew Marcus (who once grew a mustache for my amusement), in particular, for their friendship as well as their willingness to be the guinea pigs for many of my culinary experiments (some more successful than others).

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jumped fence to join “team sulfinamide” and I have appreciated the chemistry discussions that we have shared. I am also thankful that she knows enough about mushroom foraging that I wasn’t poisoned when I tried those “candy cap” cookies. Katherine Rawls is extremely talented, thoughtful, and fun. She is also the mastermind behind one of the best bits of chemistry jargon ever- “$R_{optimal}$.” MaryAnn Robak is one of the nicest and most generous people I know. I have always had an open invitation to spend Friday and/or Saturday evenings with her and the ten other people who also had open invitations to her dinner parties. And we will always have “the review” and the six months it took us to write it. At this point I am hoping that it actually is the longest review ever. Melissa Leyva has always awed me by her extensive knowledge of all things baseball, football, and music. By the time she sees this she will have already completed her first half marathon and inspired me to think about doing one myself. I will always value her friendship and definitely plan on keeping in touch because I am pretty sure she is also going to be my most/only “internet famous” friend (and not in a bad way!). Andy “AndyPat” Patterson has been, by far, the humor compass of the Ellman group which thankfully kept the lab atmosphere from getting too professional. He has made me laugh for five years straight from the VTC and the coffee harem to ramen casserole and vampire lore. I am especially grateful for the signature bottle of bleach he gave me as it has proven to be quite useful. As for Denise Colby, I am not completely certain I would have made it through all five years of graduate school if I had not had her friendship. There were a lot of laughs (fry party, Half Dome, pumpkin carving, wedding planning, and futon chatting) and a fair amount of panics (qualifying exam, Half Dome, and our innate personalities). I have loved every minute of it all. I

sincerely hope we will find ourselves living in close proximity again in the not so distant future.

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Of course none of this work would have been possible without the love and support of my family. I doubt I would have even considered graduate school if my dad hadn't taken me to work with him when I was a kid and let me use his paper shredder, dry erase markers, etc. Interestingly, you don't actually need an advanced degree to access these office supplies, but I guess it took me awhile to figure that out. My mom has always been the one to make sure I was doing okay, exercising enough, eating vegetables, and taking deep breaths. I don't know which one of us is more relieved that I made it through graduate school in one piece. My brother has put up with a lot coming from me including nicknames such as "the beta child" and "Moo", but I am very proud of him and look forward to seeing how successful he will be in the future. And even though I was the four year old child pretending to type in front of Dad's old computer in a family photograph, at least one of us actually knows how to use one. My new Herbage family has welcomed me into their lives as if I had always been there and I look forward to all our future Oregon State football games, Mexico trips (no fishing for me, please), and card games around the table. Lastly, I want to thank my husband Jeff (el Jeffe) for everything. He is, hands down, my favorite. I do not know how he has managed to put up with me for so long, but I am constantly spoiled rotten by his unwavering support and acceptance of me as well as his ability to always make me laugh. I hope he is looking forward to our future together (with poodles!) as much as I am.

Chapter 1. The Synthesis of α-Amino Acids and Their Derivatives From *N-tert*-Butanesulfinyl Imines

The synthesis of enantiomerically pure α-amino acids and their derivatives is very important in pharmaceutical, biological, and synthetic chemistry. Methods for the preparation of α-amino acid derivatives prepared from N-tert-*butanesulfinyl imines are reviewed. This material will be published as part of a review on the preparation of* tert-*butanesulfinamide and its many applications in organic chemistry for the efficient synthesis of amines.* (Herbage, M. A.; Robak, M. T.; Ellman J. A. *tert*-Butanesulfinamide: Synthesis, Methods, and Applications. *Chem. Rev*. manuscript in preparation).

Introduction

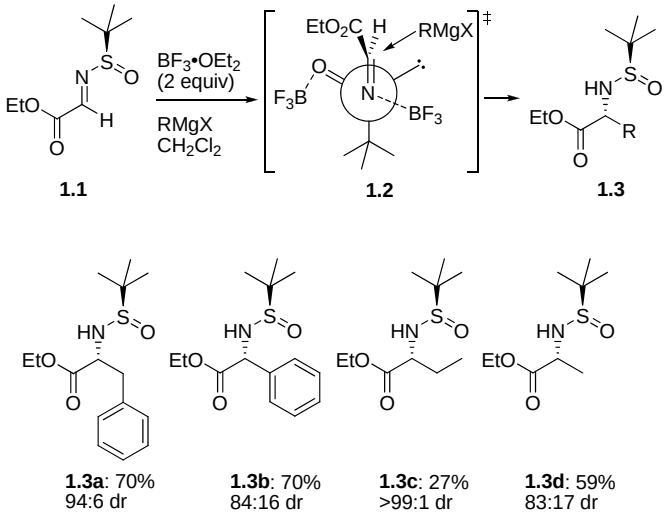
The importance of efficient asymmetric syntheses of amine derivatives is highlighted by the prevalence of the amine functional group in biologically active natural products, pharmaceutical agents, and asymmetric catalysts. Since its development, enantiomerically pure *tert*-butanesulfinamide has been used extensively for the synthesis of chiral amines due to its competitive price, the ease with which *N*-*tert*-butanesulfinyl imines can be prepared, the high levels of stereocontrol achieved for numerous synthetic transformations, and the facile removal of the *tert*-butanesulfinyl group under mild acidic conditions. Indeed, the utility of *tert*-butanesulfinamide as a chiral amine reagent has been demonstrated by its use in a number of elegant total syntheses and routes to drug candidates. In particular, *N*- *tert*-butanesulfinyl imines have been exploited for the asymmetric synthesis of α-amino acids and their derivatives via the 1,2-additions of nucleophiles to *N*-*tert*-butanesulfinyl imino esters or the 1,2-additions of carboxylic acid equivalents to *N*-*tert*-butanesulfinyl imines.

1,2-Additions of Nucleophiles to *N*-*tert*-Butanesulfinyl Imino Esters

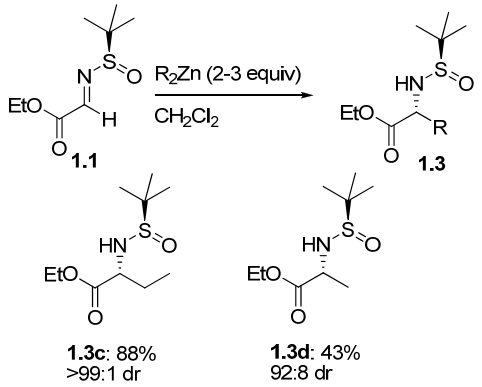
In 1999 Davis and coworkers published one of the earliest reports on the additions of organometallic reagents to *N*-*tert*-butanesulfinyl imino esters, providing a direct route for the synthesis of *N*-sulfinyl protected amino acid derivatives.[1] The addition of BnMgCl to the *N*-*tert*-butanesulfinyl aldimine **1.1** proceeded with good diastereoselectivity (90:10) but poor yield (<30%). However, the precomplexation of the imine with two equivalents of $BF_3 \cdot OEt_2$ followed by addition of the Grignard

provided **1.3a** in good yield and with high diastereoselectivity (Scheme 1.1). Interestingly, lower yields and selectivities were observed for the addition to the corresponding *N*-p-toluenesulfinyl imino ester. The stereoselectivity of this reaction, which is opposite to that observed for Grignard additions to unfunctionalized imines, was explained by open transition state **1.2**, in which Lewis acid coordination to both the sulfinyl oxygen and the imino nitrogen disrupts formation of a chelated transition state. Unfortunately, this protocol was not amenable to the use of EtMgBr, providing a low yield of the desired adduct **1.3c**, with competitive imine reduction. However, in this case, Et_2Zn was found to be a suitable nucleophile, allowing isolation of **1.3c** in 88% yield with >99:1 dr (Scheme 1.2). The less reactive Me_2Zn provided only a 43% yield of product **1.3d**, although with higher stereoselectivity than the corresponding Grignard addition.

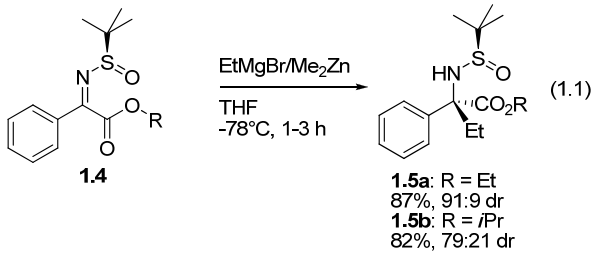
Scheme 1.1. Grignard Addition to α-Imino Esters.



Scheme 1.2. Dialkylzinc Addition to α-Imino Esters.



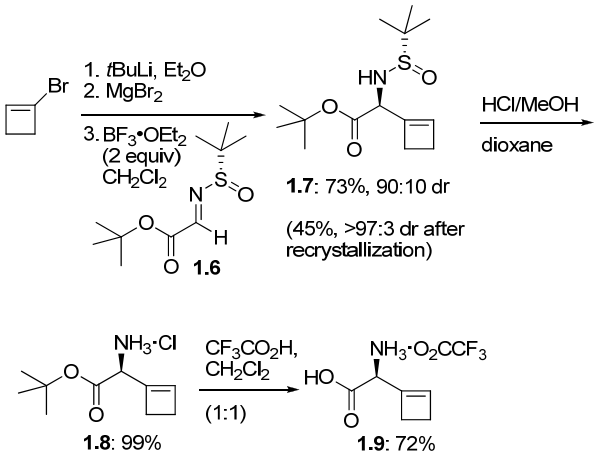
A triorganozincate reagent, prepared by mixing EtMgBr with dimethylzinc, has been used as the nucelophile for the asymmetric synthesis of α,α-disubstituted amino acids from *N*-*tert*-butanesulfinyl ketimino esters as reported by Yus and coworkers (eq 1.1).[2] Dimethylzinc is used due to the inability of methyl groups to transfer from the triorganozincate reagents. The additions to imine **1.4** were carried out at low temperature in THF and the desired ethylation products **1.5a** and **1.5b** were obtained in high yields (82-87%) and with good to excellent diastereoselectivities (79:21-91:9). As further evidence for the presence of a triorganozincate reagent, a switch in diastereoselectivity was observed when the Grignard reagent was used as the nucleophile in the absence of dimethylzinc, providing **1.5a** and **1.5b** in 15:85 and 21:79 dr, respectively.



(1.1)

Standaert and coworkers utilized the conditions developed by Davis and coworkers for addition of a cyclobutenyl Grignard reagent to imino ester **1.6** in the asymmetric synthesis of unnatural amino acid **1.9** for incorporation into proteins using the in vitro protein biosynthetic machinery (Scheme 1.3).[3] While the imino ethyl ester **1.1** was a suitable substrate for the addition reaction, the subsequent saponification of the ester was unsuccessful due to epimerization and decomposition. Therefore, *tert*-butyl ester **1.6** was used, providing **1.7** in high yield and with 90:10 dr. Diastereomerically pure material was obtained by recrystallization of the crude material. HCl-mediated removal of the sulfinyl group followed by treatment with TFA to cleave the *tert*-butyl ester then provided free amino acid **1.9** in 71% overall yield without epimerization.

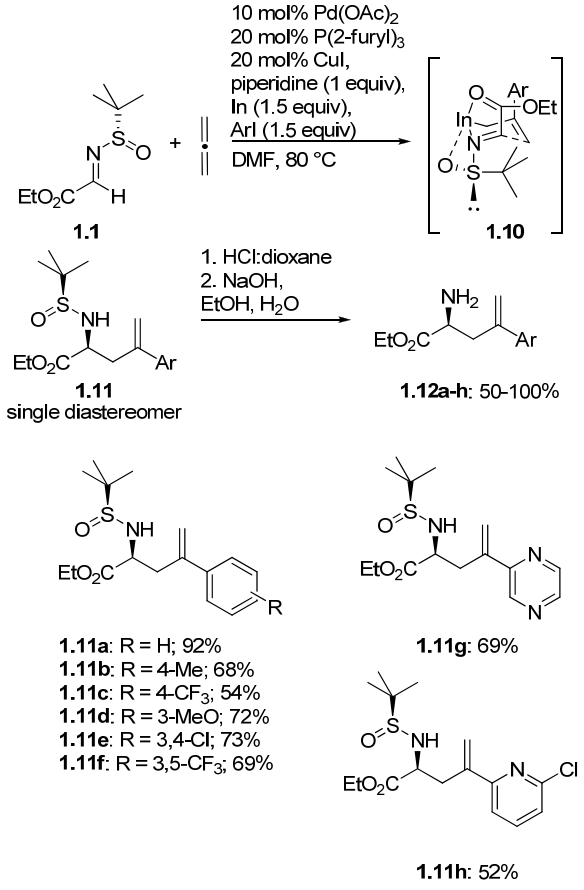
Scheme 1.3. Synthesis of 1-(1-Cyclobutenyl)glycine



The addition of organoindium reagents to *N*-*tert*-butanesulfinyl imino esters has also been examined. Grigg and coworkers demonstrated allylations of *N*-*tert*-butanesulfinyl imino ester **1.1** via a bimetallic Pd/In mediated cascade sequence for the synthesis of non-proteinogenic α-amino acid derivatives (Scheme 1.4).[4] With this *N*-*tert*-

butanesulfinyl electrophile slight modifications to their previously employed reaction conditions for the analogous transformation with aryl or alkyl *N*-*tert*-butanesulfinyl aldimines (catalytic $Pd(OAc)_2$, $P(2\text{-furyl})_3$, In, ArI, DME) were implemented, including the addition of a catalytic amount of copper iodide, an equivalent of piperidine, and the use of DMF as the solvent as opposed to DME. The authors propose that the copper iodide additive may facilitate formation of InI, which is more easily transferred from the solid to the solution phase, but could not rule out the possibility of a copper allyl species.[5] A number of aryl iodides were employed to evaluate the scope of the reaction. Electron-rich and electron-poor substituents on the aryl ring as well as heteroaromatic substituents were all incorporated to provide **1.11a-h** as single diastereomers in yields ranging from 52-92%. The free amine products **1.12a-h** were generated in 50-100% yield after a two step deprotection sequence. The same synthetic sequence was also demonstrated with the (*R*)-enantiomer of *N*-*tert*-butanesulfinyl imino ester **1.1**. The absolute configuration of **1.11e** was established by X-ray structural analysis. This outcome was rationalized by the chelated transition state **1.10**, which displayed the most exothermic heat of formation according to semi-empirical calculations.

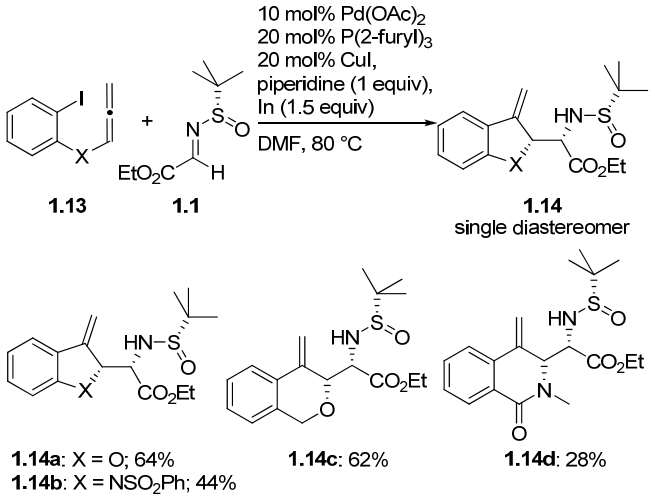
Scheme 1.4. Synthesis of Non-Proteinogenic α-Amino Acids via the Bimetallic Cascade Allylation of *N*-*tert*-Butanesulfinyl Imino Esters



Tethered aryl iodide/allene substrates **1.13** were also employed to further extend the scope of this methodology (Scheme 1.5). Using the same reaction conditions (*vide supra*), **1.14a-d** were formed regioselectively in moderate yields (28-64%) with complete stereocontrol over the two new contiguous stereocenters. The absolute configuration of **1.14b** was determined by X-ray structural analysis and was consistent with the previously proposed chelated transition state **1.10** (see Scheme 1.4). The

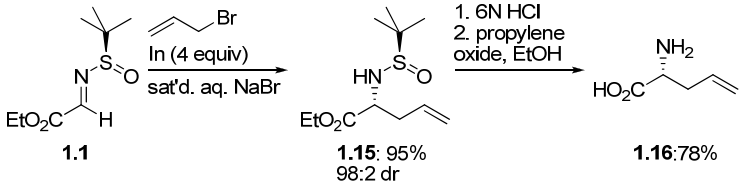
authors also carried out the synthesis of the enantiomer of **1.14** by employing the (*R*)-enantiomer of *N*-*tert*-butanesulfinyl imino ester **1.1**.

Scheme 1.5. Tandem Cyclization-Allylation Cascades with *N*-*tert*-Butanesulfinyl Imino Ester **1.1**



The allylation of *N*-*tert*-butanesulfinyl imino ester **1.1** with an organoindium reagent in aqueous media was demonstrated for the first time by Lin, Xu, and coworkers (Scheme 1.6).[6] The effects of saturated aqueous salt solutions were probed, with NaBr providing the highest yield of the desired product. Under these reaction conditions the resulting homoallylic *N*-*tert*-butanesulfinyl imino ester **1.15** was produced in excellent yield and diastereoselectivity and was subsequently converted to D-allylglycine **1.16** after deprotection of the sulfinyl and ester groups. Interestingly, the stereochemical outcome for this transformation was opposite to that observed with unfunctionalized *N*-*tert*-butanesulfinyl imines and was rationalized by a transition state change in which coordination of the ester carbonyl to the indium plays a significant role (see **1.10**, Scheme 1.4).

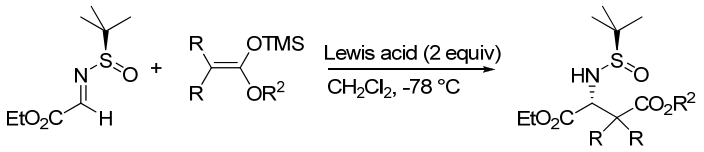
Scheme 1.6. Synthesis of D-Allylglycine **1.16**



The addition of silyl ketene acetals **1.17** to an *N-tert*-butanesulfinyl imino ester **1.1** for the synthesis of aspartic acid derivatives **1.18** was explored by Skrydstrup and Jacobsen (Table 1.1).[7] Initial reaction optimization revealed that the presence of a Lewis acid was required to obtain the desired product, and that the best yield and diastereoselectivity were achieved when two equivalents of $BF_3{\cdot}OEt_2$ were used for the reaction between **1.1** and silyl ketene acetal **1.17** (R = Me, entry 1). For this transformation the use of $AlMe_3$ as the Lewis acid resulted in a diminished yield and diastereoselectivity (entry 2). However, when silyl ketene acetal **1.17** (R = H) was used, $AlMe_3$ was the most effective Lewis acid (compare entries 3 and 4). The diastereoselectivity could be further increased in the presence of either $BF_3{\cdot}OEt_2$ or $AlMe_3$ by employing the more sterically demanding silyl ketene acetal **1.17** (R^2 = *t*Bu), but eight equivalents of **1.17** were required to obtain appreciable amounts of **1.18** (entries 5 and 6). The absolute configurations of the major diastereomers of **1.18b** and **1.18c** were determined by chemical correlation experiments, and the major diastereomer of **1.18a** was assigned by analogy. The stereochemical outcome was rationalized by an open transition state where the Lewis acid coordinates to both the sulfinyl oxygen and the imine nitrogen and addition of the nucleophile occurs from the *Re* face of the imine bond (see **1.2** Scheme 1.1). A one-pot procedure for the synthesis

of β-lactams was also developed using the silyl ketene acetal **1.19**, derived from 2-pyridyl thioacetate, and *N*-*tert*-butanesulfinyl imino ester **1.1** (eq 1.2). However, product **1.20** was isolated in only a moderate yield and with poor diastereoselectivity.

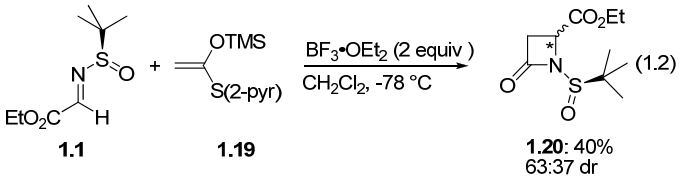
Table 1.1. Lewis Acid Promoted Addition of Silyl Ketene Acetals to **1.1**



1.1 **1.17** **1.18**

entry	R	R^2	Lewis acid	Product	yield (%)	dr
1	Me	Et	$BF_3{\cdot}OEt_2$	**1.18a**	81	87:13
2	Me	Et	$AlMe_3$	**1.18a**	50	80:20
3	H	Et	$BF_3{\cdot}OEt_2$	**1.18b**	67	90:10
4	H	Et	$AlMe_3$	**1.18b**	78	93:7
5[a]	H	*t*Bu	$BF_3{\cdot}OEt_2$	**1.18c**	17	96:4
6[a]	H	*t*Bu	$AlMe_3$	**1.18c**	86	97:3

[a] Eight equivalents of the silyl ketene acetal were used.

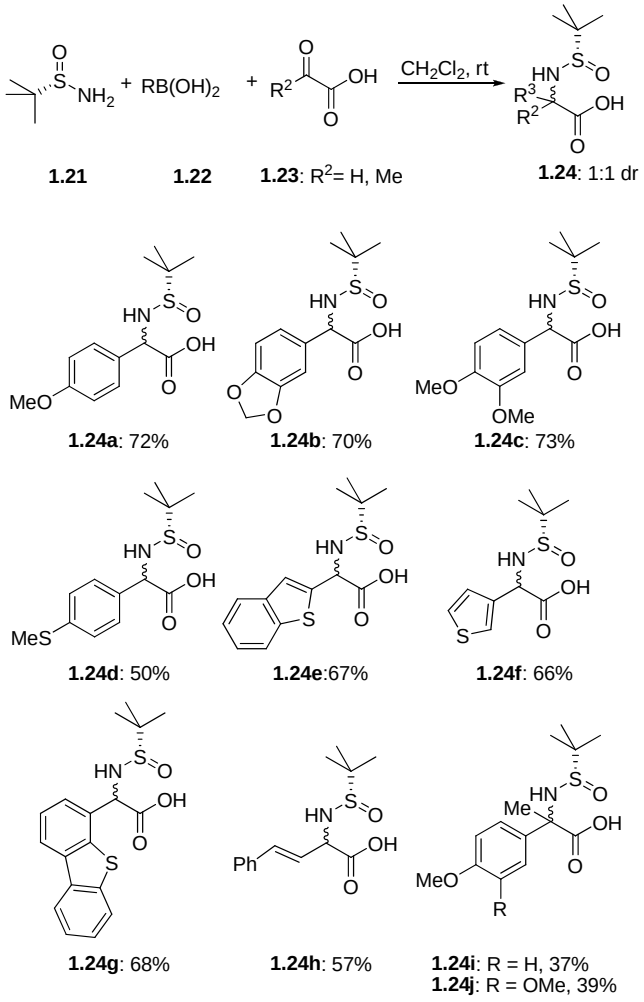


1.1 **1.19** **1.20**: 40%
63:37 dr

α-Arylglycines are a particularly important class of amino acids because they are components of a number of pharmaceutical agents, including vancomycin and related glycopeptide antibiotics,[8] the norcardicin antibacterial agents,[9] and the cardiovascular drug Plavix.[10] Naskar and coworkers reported the first general method for the preparation of *N*-*tert*-butanesulfinyl α-arylglycines through use of *tert*-butanesulfinamide as the amine component in the Petasis boronic acid Mannich reaction (Scheme 1.7).[11] The one-pot, three component coupling of *tert*-

butanesulfinamide (**1.21**), a boronic acid (**1.22**), and glyoxylic acid monohydrate or pyruvic acid (**1.23**) took place under mild reaction conditions (ambient temperature in CH_2Cl_2) providing adducts **1.24a-j** as a 1:1 mixture of diastereomers. The scope of the reaction was examined with a number of electron-rich aromatic and heteroaromatic boronic acids, which provided **1.24a-g** in 50-73% isolated yields. An alkenyl boronic acid was also employed, providing **1.24h** in 57% yield. When pyruvic acid was used (**1.23**, R^2 = Me), the desired products **1.24i** and **1.24j** were generated, but yields were diminished (37-39%). Although this reaction is not diastereoselective, the authors demonstrated that the diastereomers of **1.24a** could be separated by preparative HPLC.

Scheme 1.7. Synthesis of α-Arylglycines **1.24** by the Petasis Reaction

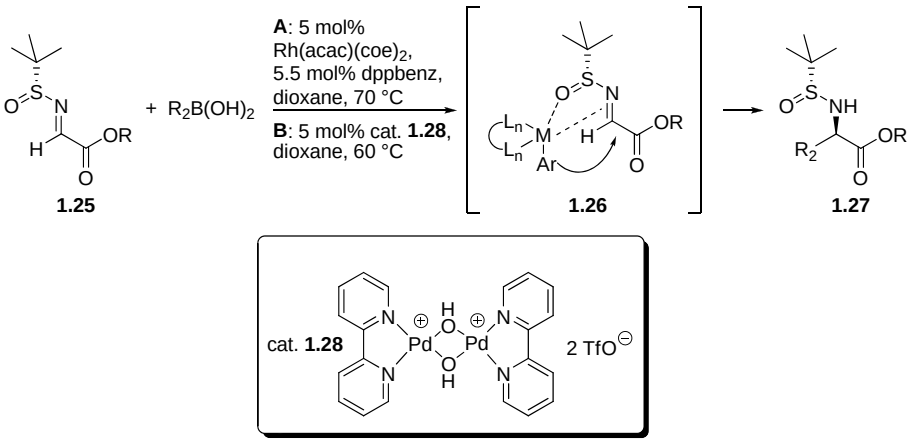


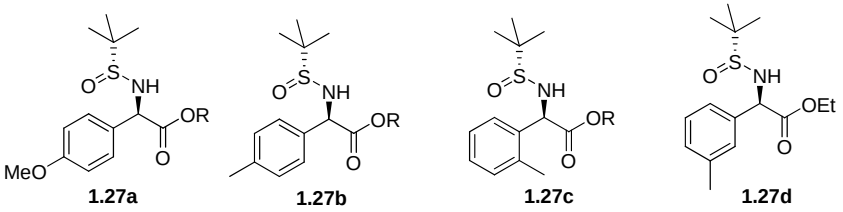
N-tert-Butanesulfinyl protected α-arylglycine derivatives have also been synthesized by the transition metal-catalyzed addition of arylboronic acids to *N-tert*-butanesulfinyl imino esters. The first example of this transformation was disclosed by Ellman, Beenen, and Weix (see Chapter 2).[12] Building on their previous success with the $Rh(acac)(coe)_2$ and 1,2-bis(diphenylphosphinyl)benzene (dppbenz) catalyst system for additions of arylboronic acids to aromatic and aliphatic *N*-tert-butanesulfinyl aldimines,[13] these conditions were applied to additions to *N-tert*-butanesulfinyl imino

esters **1.25** to provide access to diverse α-arylglycine derivatives (method A, Scheme 1.8). Methyl, benzyl, and *tert*-butyl esters of **1.25** all provided high yields and selectivities thereby maximizing flexibility in the choice of ester protecting group (**1.27a**, method A). High yields and diastereoselectivities were achieved for arylboronic acids with either electron-donating or electron-neutral substituents (**1.27a-c**, **1.27e**), and ortho-substitution resulted in only a modest reduction in yield (**1.27c**). Importantly, arylboronic acids bearing electron-withdrawing substituents could also be incorporated (**1.27h-k**), which are ineffective coupling partners in the Petasis reaction (see Scheme 1.7).[14] It is notable that for all of the ester derivatives of **1.25** and for all types of arylboronic acids, the products were obtained in ≥ 98:2 dr. This chemistry will be discussed in further detail in Chapter 2.

Following this initial report, Lu and Dai published a cationic palladium-catalyzed addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters (catalyst **1.28**, method B, Scheme 1.8).[15] Similar yields and diastereoselectivities that approached those obtained for the rhodium-catalyzed additions were observed for a variety of arylboronic acid coupling partners (**1.27a-g**, **j**, and **k**). However, neither the Pd(0) or Rh(0) catalyzed reaction conditions, methods A and B, respectively, resulted in successful addition of pyridylboronic acids. The sense of induction observed for both methods is consistent with addition of the aryl group to the re-face of the imine, opposite to the *tert*-butyl group (**1.26**, Scheme 1.8).

Scheme 1.8. Transition Metal Catalyzed Synthesis of *N*-*tert*-Butanesulfinyl Protected α-Arylglycines.





1.27a

method A:
R = Et; 89%, 98:2 dr
R = Me; 89%, 99:1 dr
R = Bn; 85%, 98:2 dr
R = *t*Bu; 78%, 98:2 dr
method B:
R =Et; 90%, 97:3 dr

1.27b

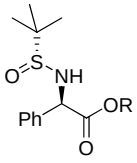
method A:
R = Me; 90%, 98:2 dr
method B:
R = Et; 65%, 98:2 dr

1.27c

method A:
R = Me; 61%, 99:1 dr
method B:
R = Et; 69%, 96:4 dr

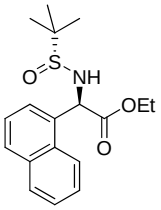
1.27d

method B:
73%, 95:5 dr



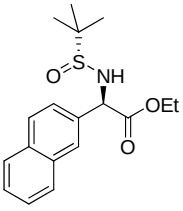
1.27e

method A:
R = Me; 79%, 99:1 dr
method B:
R = Et; 86%, 98:2 dr



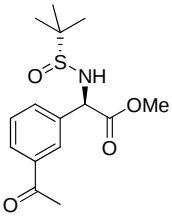
1.27f

method B:
66%, 94:6 dr



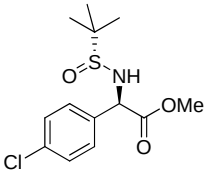
1.27g

method B:
84%, 97:3 dr



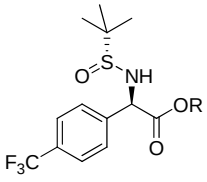
1.27h

method A:
87%, 99:1 dr



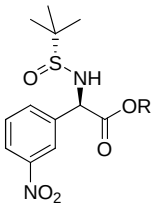
1.27i

method A:
82%, 99:1 dr



1.27j

method A:
R = Me; 74%, 98.5: 1.5 dr
method B:
R = Et; 57%, 95.5:4.5 dr

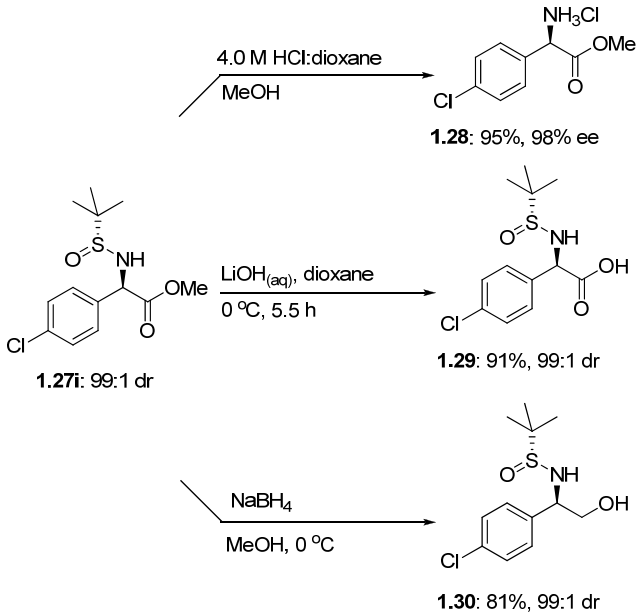


1.27k

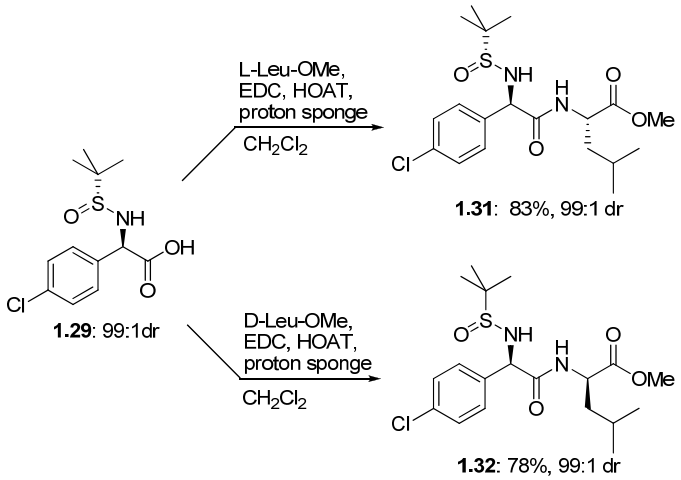
method A:
R = Me; 69%, 99:1 dr
method B:
R = Et; 62%, 94:6 dr

Ellman and coworkers also demonstrated that the enantiomerically enriched *N*-*tert*-butanesulfinyl protected α-arylglycine esters could undergo subsequent, selective transformations such as sulfinyl deprotection (**1.28**), hydrolysis to the free carboxylic acid (**1.29**), and reduction to the β-amino alcohol (**1.30**) in each case with minimal to no racemization (Scheme 1.9). Moreover they rigorously established that the *N*-sulfinyl α-arylglycine **1.29** obtained upon ester hydrolysis can be employed in peptide synthesis without racemization using (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), 1-hydroxy-7-azabenzotriazole (HOAT), and proton sponge under the reaction conditions developed by Carpino for the coupling of N-Boc-α-arylglycines without epimerization.[16] This chemistry will be discussed in further detail in Chapter 2.

Scheme 1.9. Further Synthetic Transformations of *N*-*tert*-Butanesulfinyl Protected α-Arylglycine Products



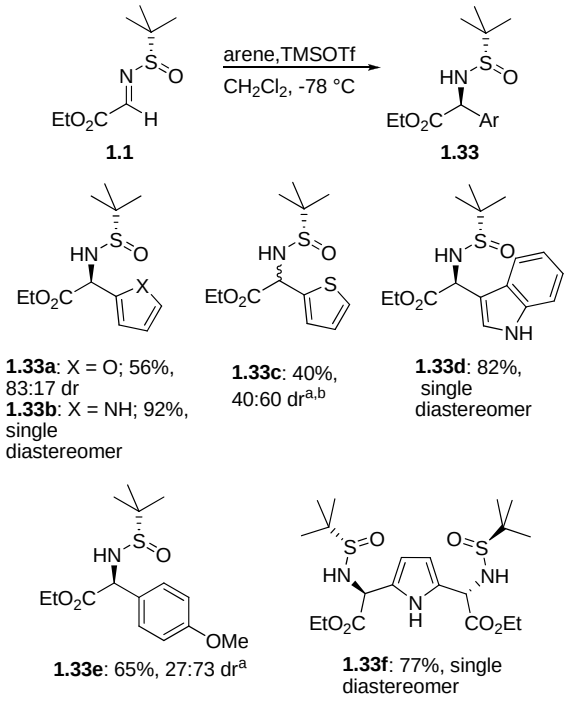
Scheme 1.10. Peptide Coupling of *N-tert*-Butanesulfinyl α-Arylglycine **1.29**



Recently, a trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoted addition of electron rich arenes to *N-tert*-butanesulfinyl imino ester **1.1** has also been demonstrated by Gautun and coworkers to furnish *N-tert*-butanesulfinyl protected α-heteroaryl- and arylglycine esters (Scheme 1.11).[17] A series of heterocyclic aromatic compounds were tested, with addition of furan, pyrrole, and indole generating **1.33a**, **1.33b**, and **1.33d** in moderate to high yields and diastereoselectivities. For the less reactive thiophene an increase in reaction temperature to -20 °C was required, providing **1.33c** with poor diastereoselectivity and a modest 40% yield. The reaction between anisole and **1.1** also required increased reaction temperatures (-20 °C) to give **1.33e** as a mixture of diastereomers in a combined 65% yield. In contrast, addition of pyridine to **1.1** was unsuccessful, even upon increasing the reaction temperature. The C_2 symmetric adduct **1.33f** was obtained in 77% yield as a single diastereomer by treatment of pyrrole with two equivalents of **1.1**. The absolute configurations of **1.33d** and **1.33f** were determined by X-ray structural analysis and **1.33b** was assigned in

accordance with **1.33f**. The absolute configurations of **1.33a** and **1.33e** were established by chemical correlation experiments. The observed stereochemical outcome for compounds **1.33a**, **1.33b**, and **1.33d** is consistent with an open transition state model (see **1.2**, Scheme 1.1).

Scheme 1.11. Synthesis of Heteroaromatic *N-tert*-Butanesulfinyl Protected α-Amino Esters

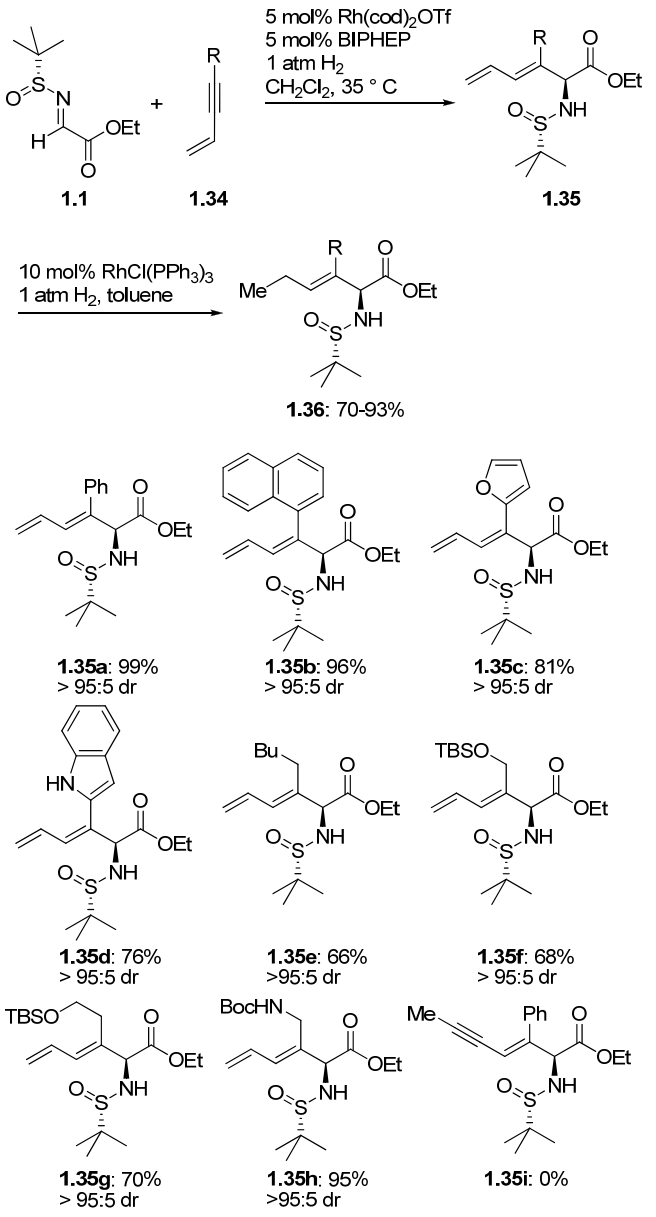


[a] This reaction was conducted at -20 °C. [b] The configuration of the major diastereomer was not determined.

N-tert-Butanesulfinyl imino esters have been used as the electrophilic partners in the rhodium-catalyzed hydrogen-mediated reductive coupling of 1,3-enynes or 1,3-diynes to form α-amino ester products (Scheme 1.12).[18] Krische and coworkers disclosed that hydrogen-mediated coupling of a 1,3-enyne to *N-tert*-butanesulfinyl imino esters at

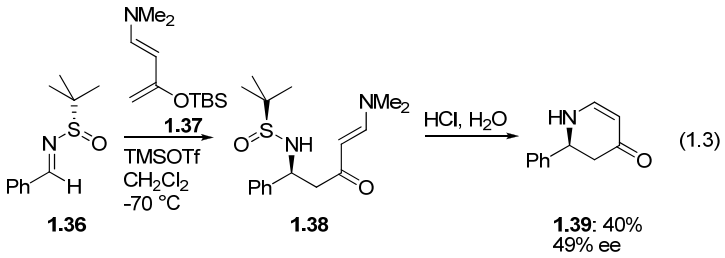
ambient pressure and temperature could be achieved in the presence of a rhodium catalyst generated from $[Rh(cod)_2]OTf$ and the bidentate ligand 2,2'-bis(diphenylphosphino)-1,1'-biphenyl (BIPHEP). Initial studies used an *N*-*p*-toluenesulfinyl imino ester as the electrophile. While this substrate provided high yields of the desired product, poor diastereoselectivity was observed. In contrast, reductive coupling with the *N*-*tert*-butanesulfinyl imino ester **1.1** gave the expected coupled adduct **1.35a** as a single regio- and stereoisomer in 55% yield. Increasing the concentration from 0.1 to 0.3 M in CH_2Cl_2 and raising the temperature slightly from room temperature to 35 °C further increased the yield to 99%. The method is applicable to a variety of enynes yielding the desired dienes in good yields (66-99%) and >95:5 diastereomeric ratios (**1.35a-h**). Attempts to couple 1-phenyl-1,3-pentadiyne to the *N*-*tert*-butanesulfinyl imino ester **1.1** under the reaction conditions optimized for enyne reductive couplings failed to give any of the desired product **1.35i**. For this transformation, the *N*-2,4,6-triisopropylbenzenesulfinyl imino ester was a more effective coupling partner. Regioselective hydrogenations of the terminal alkenes were achieved in 70-93% yield in the presence of Wilkinson's catalyst (Scheme 1.12). Exhaustive hydrogenation of the diene side chain was also achieved using Crabtree's catalyst, but replacement of the sulfinyl group with a carbamate protecting group was necessary.

Scheme 1.12 Hydrogen-Mediated Reductive Coupling of Conjugated Alkynes with *N*-*tert*-Butanesulfinyl Imino Ester **1.1**

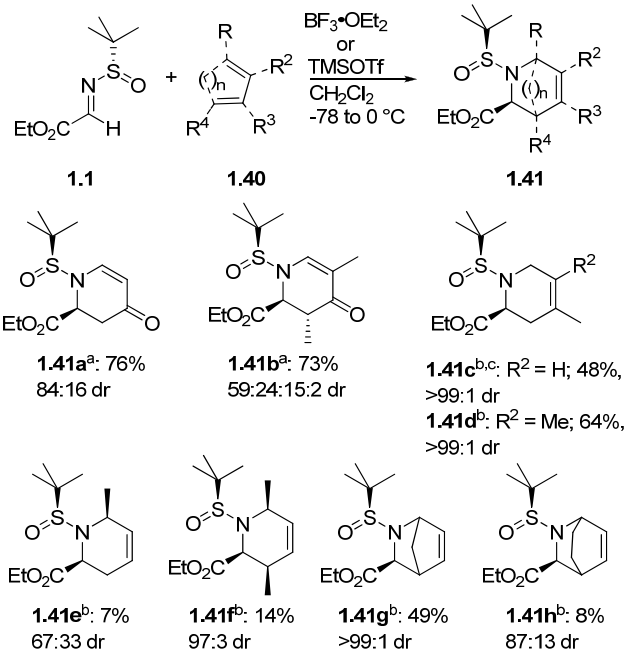


The diastereoselective aza-Diels-Alder with *N*-*tert*-butanesulfinyl imino esters was developed by Gautun and coworkers.[19] A previous study by Kawecki had demonstrated that an aryl *N*-*tert*-butanesulfinyl aldimine could serve as the

electrophile upon reaction with the highly reactive Rawal's diene to give the piperidone product **1.39** (eq 1.3).[20] To expand the scope of the reaction to include dienes other than Rawal's diene **1.37**, the highly activated *N*-*tert*-butanesulfinyl imino ester **1.1** was employed as the dieneophile (Scheme 1.13). The *p*-toluenesulfinyl protecting group was also evaluated, but higher diastereoselectivities were achieved in all cases with the *tert*-butanesulfinyl group. A number of Lewis acids were screened to promote the aza-Diels-Alder reaction, with $BF_3 \cdot OEt_2$ and TMSOTf providing the highest yields and selectivities. The reaction between **1.1** and a number of dienes was evaluated, providing **1.41a-h** in moderate yields (7-76%) and moderate to excellent diastereoselectivities. Notably, some of the dienes underwent polymerization, especially isoprene, and therefore a large excess of this reagent was required to obtain **1.41c** in moderate yield. The absolute configurations of **1.41a** and **1.41b** were established by X-ray structural analysis, while the configurations of **1.41c**, **1.41d**, and **1.41g** were determined by chemical correlation. The (*S*)-configurations at the alpha-carbon of **1.41e**, **1.41f**, and **1.41h** were assigned by analogy while ^{1}H NMR was used to determine the relative configuration between the ester and methyl groups.



Scheme 1.13 Aza Diels-Alder Reaction of **1.1** with Dienes



[a] $BF_3 \cdot OEt_2$ was used as the Lewis acid. [b] TMSOTf was used as the Lewis acid. [c] 20 equiv of diene was used.

1,2-Additions of Nucleophilic Carboxylic Acid Precursors to *N-tert*-Butanesulfinyl Imines

The Strecker Reaction with N-tert-*Butanesulfinyl Imines*

The asymmetric Strecker reaction is an important method for the synthesis of α-amino nitriles and the corresponding α-amino acids.[21] The addition of a cyanide nucleophile to a chiral imine is an expedient method for introducing asymmetry in the Strecker reaction. While the use of *p*-toluenesulfinyl aldimines as the imine input in the asymmetric Strecker reaction has been well developed,[22, 23] fewer examples of the analogous reaction with *N-tert*-butanesulfinyl imines have been reported.

The first example of an asymmetric Strecker reaction using an *N*-*tert*-butanesulfinyl aldimine was presented by Cordi and Mabic in their evaluation of the reaction between ethylaluminum cyanoisopropoxide [EtAl(O*i*Pr)CN] (eq 1.4) or TMSCN with **1.42** (Table 1.2).[24] Ethylaluminum cyanoisopropoxide [EtAl(O*i*Pr)CN], which can be generated in situ from diethylaluminum cyanide and *i*PrOH, was chosen because it had previously been the most successful cyanide delivery agent for the asymmetric Strecker reaction with *p*-toluenesulfinyl aldimines.[22] When [EtAl(O*i*Pr)CN] was used with the *N*-*tert*-butanesulfinyl aldimine **1.42** in THF the reaction took place in high yield and with high diastereoselectivity (eq 1.4). Similar results were obtained in other solvents of diverse polarity and chelating ability. The absolute configuration of the newly formed chiral center was determined as (*R*) by X-ray structural analysis **1.43a**.

The reaction between imine **1.42** and TMSCN did not proceed in the absence of a Lewis acid or when the temperature was below 10 °C. A large variety of Lewis acids were screened, revealing that the nature of the metal as well as the salt form of the metal had a significant influence on the yield and diastereoselectivity of the reaction (Table 1.2). The use of ZnI_2, $SnCl_4$, $BF_3{\cdot}OEt_2$, or $Yb(OTf)_3$ generated mixtures of **1.43a** and **1.43b** in moderate to good yield with diastereoselectivities of up to 80:20 favoring **1.43b** (entries 1-4). However an inversion in the diastereoselectivity was observed with triflate salts $Sc(OTf)_3$, $Y(OTf)_3$, and $La(OTf)_3$. These Lewis acids provided **1.43a** in moderate to good yield and with very high diastereoselectivities (entries 5-7). Other Lewis acids evaluated also favored the formation of **1.43a**, albeit with inferior diastereomeric ratios. The utility of this product was demonstrated by the conversion of **1.43a** to imidazoline **1.45** (Scheme 1.14). Treatment of **1.43a** with

borane dimethyl sulfide complex under reflux conditions followed by hydrolysis of the boride intermediate and cleavage of the sulfinyl group under acidic conditions provided the ethylene diamine **1.44** as the bis-hydrochloride salt in 67% yield. Cyclization of the diamine with formamidine acetate afforded **1.45**, which was isolated as the hemi-fumarate in 67% yield after crystallization.

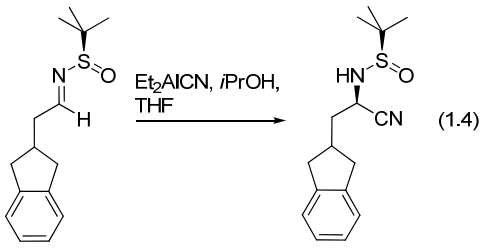
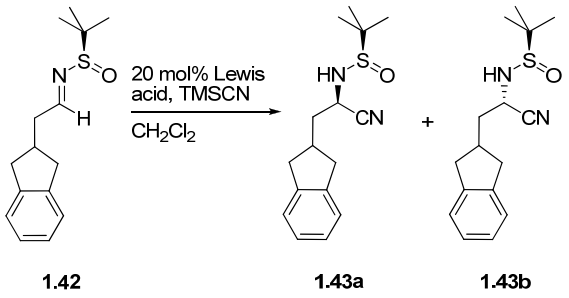
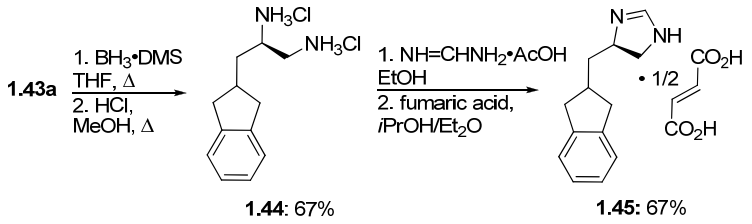


Table 1.2. Evaluation of Several Lewis Acids



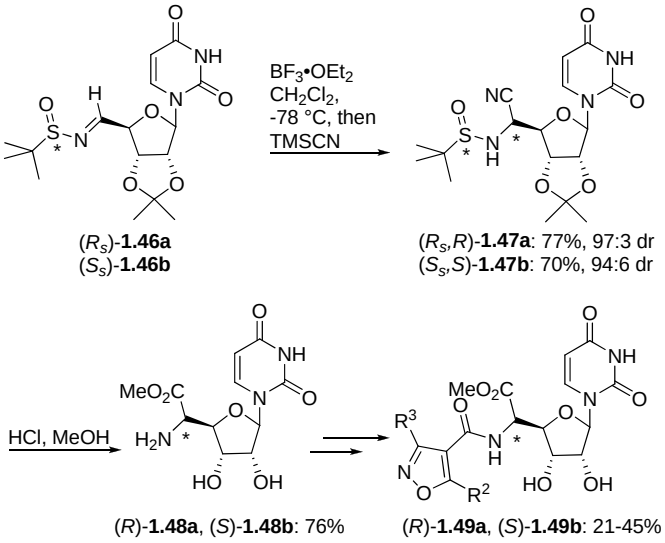
entry	catalyst	yield	dr
1	ZnI_2	80	30:70
2	$SnCl_4$	74	35:65
3	$BF_3{\cdot}OEt_2$	72	32:68
4	$Yb(OTf)_3$	38	20:80
5	$Sc(OTf)_3$	98	97:3
6	$Y(OTf)_3$	90	98:2
7	$La(OTf)_3$	48	98:2

Scheme 1.14. Synthesis of **1.45** from *N*-Sulfinyl α-Aminonitrile **1.43a**

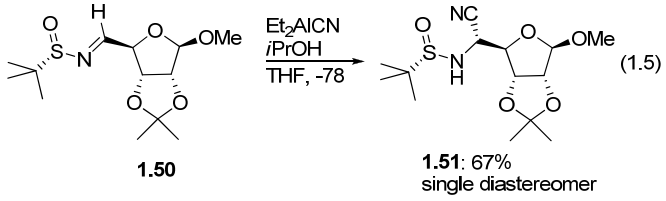


The Lewis acid-catalyzed addition of TMSCN to an *N-tert*-butanesulfinyl aldimine was exploited by Plant, Williams, and Thompson (Scheme 1.15).[25] The *N-tert*-butanesulfinyl imine derivatives of uridine **1.46a** and **1.46b** were examined as precursors to novel chitin synthase inhibitors, which could be utilized as potential pesticidal agents. Contrary to Cordi and Mabic's findings (*vide supra*), with these more electrophilic imines, high yields and disastereoselectivities were achieved when the reactions were conducted at low temperature (-78 °C) using $BF_3 \cdot OEt_2$ as the Lewis acid. Under these conditions, (R_S,*R*)-**1.47a** was generated in 77% yield and 97:3 dr (Scheme 1.15). Comparable results were obtained when imine (S_S)-**1.46b** was utilized, providing (S_S,*S*)-**1.47b** in 70% yield and 94:6 dr. Treatment of (R_S,*R*)-**1.47a** or (S_S,*S*)-**1.47b** with HCl in MeOH produced the corresponding methyl esters (*R*)-**1.48a** and (*S*)-**1.48b** with concomitant removal of the sulfinyl and isopropylidene protecting groups. Coupling of the free amine (*R*)-**1.48a** or (*S*)-**1.48b** with isoxazole carboxylic acid analogues provided several derivatives of (*R*)-**1.49a** and (*S*)-**1.49b** in 21-45% yield.

Scheme 1.15. Stereoselective Cyanide Addition to *N-tert*-Butanesulfinyl Imine **1.46**



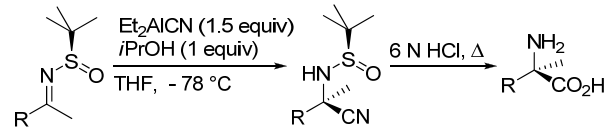
Recently, Xu and coworkers demonstrated that the *N-tert*-butanesulfinyl imine **1.50**, derived from D-ribose, was an excellent substrate for the asymmetric Strecker reaction following the Et_2AlCN/*i*PrOH protocol developed by Davis and coworkers (*vide supra*), providing adduct **1.51** in 67% yield as a single diastereomer (eq 1.5).[26] Unfortunately, all attempts to hydrolyze the nitrile to furnish the desired carboxylic acid under acidic conditions failed due to the instability of **1.51** under the reaction conditions.



The first example of an asymmetric Strecker reaction utilizing an *N-tert*-butanesulfinyl ketimine was reported by Davis and coworkers in 2000 (Scheme 1.16).[27] While the primary focus of Davis' study was the use of his Et_2AlCN/*i*PrOH

protocol for additions to *N*-*p*-toluenesulfinyl ketimines, the *N*-*tert*-butanesulfinyl ketimines **1.52a** and **1.52b** were also tested to probe the effects of the bulkier *tert*-butanesulfinyl group on the diastereoselectivity of the reaction. Ketimine **1.52a**, which exists as a single imine isomer, was converted to the corresponding amino nitrile **1.53a** in a 92:8 diastereomeric ratio, and a 56% yield of the pure major diastereomer was obtained after recrystallization. A lower diastereomeric ratio (83:17 dr) was observed for additions to the more challenging *N*-*tert*-butanesulfinyl ketimine substrate **1.52b**, and compound **1.53b** could not be purified to diastereomeric purity. The diastereoselectivity observed for **1.53a** and **1.53b** was higher than that obtained for the corresponding *N*-*p*-toluenesulfinyl amino nitriles (80:20 and 75:25 dr, respectively). The free amino acid **1.54a** could be generated in good yield (64%) without epimerization by hydrolysis of **1.53a** in refluxing 6 N HCl (Scheme 1.16).

Scheme 1.16. Addition of Et_2AlCN/*i*PrOH to Ketimines **1.52a** and **1.52b**

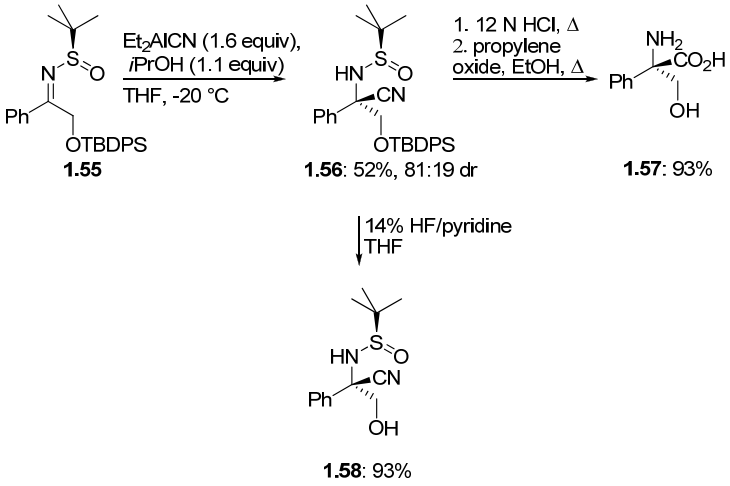


[a] Yield of the major diastereomer after recrystallization. [b] Isolated yield of both diastereomers.

Later, Davis' protocol was utilized by Avenoza, Peregrina, and coworkers for the synthesis of α-phenylserine **1.57** (Scheme 1.17).[28] Treatment of ketimine **1.55** with ethylaluminum cyanoisopropoxide [EtAl(O*i*Pr)CN] at -20 °C provided **1.56** in 52% yield as an 81:19 mixture of diastereomers. Attempts to increase the

diastereoselectivity of the reaction by lowering the temperature were unsuccessful due to attenuated reactivity. However, diastereomerically pure **1.56** was obtained after column chromatography. Selective cleavage of the silyl group by treatment with HF in pyridine provided alcohol **1.57** in high yield. A crystal structure of **1.58** was obtained to unambiguously establish the (*R*)-configuration at the newly formed stereocenter. Treatment of diastereomerically pure **1.56** with 12 N aqueous HCl at reflux successfully removed both the sulfinyl and silyl groups and hydrolyzed the nitrile group. Conversion of the amine hydrochloride salt to (*S*)-α-phenylserine **1.57** was achieved in high yield (93%) after treatment with propylene oxide in EtOH under reflux conditions (Scheme 1.17). The opposite enantiomer of **1.57** was also generated in the same manner by utilizing (S_s)-*N*-*tert*-butanesulfinyl ketimine **1.55**, constituting an efficient route to either enantiomer of α-phenylserine.

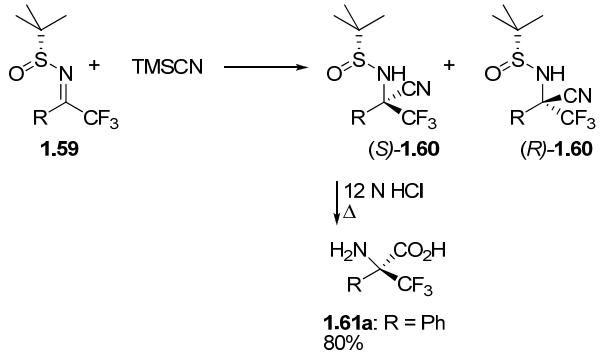
Scheme 1.17. Synthesis of α-Phenylserine **1.57**



The asymmetric Strecker reaction for the synthesis of α-trifluoromethyl α-amino acids from CF_3-substituted *N*-*tert*-butanesulfinyl ketimines **1.59** was demonstrated by

Lu and coworkers (Table 1.3).[29] The reaction conditions were optimized for the addition of TMSCN to the *N-tert*-butanesulfinyl imine **1.59a**. A panel of solvents was investigated, revealing that hexanes provided the desired adduct (R_s,*S*)-**1.60a** in the highest yield and diastereoselectivity (99:1 dr, entry 1, Table 1.3). Interestingly, the reaction in DMF provided (R_s,*R*)-**1.60a** in 72% yield and with 86:14 diastereoselectivity (entry 1), signifying a switch in diastereoselectivity from the reaction conducted in hexanes (entry 1). The effects of electron-donating or withdrawing substituents on the reaction outcome were also evaluated. Yields and diastereoselectivities remained high regardless of the aryl substituent for reactions performed in hexanes and DMF (entries 2-4). Several CF_3-substituted aliphatic *N-tert*-butanesulfinyl ketimines (R = alkyl) also underwent the Strecker reaction in hexanes providing (R_s,*S*)-1**.60e-h** in 69-92% yield and up to 96:4 dr while the corresponding reactions in DMF also gave good yields of (R_s,*R*)-**1.60e-h** (71-89%) and diastereomeric ratios ranging from 91:9 to 95:5 (entries 5-8). Compound (R_s,*S*)-**1.60a** was then hydrolyzed to (*S*)-2-amino-2-phenyl-1,1,1-trifluoropropanoic acid **1.61a** in 80% yield (Table 1.3). While the asymmetric Strecker reaction proceeded in high yields for a range of ketimines **1.59**, the authors noted that *N-tert*-butanesulfinyl ketimines without a CF_3 substituent were not compatible coupling partners under these conditions.

Table 1.3. Addition of TMSCN to CF_3-Substituted *N-tert*-Butanesulfinyl Ketimines



entry	imine	R	Hexanes, rt		DMF, -35 °C	
			dr (R_s,*S*)-**1.60**	yield (%) (R_s,*S*)-**1.60**	dr (R_s,*R*)-**1.60**	yield (%) (R_s,*R*)-**1.60**
1	**1.59a**	Ph	99:1	85	86:14	72
2	**1.59b**	4-Me-Ph	92:8	87	87:13	69
3	**1.59c**	4-MeO-Ph	93:7	89	90:10	78
4	**1.59d**	4-Cl-Ph	89:11	83	86:14	71
5	**1.59e**	Me	96:4	69	95:5	71
6	**1.59f**	Et	87:13	77	91:9	76
7	**1.59g**	Hexyl	93:7	88	92:8	84
8	**1.59h**	$BnCH_2$	87:13	92	94:6	89

The stereochemical outcome of this reaction was established by X-ray structural analysis of **1.60a** and **1.60b**. Based upon this observed sense of induction, the authors rationalized the solvent dependence of the stereochemical outcome by proposing divergent reaction pathways (Figure 1.1). In hexanes a chelated transition state (**1.62**) was invoked where the sulfinyl group activates the TMSCN to undergo the Strecker reaction. Placing the CF_3 moiety in the equatorial position minimizes electrostatic repulsion between the CF_3 substituent and the sulfur lone pair providing the major product with (R_s, *S*) configuration. The authors propose an open transition state for the

Strecker reaction in DMF, where the Lewis basic DMF can activate TMSCN instead of the sulfinyl group (**1.63**). Under these conditions the major product has an (R_s, R) configuration.

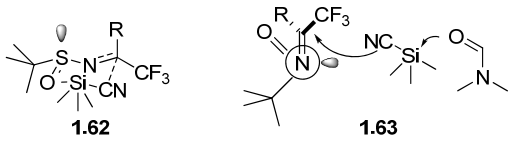


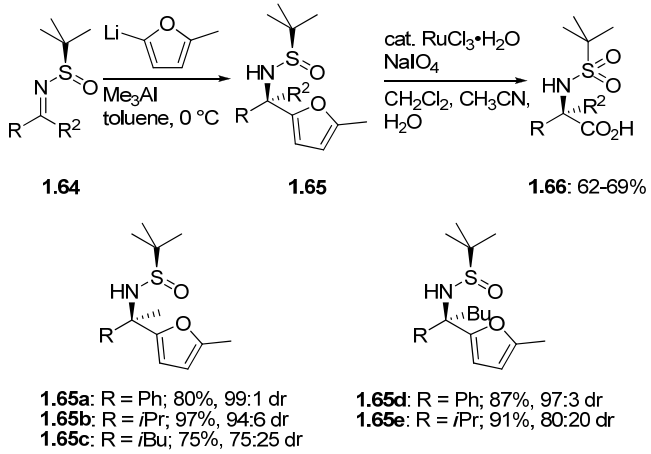
Figure 1.1. Proposed Transition States for the Asymmetric Strecker Reaction

Addition of Furanyl Lithium Reagents to N-tert-*Butanesulfinyl Imines*

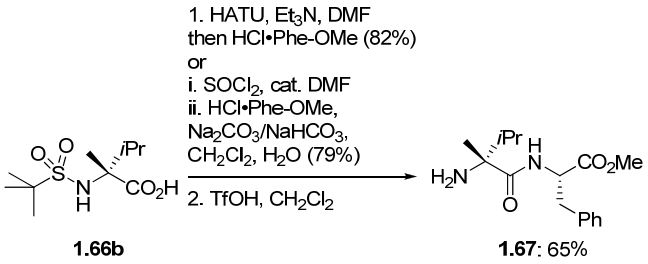
α-Amino acids have also been prepared by the addition of furanyllithium derivatives to *N-tert*-butanesulfinyl aldimines and ketimines wherein the furan substituent in the addition products is subsequently oxidized to a carboxy group. Ellman and coworkers first developed this approach for the expedient synthesis of α,α-disubstituted amino acids by the 1,2-addition of 5-methylfuryllithium to *N-t*er*t*-butanesulfinyl ketimines (Scheme 1.18).[30] The conditions previously optimized for the addition of other organolithium reagents to *N-tert*-butanesulfinyl ketimines were employed (Me_3Al, toluene, -78 °C), except that for this nucleophile the reaction is carried out at 0 °C to achieve the best yields. The scope of this transformation with respect to the ketimine **1.64** was probed, and high yields and moderate to high diastereoselectivities were achieved for α,α-dialkyl and α-aryl-α-alkyl adducts **1.65a-e**. Oxidation of the resulting *N*-sulfinyl amines **1.65a-e** to the *N-tert*-butanesulfonyl (Bus)-protected amino acids **1.66a-e** was achieved with $NaIO_4$ and catalytic $RuCl_3$, in a CH_2Cl_2, CH_3CN, and H_2O solvent comixture. Removal of the Bus-protecting group and conversion of the

resulting amine to the (+)- and (-)-MTPA amides rigorously established that no racemization had occurred during this synthetic sequence. The utility of these compounds was demonstrated by using **1.66b** as a reagent for peptide synthesis (Scheme 1.19). The coupling of **1.66b** to HCl·Phe-OMe under two different amide bond formation conditions was evaluated, with each transformation proceeding in good yields. Cleavage of the Bus group from the resulting dipeptide using TfOH/CH_2Cl_2 provided the free amine **1.67** in 65% yield.

Scheme 1.18. 1,2-Addition of 5-Methylfuryllithium to *N*-*tert*-Butanesulfinyl Ketimines

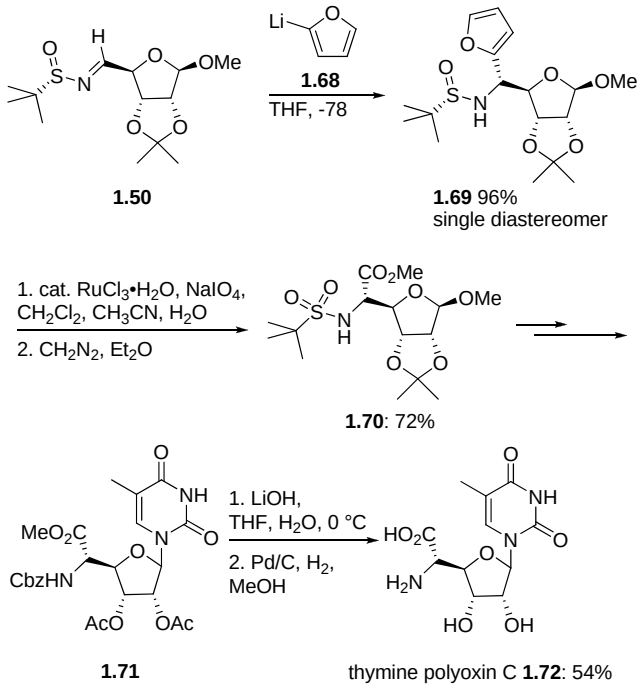


Scheme 1.19. Use of **1.66b** as a Reagent for Peptide Synthesis



Xu and coworkers utilized the nucleophilic addition of 2-lithiofuran **1.68** to *N-tert*-butanesulfinyl aldimine **1.50** in their total synthesis of thymine polyoxin C **1.72**, a core structure of the polyoxin and nikkomycin antibiotics (Scheme 1.20).[26, 31] The reaction proceeded in high yield and provided **1.69** as a single diastereomer. The absolute configuration of the newly set stereocenter was confirmed by X-ray structural analysis of **1.69**, and was consistent with a chelated transition state. Concomitant oxidative cleavage of the furan ring to the carboxylic acid and oxidation of the sulfinyl group to the Bus group was achieved with catalytic $RuCl_3$ and excess $NaIO_4$. Subsequent conversion of the carboxylic acid to the methyl ester using diazomethane provided **1.70** in 72% yield over two steps. Further synthetic transformations provided the protected thymine polyoxin C **1.71** which was then converted to thymine polyoxin C, providing **1.72** in reasonable yield over the two-step deprotection sequence.[31]

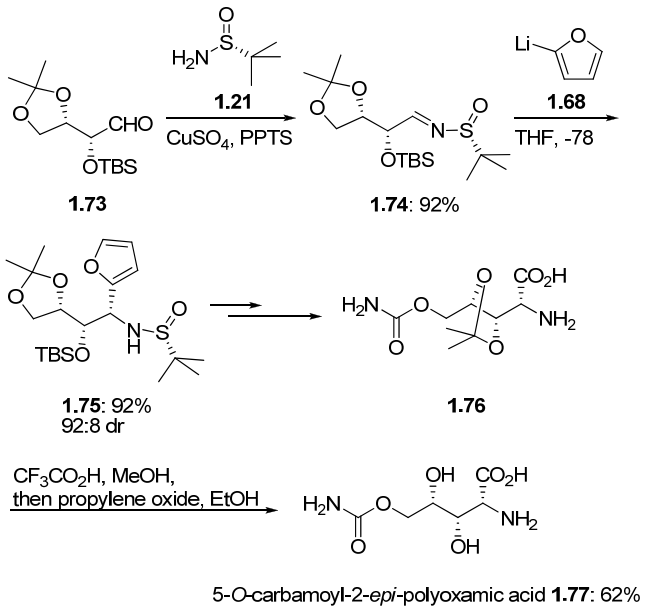
Scheme 1.20. Synthesis of Thymine Polyoxin C **1.72**



In order to facilitate the synthesis of polyoxin analogues, Xu and coworkers synthesized 5-*O*-carbamyl-2-*epi*-polyoxamic acid **1.77**, a common side chain in many members of the polyoxin family (Scheme 1.21).[31] A modified procedure for the condensation of (*R*)-*tert*-butanesulfinamide with aldehyde **1.73** was developed, where addition of one equivalent of PPTS in the presence of anhydrous copper sulfate provided the desired imine **1.74** in excellent yield. Subsequent nucleophilic addition of **1.68** to imine **1.74** under the previously optimized reaction conditions (*vide supra*) provided **1.75** in 92% yield and 92:8 diastereomeric ratio. The high diastereoselectivity observed for this transformation was attributed to a matched combination of the chirality of the (*R*)-sulfinyl group and the protected triol moiety, which was experimentally confirmed by the lowered diastereoselectivity obtained for addition of **1.68** to the (*S*)-*N*-*tert*-butanesulfinyl imine diastereomer. Subsequent

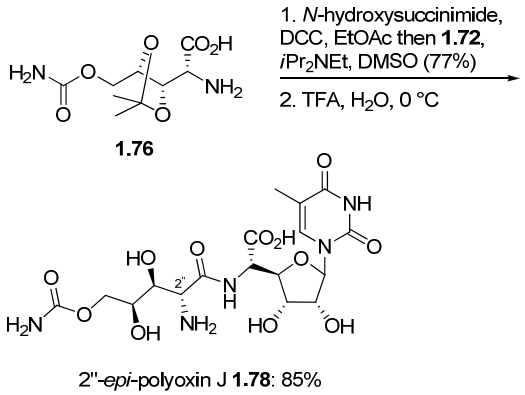
synthetic transformations provided **1.76** which afforded 5-*O*-carbamyl-2-*epi*-polyoxamic acid **1.77** after facile deprotection.

Scheme 1.21. Synthesis of 5-*O*-Carbamyl-2-*epi*-Polyoxamic Acid **1.77**



Xu and coworkers then developed a convergent synthesis of 2”-epi-polyoxin J **1.78** via amide bond coupling of the two intermediates prepared via *tert*-butanesulfinamide chemistry, **1.76** and **1.72**, followed by deprotection (Scheme 1.22).[31]

Scheme 1.22. Synthesis of 2"-*epi*-Polyoxin J **1.78**

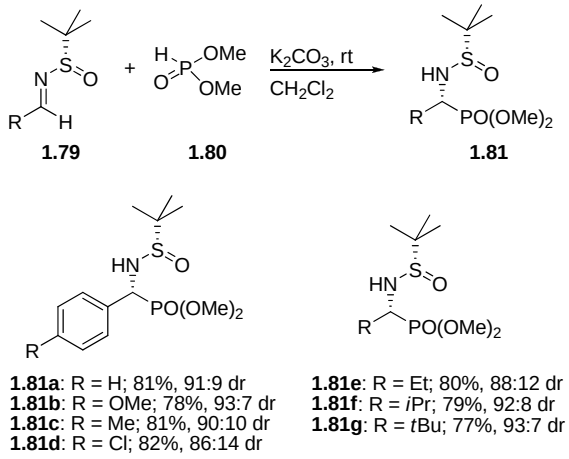


Synthesis of α-Amino Phosphonic Acids

Recently, *N-tert*-butanesulfinyl aldimines and ketimines have been utilized for the asymmetric synthesis of α-aminophosphonic acids, the phosphonic acid analogues of α-amino acids. Indeed, many natural and synthetic α-aminophosphonic acids display pharmacological properties, behave as enzyme inhibitors, are growth regulators in plants, or function as potent antimicrobial agents.[32]

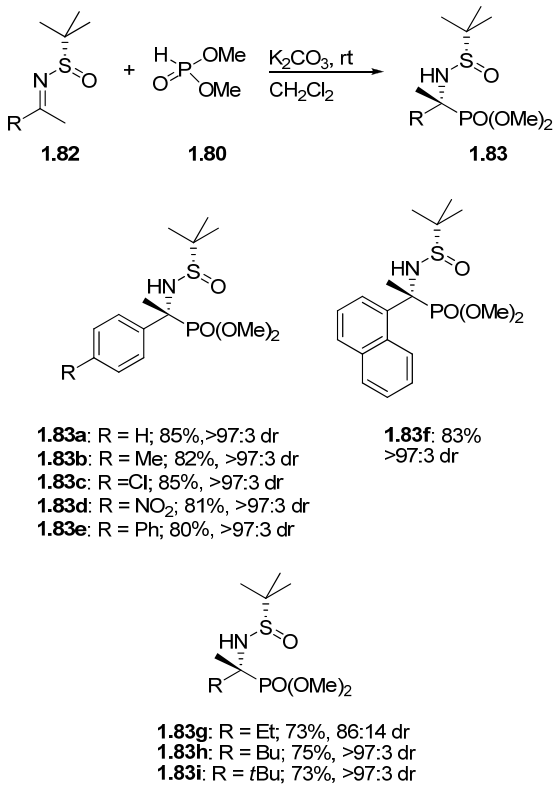
Yuan and Chen reported the first addition of dimethyl phosphite **1.80** to *N-tert*-butanesulfinyl imines **1.79** affording α-aminophosphonates **1.81** (Scheme 1.23).[33] A screen of temperature, solvent, and base with the *N-tert*-butanesulfinyl imine derived from benzaldehyde revealed that the best yield and diastereoselectivity for the desired adduct **1.81a** was obtained using K_2CO_3 as a base in CH_2Cl_2 at room temperature (81%, 91:9 dr). The optimized protocol was then applied to include a variety of aryl and alkyl *N-tert*-butanesulfinyl aldimines, generating the *N-tert*-butanesulfinyl α-aminophosphonates **1.81b-g** in good yields (77-82%) and diastereoselectivities (86:14-93:7), and the major diastereomers was isolable by column chromatography.

Scheme 1.23 Synthesis of *N*-Sulfinyl α-Aminophosphonates from Aldimines



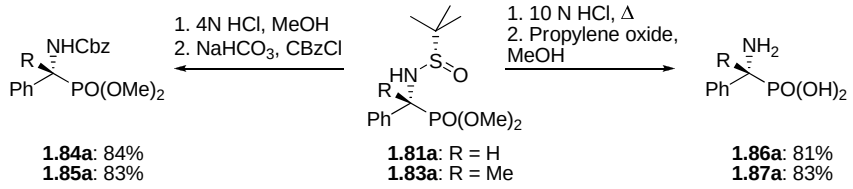
The synthesis of quaternary α-aminophosphonates from *N*-*tert*-butanesulfinyl ketimines was also demonstrated (Scheme 1.24). A brief screen of dialkyl phosphites (R = Me, Et, Pr, *i*Pr) revealed that dimethyl phosphite **1.80** added the most rapidly as well as with the highest diastereoselectivity.[34] Using the reaction conditions optimized for the addition of **1.80** to *N*-*tert*-butanesulfinyl aldimines, a variety of alkyl and aryl *N*-*tert*-butanesulfinyl quaternary α-aminophosphonates **1.83a-i** were synthesized in good yields (73-85%).[33] The addition of dimethyl phosphite **1.80** to all of the *N*-*tert*-butanesulfinyl ketimines surveyed proceeded with > 97:3 dr except for the addition to the particularly challenging substrate **1.82** (R = Et), which gave α-aminophosphonate **1.83e** in a quite respectable 86:14 diastereomeric ratio.

Scheme 1.24 Synthesis of Quaternary α-Aminophosphonates from *N-tert*-Butanesulfinyl Ketimines



Nitrogen protecting group manipulation was demonstrated by selective cleavage of the sulfinyl group and replacement with a Cbz group to give products **1.84a** and **1.85a** in high yields (Scheme 1.25). The free aminophosphonic acids **1.86a** and **1.87b** were also obtained by refluxing **1.81a** or **1.83a** in 10 N HCl followed by addition of propylene oxide. The absolute configurations of the α-aminophosphonic acids **1.86a** and **1.87a** were determined by correlation to known compounds, thus establishing the stereochemical outcome of the addition reaction.

Scheme 1.25. Further Transformations of the *N*-*tert*-Butanesulfinyl α-Amino Phosphonates



1.84a: 84%
1.85a: 83%

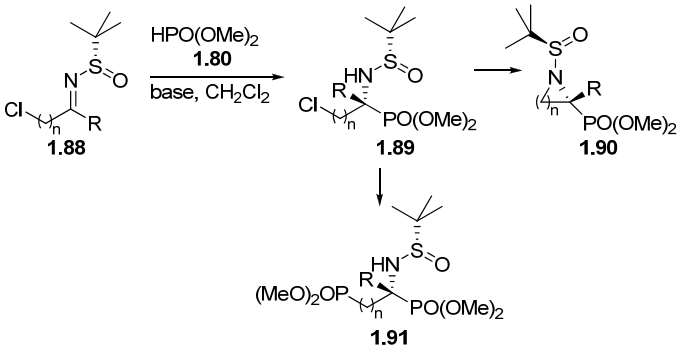
1.81a: R = H
1.83a: R = Me

1.86a: 81%
1.87a: 83%

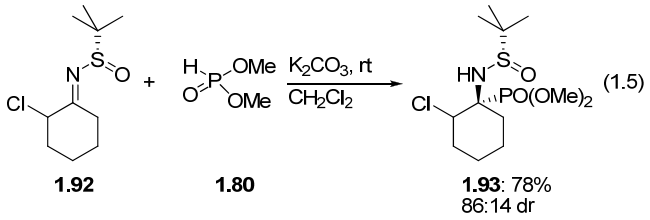
Yuan and coworkers also explored the reaction between chloro-substituted *N*-*tert*-butanesulfinyl aldimines and ketimines and dimethyl phosphite **1.80**.[34] For these substrates they found that the product obtained depended on the choice of base used as well as the structure of the starting *N*-*tert*-butanesulfinyl imine (Table 1.3). For the *N*-*tert*-butanesulfinyl ketimine (R= Me, n = 1) the cyclic product **1.90** was obtained in the presence of either K_2CO_3 or KF, but the diastereoselectivity was highest with the latter base (entry 1). However, when the corresponding aldimine was examined with K_2CO_3 as the base the 2-phosphoryl-1-aminophosphate **1.91** was generated with very high diastereoselectivity (entry 2). When the alkyl chain length was increased (n = 2) the cyclobutane product was obtained in the presence of K_2CO_3 (entry 3), but Cs_2CO_3 promoted the formation of the diphosphonate **1.91**, albeit with poor selectivity (entry 4). Further extension of the alkyl side chain to n = 3 on the dialkyl *N*-*tert*-butanesulfinyl ketimine **1.88** (R = Me) provided the 4-chloro-1-methyl-1-amino-phosphonate **1.89** when K_2CO_3 was employed (entry 5) whereas cylization to **1.90** occurred for aryl substituted *N*-*tert*-butanesulfinyl ketimine **1.88** (R = Ph) when Cs_2CO_3 was used as the base (entry 6). The reaction conditions were also applied to the addition of **1.80** to cyclic *N*-*tert*-butanesulfinyl ketimine **1.92**, providing **1.93** in

good yield and with moderate diastereoselectivity (eq 1.5). While not rigorously determined, the absolute configurations of products **1.89**, **1.90**, or **1.91** were predicted by analogy to the previous study conducted by Yuan and Chen on the addition of **1.80** to *N-tert*-butanesulfinyl aldimines and ketimines (*vide supra*).

Table 1.3. Addition of **1.80** to Chloro-Substituted *N-tert*-Butanesulfinyl Imines **1.88**



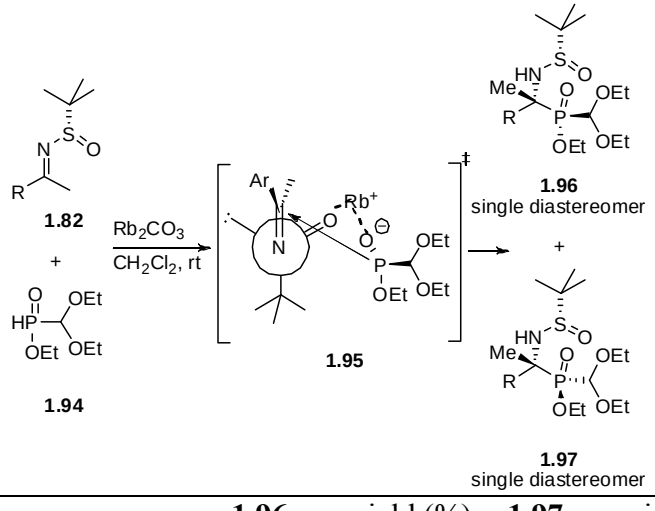
entry	n	R	base	Yield (%) **1.89**	Yield (%) **1.90**	Yield (%) **1.91**	dr
1	1	Me	KF	-	75	-	92:8
2	1	H	K_2CO_3	-	-	86	>97.:3
3	2	Ph	K_2CO_3	-	82	-	89:11
4	2	Ph	Cs_2CO_3	-	-	87	61:39
5	3	Me	K_2CO_3	85	-	-	93:7
6	3	Ph	Cs_2CO_3	-	83	-	71:29



Yuan and Zhang have also reported the synthesis of α-amino-phosphinates (**1.96** and **1.97**) via the addition of ethyl diethoxymethyl phosphinate **1.94** to *N-tert*-butanesulfinyl imines **1.82** (Table 1.4).[35] Based on their previous conditions for the

addition of dimethyl phosphite to several *N*-*tert*-butanesulfinyl ketimines, the use of K_2CO_3 as the base was first explored, but this gave low yields after prolonged reaction times. In contrast, Rb_2CO_3 effectively promoted the reaction between several aryl, heteroaryl, and one alkyl ketimine and **1.94** (entries 1-17). The products were obtained as a mixture of phosphorous stereoisomers **1.96** and **1.97**, which were separable by column chromatography. A crystal structure of each isomer was obtained, revealing that **1.96** (with S_P stereochemistry) and **1.97** (with R_P stereochemistry), both displayed *R* stereochemistry at the newly formed stereogenic center. High imine diastereofacial selectivity was observed, as demonstrated by single peaks in each ^{31}P NMR for **1.96a-q** and **1.97a-q** and by chiral HPLC analysis of selected oxidized derivatives.

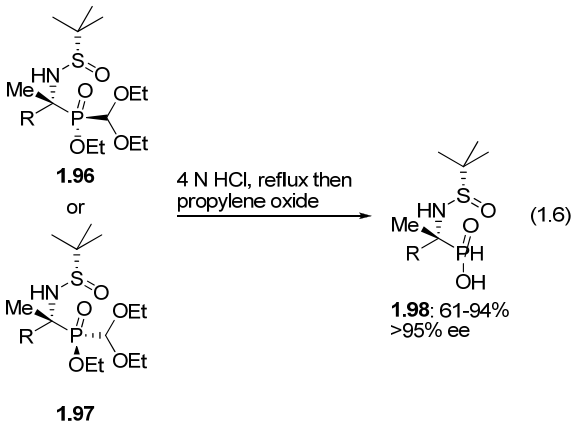
Table 1.4. Synthesis of α-Amino-Phosphinates **1.96** and **1.97**



entry	R	**1.96**	yield (%)	**1.97**	yield (%)
1	Ph	**1.96a**	46	**1.97a**	50
2	4-Me-Ph	**1.96b**	37	**1.97b**	48
3	4-MeO-Ph	**1.96c**	48	**1.97c**	50
4	4-CH_3S-Ph	**1.96d**	37	**1.97d**	34
5	4-morpholino-Ph	**1.96e**	29	**1.97e**	36
6	2-F-Ph	**1.96f**	37	**1.97f**	36
7	4-F-Ph	**1.96g**	43	**1.97g**	50
8	4-Cl-Ph	**1.96h**	46	**1.97h**	48
9	4-Br-Ph	**1.96i**	41	**1.97i**	35
10	1-furyl	**1.96j**	35	**1.97j**	49
11	1-thienyl	**1.96k**	45	**1.97k**	47
12	3-pyridyl	**1.96l**	50	**1.97l**	35
13	2-naphthyl	**1.96m**	43	**1.97m**	49
14	biphenyl	**1.96n**	49	**1.97n**	49
15	4-CN-Ph	**1.96o**	41	**1.97o**	48
16	4-NO_2-Ph	**1.96p**	32	**1.97p**	38
17	hexyl	**1.96q**	45	**1.97q**	30

The free α-amino-H-phosphinic acids **1.98** were obtained by refluxing **1.96** or **1.97** with 4 N HCl (eq 1.6). The authors noted that these monobasic acids may better

mimic α-aminocarboxylic acids and could display greater biological activity than the well-studied α-aminophosphonic acids.

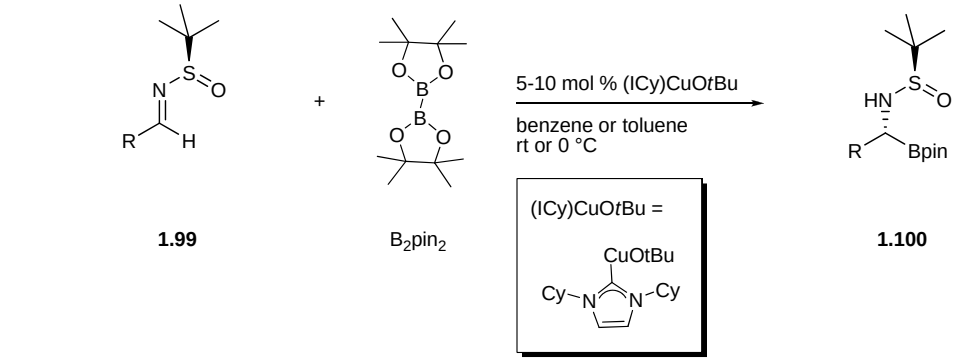


Synthesis of α-Amino Boronic Acids

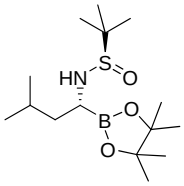
α-Amino boronic acids are another biologically important class of surrogates for α-amino acids and have been shown to be key mechanism-based pharmacophores for serine protease inhibition.[36] Ellman and Beenen have recently developed a method for the copper-catalyzed addition of bis(pinacolato)diboron to *N*-*tert*-butanesulfinyl aldimines for the synthesis of α-aminoboronate esters (see Chapter 3).[37] The optimal catalyst for this transformation was (1,3-dicyclohexylimidazol-2-ylident)copper(I) *tert*-butoxide ((ICy)CuO*t*Bu), which was developed by Sadighi and coworkers for the addition of bis(pinacolato)diboron across aromatic and aliphatic aldehydes.[38] Additions to unbranched (**1.100a-c**) and branched aliphatic aldimines (**1.100d-f**) proceeded in good yields and with high diastereoselectivites (Scheme 1.26). Aryl aldimines could also be used to synthesize the boronate ester analogues of arylglycines (**1.100g-k**), but for these substrates the best yields were obtained when the temperature

was lowered to 0 °C, the catalyst loading was increased from 5 to 10 mol%, and the equivalents of B_2pin_2 were increased. The success of the method for functionalized α-amino boronic acid analogues was demonstrated by the preparation of the α-amino boronate ester corresponding to *O*-TBDPS protected serine (**1.100l**). The utility of this method was demonstrated by the rapid synthesis of bortezomib (Velcade®), the first FDA approved proteasome inhibitor drug, which is clinically used for the treatment of multiple myeloma and mantle cell lymphoma. Bortezomib was accessed from the amine hydrochloride **1.101** after subsequent peptide coupling in 41% overall yield over four steps (Scheme 1.27). This chemistry will be discussed in further detail in Chapter 3.

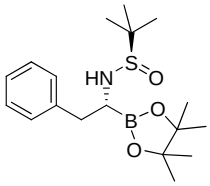
Scheme 1.26. Syntheis of α-Amino Boronate Esters



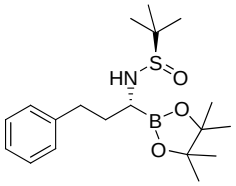
1.99 B_2pin_2 **1.100**



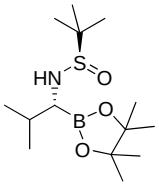
1.100a: 74% yield
> 98:2 dr



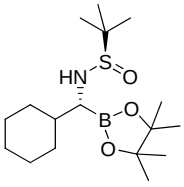
1.100b: 59% yield
> 98:2 dr



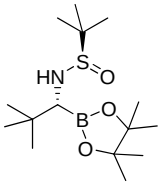
1.100c: 70% yield
99:1 dr



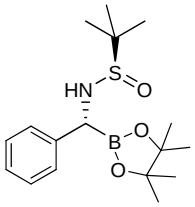
1.100d: 88% yield
> 98:2 dr



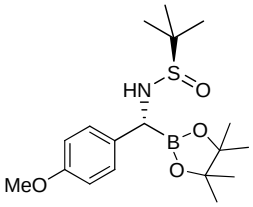
1100e: 81% yield
97:3 dr



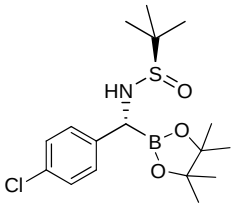
1.100f: 75% yield
96:4 dr



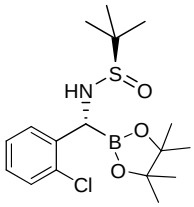
1.100g: 66% ^{1}H NMR yield
54% isolated
99:1 dr



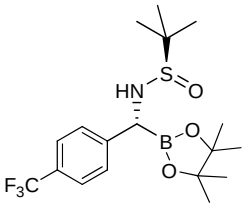
1.100h: 74% ^{1}H NMR yield
57% isolated
>98:2 dr



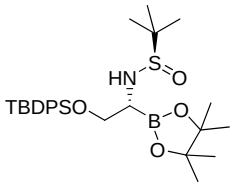
1.100i: 77% ^{1}H NMR yield
61% isolated
99:1 dr



1.100j: 79% ^{1}H NMR yield
52% isolated
> 97:3 dr

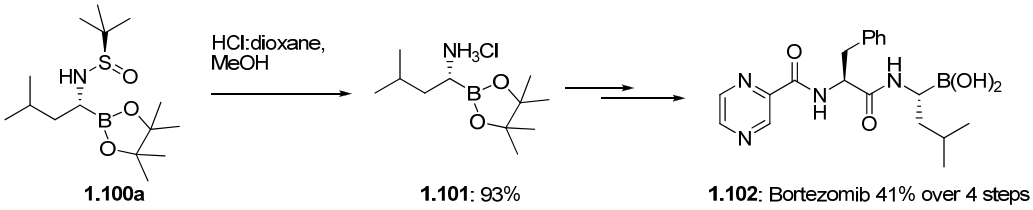


1.100k: 66% ^{1}H NMR yield
>95:5 dr



1.100l: 75% yield
99:1 dr

Scheme 1.27. Synthesis of Bortezomib



Conclusion

This literature survey serves to illustrate the extensive use of *tert*-butanesulfinamide in the asymmetric synthesis of α-amino acids and their derivatives. These methods have provided diverse synthetic routes towards this highly important class of chiral amine-containing compounds. Within this area, significant advances have been made that have enabled the efficient synthesis of α-arylglycines by a rhodium-catalyzed addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters. Additionally, new methodology has been developed to facilitate the synthesis of α-amino boronic acid derivatives from *N*-*tert*-butanesulfinyl aldimines. These advancements will be fully explored in Chapters 2 and 3.

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Chapter 2. The Rhodium-Catalyzed Addition of Arylboronic Acids to *N-tert*-Butanesulfinyl Imines

The rhodium-catalyzed addition of arylboronic acids to N-tert-*butanesulfinyl imino esters is described. This chemistry is compatible with a variety of electronically and sterically diverse arylboronic acids providing the* N-tert-*butanesulfinyl protected α-arylglycine products in good yields and with high diastereoselectivities. In addition, the utility of this method is demonstrated by subjecting the enantiomerically enriched* N-tert-*butanesulfinyl protected products to selective synthetic manipulations with little to no racemization. The majority of this work was published as a communication.* (Beenen, M. A.; Weix, D. J.; Ellman, J. A. Asymmetric Synthesis of Protected Arylglycines by Rhodium-Catalyzed Addition of Arylboronic Acids to *N-tert*-Butanesulfinyl Imino Esters. *J. Am. Chem. Soc.* **2006**, *128*, 6304-6305.)

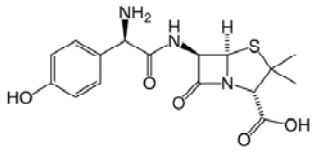
A novel synthesis of 3-substituted-3-amino-2-oxindole is also explored, in brief. The synthesis of an N-tert-*butanesulfinyl isatin imine and its use in the rhodium-catalyzed addition of arylboronic acids is described. Preliminary results indicate that N-tert-butanesulfinyl isatin imines may be suitable electrophiles for these transformations.*

Authorship

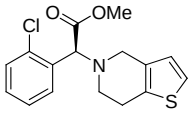
The work on the synthesis of imine **2.34** and its application in rhodium-catalyzed additions of arylboronic acids to *N-tert*-butanesulfinyl imines was conducted in collaboration with Chihui An, an undergraduate who I mentored.

Introduction

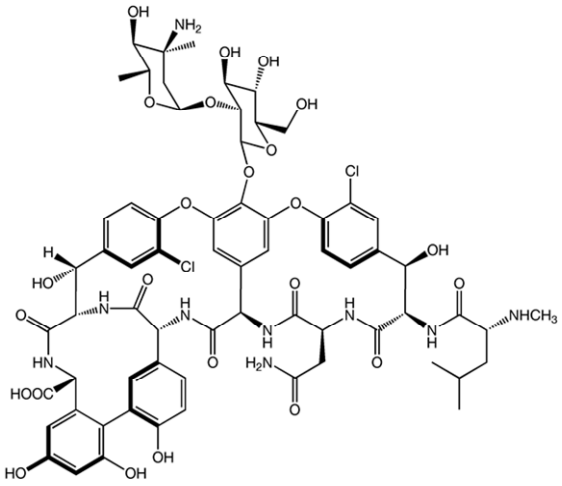
α-Arylglycines are a highly important class of nonproteinogenic amino acids and are components of a number of significant drugs. One of the most widely known types of naturally occurring α-arylglycines are the glycopeptide antibiotics such as vancomycin (**2.3**),[1] which is used in the treatment of severe staphylococcal infections (Figure 2.1). Synthetic α-arylglycines are also prevalent in pharmaceutical agents and are important moieties in the β-lactam antibiotics such as amoxicillin (**2.1**),[2] and the antiplatelet cardiovascular agent plavix (**2.2**).[3] One of the key challenges to the asymmetric synthesis of α-arylglycines is the facile base-catalyzed epimerization at the α-stereocenter making the enantiomerically pure construction of these molecules difficult. However, given their biological significance, the synthesis of α-arylglycines is an important goal in organic chemistry and many asymmetric methods have been developed.[4]



Amoxicillin: **2.1**



Plavix:**2.2**

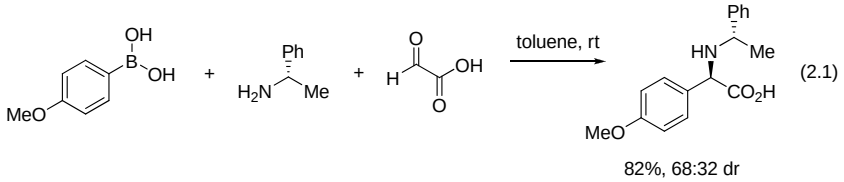


Vancomycin: **2.3**

Figure 1.1 Representative Arylglycine Drugs

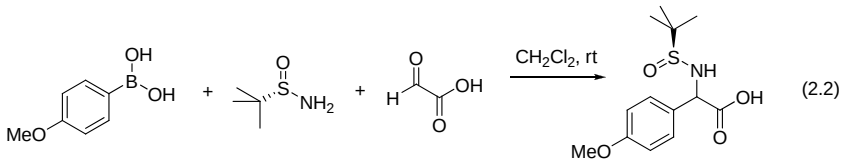
One very attractive and expedient synthesis of α-arylglycines is the Petasis reaction, a one-pot three component coupling of an amine, glyoxylic acid, and an arylboronic acid.[5] This powerful method capitalizes on the thousands of commercially available arylboronic acids to install diversity in the final arylglycine product. The scope of the reaction encompasses electron-neutral to electron-rich aryl and heteroaryl inputs, however, electron-deficient arylboronic acids are not effective coupling partners. Indeed, Follmann and coworkers discovered that electron-deficient arylboronic acids gave very poor yields in the Petasis reaction utilizing electron-poor amine components even when subjected to microwave conditions.[6] Furthermore, although attempts at

rendering this transformation asymmetric have been reported in the literature, very poor diastereoselectivity was achieved. Petasis and coworkers determined that α-methylbenzyl amine effectively participated in the reaction, but diastereomeric ratios exceeding 68:32 were not observed (eq 2.1).[5] When *tert*-butanesulfinamide was employed as a chiral amine reagent, a one to one mixture of diastereomers was obtained (eq 2.2, see Chapter One for a full description of this chemistry).[7]



(2.1)

82%, 68:32 dr



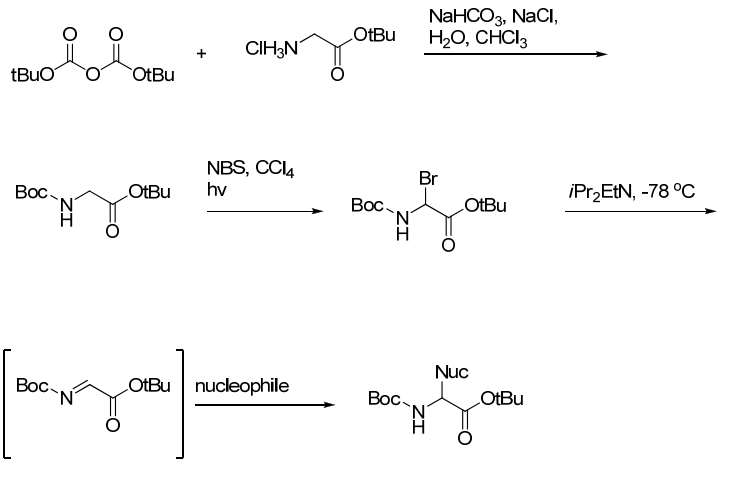
(2.2)

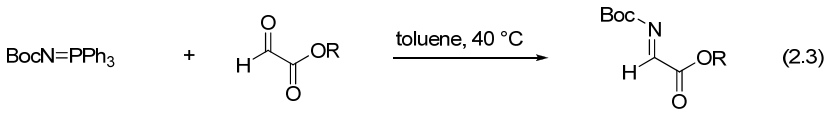
72%, 1:1 dr

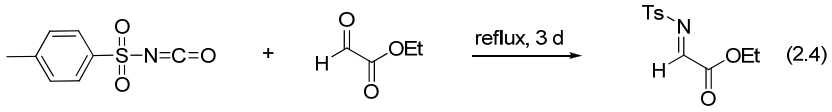
Recently, there have been numerous reports in the literature on the rhodium-catalyzed addition of arylboronic acids to imines providing α-branched amines stereoselectively.[8] The development of this strategy includes additions of arylboronic acids to aryl and alkyl *N*-sulfonyl,[9, 10] diphenylphosphinyl,[10, 11] and *tert*-butanesulfinyl imines,[11, 12] and aryl Boc[13] and *N*,*N*-dimethylsulfamoyl[14] imines, but these strategies were not extended to include imino esters as starting substrates. This could be attributed to the highly electrophilic nature of imino esters and their incompatibility with reaction conditions that include metal hydroxides, or in some cases water. Additionally, the preparation of *N*-Boc[15] or sulfonyl[16] imino esters is not facile. Two

general methods exist for the synthesis of *N*-Boc imino esters. One method requires multiple steps to access the *N*-Boc imino ester (Scheme 2.1), while the other method requires the use of the costly reagent *N*-Boc-Imino(triphenyl)phosphorane (eq 2.3). For both methods the desired imino ester must be generated *in situ* and used immediately without purification. The *N*-tosyl imino ester can be produced from the reaction between commercially available ethyl glyoxylate and *p*-toluenesulfonyl isocyanate in one step, but the resulting compound also must be used immediately without purification to avoid decomposition (eq 2.4).

Scheme 2.1. The Synthesis of *N*-Boc Imino Ester.

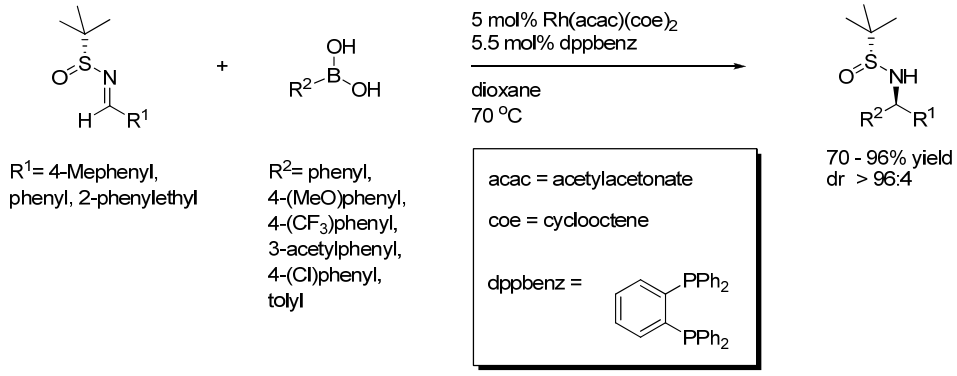






Given the success of the rhodium-catalyzed addition of arylboronic acids to aryl and alkyl *N*-*tert*-butanesulfinyl aldimines[11] (Scheme 2.2), it was hypothesized that the rhodium-catalyzed asymmetric addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters would provide a rapid entry to α-arylglycines. One of the key advantages of using *tert*-butanesulfinamide as the chiral amine reagent for this reaction is the stability of *N*-*tert*-butanesulfinyl imino esters compared to *N*-Boc or sulfonyl imino esters. Indeed, *N*-*tert*-butanesulfinyl imino esters are readily isolable by silica gel column chromatography and can be stored for prolonged periods at cold temperatures.[17-19] The ease of their synthesis and purification makes these imine precursors ideal for a diastereoselective synthesis of α-arylglycines. This chapter will describe the development of a highly diastereoselective rhodium-catalyzed addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters. The utility of this methodology is further demonstrated by performing subsequent selective transformations on the *N*-*tert*-butanesulfinyl protected α-arylglycine products. Preliminary studies towards extending the scope of this methodology to include *N*-*tert*-butanesulfinyl isatin imines are also addressed.

Scheme 2.2. Arylation of *N-tert*-Butanesulfinyl Imines with Arylboronic Acids

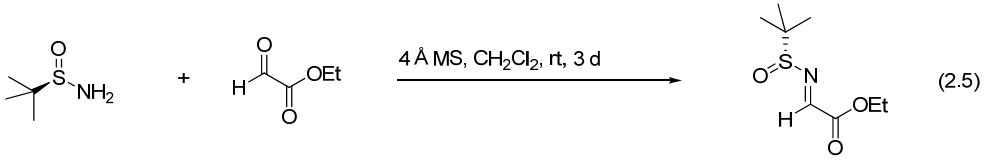


Additions of Arylboronic Acids to *N-tert*-Butanesulfinyl Imino Esters

Synthesis of Imine Substrates and Reaction Optimization

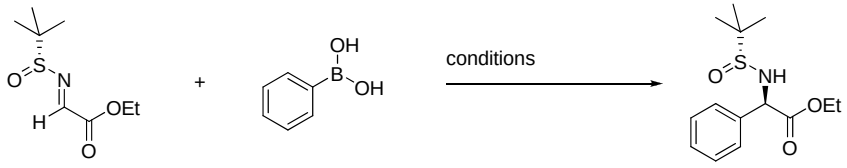
The *N-tert*-butanesulfinyl imino ester **2.6** was synthesized by the condensation of (*R*)-*tert*-butanesulfinamide (**2.4**) with ethyl glyoxylate (**2.5**) according to the procedure developed by Davis and coworkers (eq 2.5).[18] The reported reaction conditions for rhodium-catalyzed arylboronic acid additions to *N-tert*-butanesulfinyl imines were first examined using ethyl imino ester **2.6** (Table 2.1). A high yield and diastereomeric ratio was observed using phenylboronic acid (**2.7**) with dioxane as the solvent and a rhodium 1,2–bis-(diphenylphosphinyl)benzene complex as the catalyst (entry 1).[11] The cationic rhodium catalyst reported by Batey and coworkers for the addition of arylboronic acids to *N-tert*-butanesulfinyl aldimines was also prepared according to literature procedure[20] and tested using **2.6**.[12] However, when these reaction conditions were employed a poor yield was obtained (entry 2). Batey reported that these ligand free conditions required water as a cosolvent to obtain appreciable amounts of the desired product, but the augmented electrophilicity of starting substrate **2.6** made

water an incompatible solvent choice, presumably due to imine hydrolysis. Batey also reported that Et_3N was a necessary additive that accelerated the rhodium-catalyzed arylboronic acid additions to imines in water,[12] therefore, this base was also added to the reaction conducted in dioxane (entry 3). Although the reaction proceeded to high conversion, a loss of diastereoselectivity was observed due to base-mediated epimerization of the product. Indeed, even at room temperature the use of Et_3N resulted in some degradation of diastereomeric purity (entry 2). A control reaction was also performed to demonstrate that without the rhodium catalyst, no reaction occurred (entry 4). This result is in agreement with the proposed mechanism of the Petasis reaction where a free carboxylic acid is required to activate the boronic acid as the boronate species before transfer of the aryl group can occur.



2.4 **2.5** **2.6**: 70% (2.5)

Table 2.1. Reaction Optimization



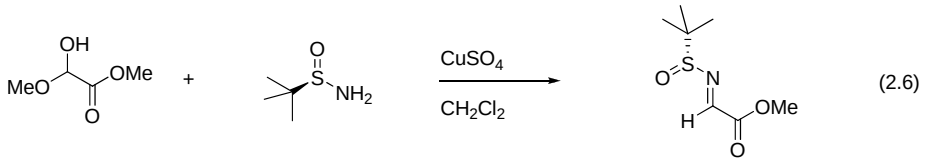
2.6 **2.7** **2.8**

entry	catalyst/base	solvent	temp (°C)	yield (%)[a]	dr[b]
1	$Rh(acac)(coe)_2$, dppbenz	dioxane	70	89	97:3
2	$[Rh(cod)(CH_3CN)_2]BF_4$, Et_3N	1:2 dioxane:H_2O	rt	6	91:9
3	$Rh(acac)(coe)_2$, dppbenz, Et_3N	dioxane	70	92	82:18
4	none	dioxane	70	0	-

[a.] Isolated yields. [b.] Diastereomeric ratios were determined by HPLC.

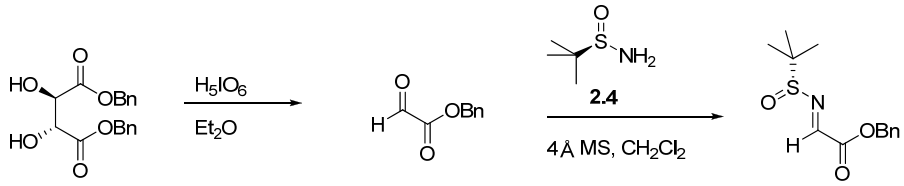
Several *N*-*tert*-butanesulfinyl imino esters were synthesized to explore the scope of the reaction with respect to the starting imino ester substrate. The methyl imino ester **2.10** was prepared in 55% yield by the facile condensation of **2.4** with 2-hydroxy-2-methoxy acetic acid methyl ester (**2.9**) (eq 2.6).[17] The benzyl substrate was synthesized by the oxidative cleavage of dibenzyl tartrate with periodic acid to afford benzyl glyoxylate (**2.12**),[21] which was then condensed with **2.4** to generate **2.13** in 43% yield over the two steps (Scheme 2.3). The *N*-*tert*-butanesulfinyl imino *tert*-butyl ester **2.17** was synthesized in three steps and a 25% overall yield starting with the dimerization of *tert*-butyl acrylate (**2.14**) to di-*tert*-butyl fumarate (**2.15**) in the presence of Grubb's second generation olefin metathesis catalyst (Scheme 2.4).[22] The desired *tert*-butyl glyoxylate (**2.16**) was then prepared by ozonolysis of **2.15,**[21] and the crude mixture, which contained a mixture of **2.16** and DMSO, was used directly in the

condensation reaction with **2.4**.[19] The *N*-*tert*-butanesulfinyl imino esters (**2.6**, **2.10**, **2.13**, and **2.17**) were then examined using the optimized reaction conditions.



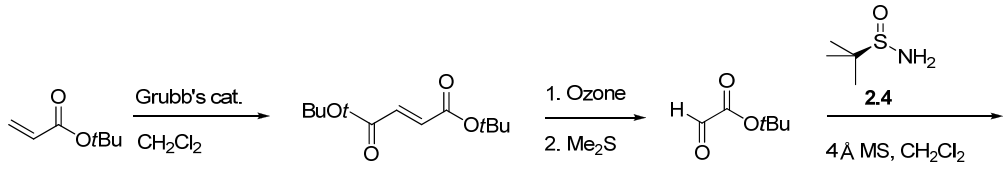
2.9 **2.4** **2.10:** 55%

Scheme 2.3. Synthesis of Benzyl Protected *N*-*tert*-Butanesulfinyl Imino Ester **2.13**

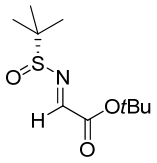


2.11 **2.12** **2.13:** 43%

Scheme 2.4. Synthesis of *tert*-Butyl Protected *N*-*tert*-Butanesulfinyl Imino Ester **2.17**



2.14 **2.15** **2.16**



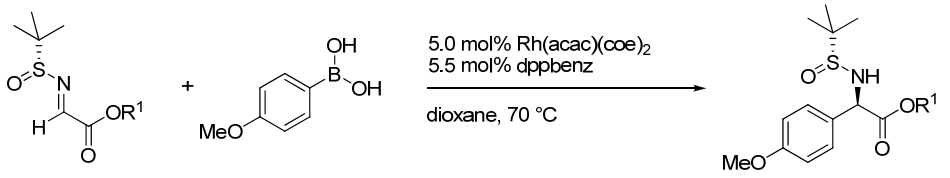
2.17: 25%

Exploration of Reaction Scope

To explore the scope of the addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters, **2.6**, **2.10**, **2.13**, and **2.17** were evaluated with the optimized reaction conditions using 4-methoxyphenylboronic acid (**2.18**) as the coupling partner.

Additions to the ethyl, methyl, benzyl, and *tert*-butyl esters all proceeded in high yields and with excellent diastereomeric ratios (Table 2.2 entries 1-4). The broad scope observed for this reaction for all ester protecting groups provides a high degree of flexibility in the choice of this moiety. As a result, various synthetic routes to obtain the free carboxylic acid could be employed such as acid or base promoted hydrolysis or hydrogenolysis. The methyl ester was selected as the starting substrate for further investigation of the scope of this reaction with respect to the arylboronic acid.

Table 2.2. Evaluation of Ester Protecting Groups



2.18 **2.19a-2.22a**

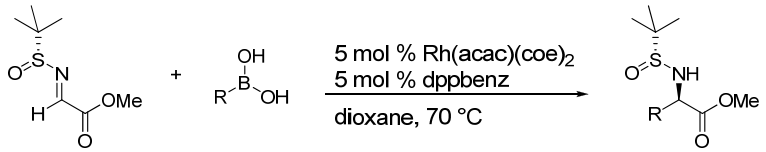
Entry	Imino Ester	R^1	Product	yield (%)[a]	dr[b]
1	**2.6**	Et	**2.19a**	89	98:2
2	**2.10**	Me	**2.20a**	89	99:1
3	**2.13**	Bn	**2.21a**	85	98:2
4	**2.17**	*t*-Bu	**2.22a**	78	98:2

[a] Isolated yields after column chromatography. [b] See Supporting Information for dr determination.

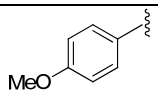
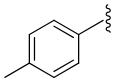
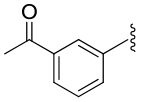
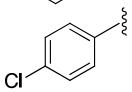
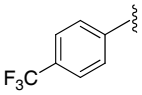
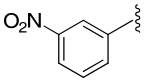
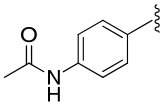
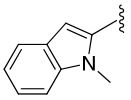
Under the optimized reaction conditions it was determined that the methodology was tolerant of many functional groups present on the arylboronic acid (Table 2.3). Similar to the Petasis reaction, high yields were achieved when an electron-donating substituent was present on the aryl ring of the boronic acid (entry1-3). While sterically hindered *ortho*-substituted aryl rings proved problematic for this same catalyst system

in the previously reported arylboronic acid addition to *N*-*tert*-butanesulfinyl aldimines, [11] *o*-tolylboronic acid was successfully incorporated into the desired arylglycine product (entry 2). Electron-neutral substituents were also tolerated (entry 4). Given the lack of success achieved with the Petasis reaction when arylboronic acids with electron-withdrawing substituents were used, [5, 7] the reaction with these substrates was next tested. The use of arylboronic acids with weakly electron-withdrawing substituents on the aryl ring cleanly afforded the desired arylglycine product (entries 5-6). Additonally, strongly electron-withdrawing substituents were also tolerated, providing an efficient route for the preparation of electron-deficient arylglycine derivatives (entries 7-8). However, no reaction was observed when 3-pyridylboronic acid, 4-acetylaminophenylboronic acid, or *N*-methyl-1H-indoleboronic acid were subjected to the optimized reaction conditions (entries 9-11). Throughout this series of experiments, all of the additions of arylboronic acids to **2.6** proceeded with very high diastereoselectivity.

Table 2.3. Synthesis of Functionalized α-Arylglycines.



2.6 **2.19a-k**

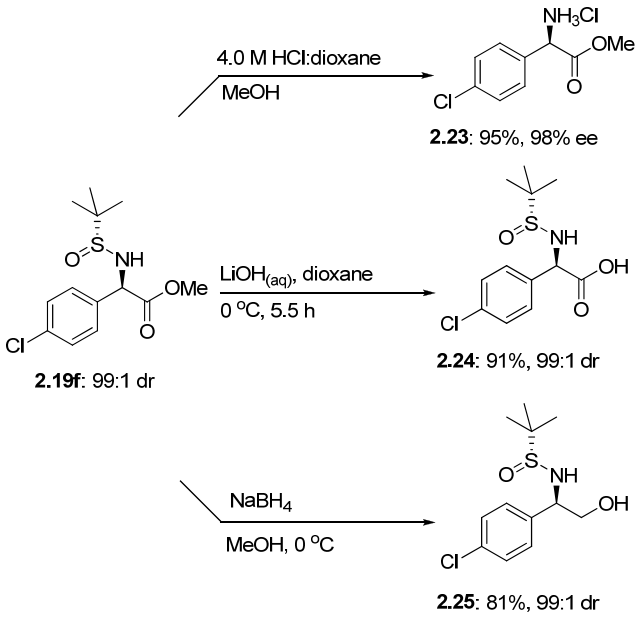
entry	R	product	yield (%)[a]	dr[b]
1[c]		**2.19a**	89	99:1
2		**2.19b**	90	98:2
3		**2.19c**	61	99:1
4[c]		**2.19d**	79	99:1
5		**2.19e**	87	99:1
6[c]		**2.19f**	82	99:1
7		**2.19g**	74	98.5:1.5
8		**2.19h**	69	99:1
9		**2.19i**	-	-
10		**2.19j**	-	-
11		**2.19k**	-	-

[a] Isolated yields after column chromatography. [b] See Experimental Section for dr determination. [c] Absolute configuration was determined by comparing the optical rotation of the corresponding free amino ester to those reported in the literature (see Experimental Section).

Further Functionalization of the N-tert-*Butanesulfinyl α-Arylglycine Products*

After the scope of this methodology with respect to the arylboronic acid was examined, the enantiomerically enriched *N*-sulfinyl protected α-arylglycine esters were utilized in additional synthetic manipulations (Scheme 2.5). The selective cleavage of the sulfinyl group from the *N-tert*-butanesulfinyl-α-amino ester product **2.19f** was accomplished in high yields under acidic conditions to liberate the amine hydrochloride salt **2.23** with no loss in stereochemical purity as determined by GC analysis of the (*R*)- and (*S*)-MTPA derivatives of **2.23**. A straightforward conversion of the methyl ester of **2.19f** to the free carboxylic acid **2.24** proceeded in high yields without epimerization as determined by HPLC after treatment of **2.24** with diazomethane affording the methyl ester **2.19f**. In addition, the amino ester **2.19f** was readily converted to the β-amino alcohol **2.25** using $NaBH_4$. Again, no epimerization was observed for this substrate as confirmed by HPLC analysis of an authentic mixture of diastereomers of **2.25**. These reactions demonstrated a key feature of this method: the versatility of the protected α-arylglycine intermediates in subsequent synthetic transformations.

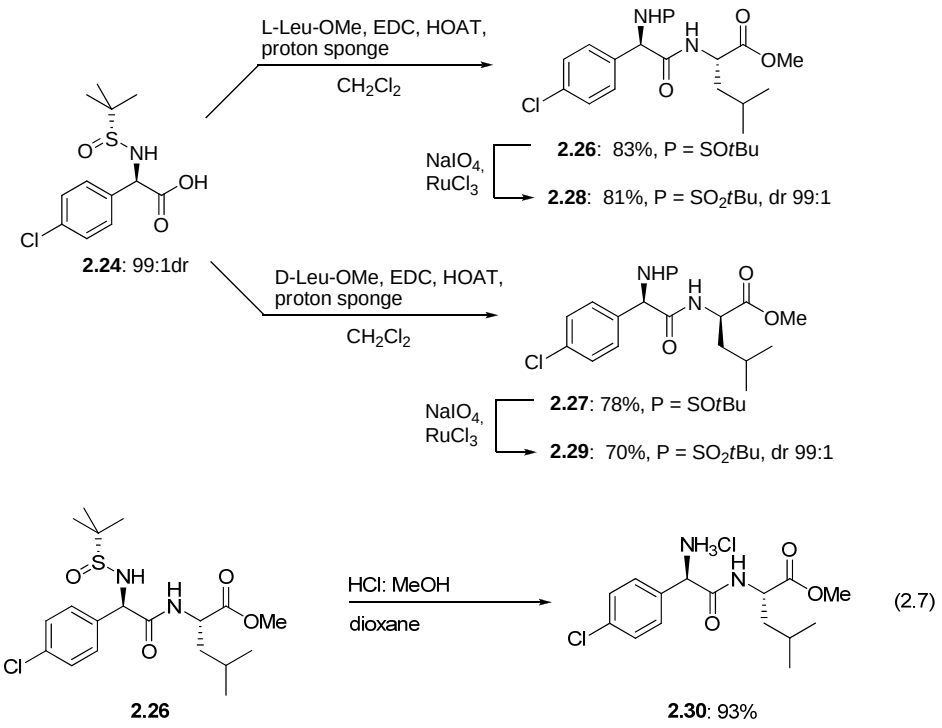
Scheme 2.5. Further Synthetic Transformations of *N*-*tert*-Butanesulfinyl Protected α-Arylglycine Products



Moreover, the applicability of the *N*-*tert*-butanesulfinyl-α-arylglycine **2.24** as a protected amino acid derivative in peptide synthesis without racemization was rigorously established for the first time.[23] The conditions developed by Carpino for the peptide coupling of *N*-Boc-arylglycines without epimerization were examined.[24] Using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), 1-hydroxy-7-azabenzotriazole (HOAT), and proton sponge as an acid scavenger, the *N*-*tert*-butanesulfinyl amino acid **2.24** was successfully coupled to both the *R*- and *S*- leucine methyl ester in good yields (Scheme 2.6). To determine the diastereomeric ratios of the dipeptide products **2.26** and **2.27**, the sulfinyl group was oxidized to a sulfonyl group using $RuCl_3$ and sodium periodate to afford the diastereomers **2.28** and **2.29**.[25] Despite the acidity of the alpha proton in arylglycines, little to no epimerization was

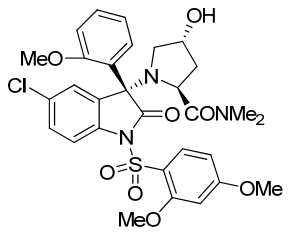
observed for either coupling reaction as determined by HPLC analysis of **2.28** and **2.29**. Removal of the sulfinyl group of **2.26** with methanolic HCl was also demonstrated, providing **2.30** in 93% yield (eq 2.7).

Scheme 2.6. Peptide Coupling of *N*-Sulfinyl Protected α-Arylglycines

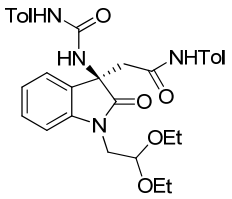


Additions of Arylboronic Acids to *N-tert*-Butanesulfinyl Isatin Imines

In an effort to extend the scope of this methodology, the additions of arylboronic acids to an *N-tert*-butanesulfinyl isatin imine were explored due to the prevalence of the 3-amino-2-oxoindole scaffold in drug candidates. For example, the 3-substituted-3-amino-2-oxindole scaffold is present in the drug candidates SSR-149415 (**2.31**),[26] a vasopressin VIb receptor antagonist that reached clinical trials for the treatment of anxiety and depression, and AG-041R (**2.32**), a gastrin/CCK-B receptor antagonist (Figure 2.2).[27]



2.31: SSR-149415

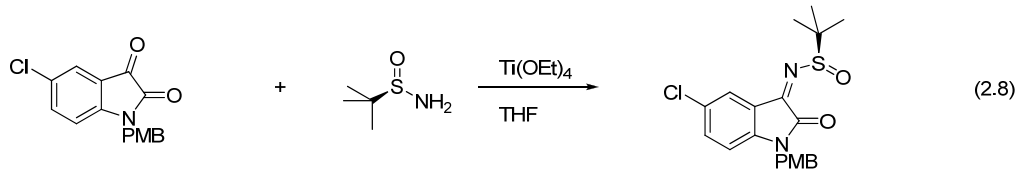


2.32: AG-041R

Figure 2.2. 3-Substituted-3-Amino-2-Oxindole Drug Candidates

Syntheses of Imine Substrates

The starting *N*-*tert*-butanesulfinyl isatin imine substrate **2.34** was obtained by condensation of 1-(*p*-methoxybenzyl)-5-chloroisatin (**2.33**), prepared according to literature procedure[28] from commercially available 5-chloroisatin, with (*R*)-*tert*-butanesulfinamide (**2.4**) in 63% isolated yield (eq 2.8). At the time this research was conducted there were no reports for the preparation of *N*-*tert*-butanesulfinyl imines derived from isatins; however, after the completion of these studies, Silvani and coworkers published a similar method to access an *N*-*tert*-butanesulfinyl imine derived from *N*-PMB-isatin.[29]



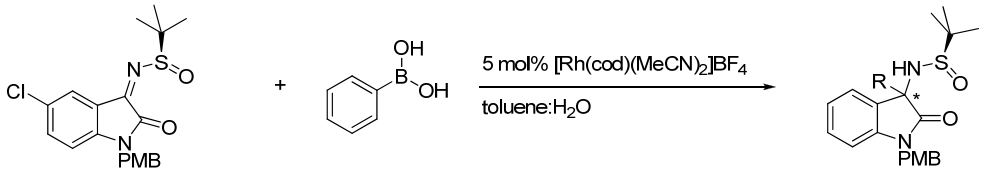
2.33 **2.4** **2.34**: 63% (2.8)

Optimization of Reaction Conditions

A brief screen of rhodium catalysts, ligands, and solvents revealed that appreciable amounts of product **2.35** were only obtained using a cationic rhodium catalyst with KF as an additive in a mixture of toluene and water. In the presence of 5 mol% of $[Rh(cod)(MeCN)_2]BF_4$ with five equivalents of KF in a 1:1 ratio of toluene to water,

2.35 was isolated in 17% yield with 80:20 diastereomeric ratio (Table 2.4, entry 1). In an attempt to increase the diastereoselectivity of this transformation the reaction temperature was lowered, but no improvement was observed (entry 2). However, under these reaction conditions (entries 1-2), an alcohol byproduct was obtained in significant amounts due to competitive imine hydrolysis accompanied by the rhodium-catalyzed addition of the arylboronic acid to the resulting isatin ketone. Unfortunately, probing the ratio of toluene to water revealed that for these substrates the presence of water was critical in obtaining detectable amounts of the desired product as substantial decreases in the amount of water resulted in <5% yield of **2.35** (entries 3-4). The amount of KF was varied, but did not significantly alter the yields or diastereoselectivities (entries 5-7). Two other additives were also evaluated, but no improvement in yield of **2.35** was observed (entries 8-9). Further reaction optimization is necessary for *N*-*tert*-butanesulfinyl isatin imines to be synthetically useful substrates for this transformation. For example, Lu and Dai recently reported the cationic Pd-catalyzed addition of arylboronic acids to *N*-*tert*-butanesulfinyl imino esters (see Chapter 1, Scheme 1.8),[30] and Itami and Bouffard very recently reported the additions of arylboronate esters to unactivated ketones (eq 2.9).[31] These studies suggest that further exploration of catalysts systems for the addition of arylboronic acids to *N*-*tert*-butanesulfinyl isatin imines would be a worthwhile pursuit.

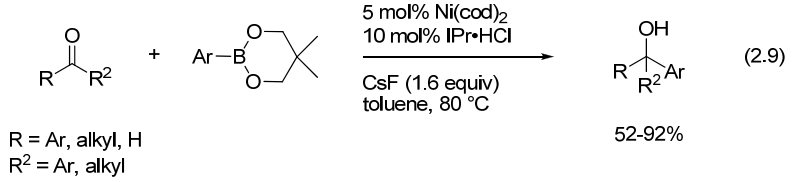
Table 2.4. Addition of Phenylboronic Acid to *N-tert*-Butanesulfinyl Imine **2.33**



2.34 **2.35**

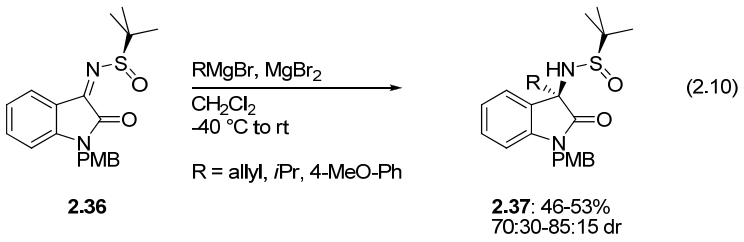
entry	additive	toluene:H_2O	temp (°C)	Yield (%)[a]	dr[b]
1	5 equiv KF	1:1	70	17	80:20
2	5 equiv KF	1:1	rt	14	80:20
3	5 equiv KF	20:1	70	5	73:27
4	5 equiv KF	40:1	70	trace	-
5	0.5 equiv KF	1:1	70	13-17	82:18
6	0.2 equiv KF	1:1	70	22	77:23
7	0.1 equiv KF	1:1	70	11	76:24
8	0.5 equiv K_3PO_4	1:1	70	8	-
9	0.5 equiv KOH	1:1	70	-	-

[a] Isolated yields after column chromatography. [b] Diasteromeric ratios determined by ^{1}H NMR.



Subsequent to this research, Silvani and coworkers disclosed a method for the addition of Grignard reagents to an isatin-derived *N-tert*-butanesulfinyl imine **2.36**, providing a rapid route for the asymmetric synthesis of quaternary 3-aminooxindoles **2.37** (eq 2.10).[29] This method is the first example of adding nucleophiles to *N-tert*-butanesulfinyl isatin imines, but the scope was limited and the diastereoselectivity of the reaction and the isolated yields of the major diastereomer were moderate (70:30-

85:15, and 46-53%, respectively). Development of a transition metal-catalyzed addition of arylboronic acids to isatin-derived *N-tert*-butanesulfinyl imines would clearly be a significant advance over this recently reported method.



2.36 **2.37**: 46-53% 70:30-85:15 dr

Conclusion

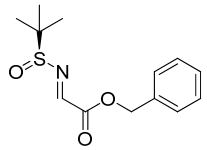
A general method for the efficient and highly diastereoselective synthesis of *N-tert*-butanesulfinyl α-arylglycines was developed that allows for the incorporation of electronically and sterically diverse arylboronic acids. The resulting *N-tert*-butanesulfinyl protected α-arylglycine products could be utilized in further synthetic transformations including selective protecting group removal, conversion to a β-amino alcohol, and direct incorporation into peptides. Each transformation proceeded in high yields with minimal to no racemization. In addition, a novel synthesis of a 3-substituted-3-amino-2-oxindole was investigated via the rhodium-catalyzed addition of an arylboronic acid to an *N-tert*-butanesulfinyl isatin imine, and preliminary results showed that this imine can act as a substrate for this transformation.

Experimental Section

General Procedure Methods. Arylboronic acids were purchased from commercial sources and purified directly before use by recrystallization from water.[32] Acetylacetonatobis(cyclooctene)rhodium and 1,2-

bis(diphenylphosphino)benzene were purchased from Strem and used without further purification. *tert*-Butanesulfinamide[33] and $[Rh(cod)(MeCN)_2]BF_4$[20, 34] were synthesized according to the literature procedures. 4 M HCl (solution in 1,4-dioxane) was purchased from Aldrich. Extra dry 1,4-Dioxane (< 50 ppm water) was purchased from Acros and passed through a column of dry, activated, basic alumina and stored over 3 Å MS in a glove box or it was distilled from sodium/benzophenone ketyl. Methanol, CH_2Cl_2, CH_3CN and NEt_3 were freshly distilled over CaH_2 prior to use. Column chromatography was carried out using Merck 60 230-240 mesh silica gel according to the general procedure of Still.[35] 3 Å MS and 4 Å MS were purchased from Aldrich and were dried according to the method of Burfield and Smithers.[5] *N*-sulfinyl imino esters **2.6**[36], **2.10**[17], and **2.17**[19] were synthesized according to literature procedure and stored in a glovebox at -30 ˚C. Arylboronic acid reactions were carried out in Kimble 5 mL microvials (Kimble product number 60700-5) using PTFE stir-vanes (Kimble product number 749060-0003) and capped with mini-inert seals (Kimble product number 749110-0022) and blue nylon caps (Kimble product number 410119-2015). The reaction vials were heated in a custom-made aluminum heating block drilled to fit the vials (UC machine shop) and the temperature was maintained by placing the block on an IKA stirrer/hotplate (RCT basic model) with a thermistor controller (ETS-D4 fuzzy). Diastereoselectivity determinations were performed using either an Agilent 1100 series LC equipped with a silica normal phase column (Microsorb Si 100 Å packing) with a multiwavelength detector or an Agilent 7683 series GC equipped with an Ultra-II column. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer and only partial data are listed. Chemical shifts for ^1H

and ^{13}C NMR spectra were recorded in ppm and referenced to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. Mass spectra were obtained from the Microanalytical Laboratory at the University of California, Berkeley.



(*R*)-*N*-(*tert*-butanesulfinyl)iminoacetic acid, benzyl ester 2.13. Benzyl glyoxylate[21] (2.95 g, 18.0 mmol, 1.0 equiv) was added to a round-bottom flask containing 4 Å molecular sieves (activated powder which had been dried overnight at 300 ˚C under vacuum) in CH_2Cl_2 (168 mL). To this rapidly stirring solution was added (*R*)-*tert*-butanesulfinamide (2.18 g, 18.0 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 4 days.[18] The reaction mixture was filtered through a pad of Celite and washed with EtOAc (3 x 70 mL). The filtrate was dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (25% EtOAc:hexanes) to yield **2.13** (2.8 g, 43 % yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 9H), 5.31 (s, 2 H), 7.33-7.38 (m, 5H), 8.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 58.8, 67.7, 126.3, 128.4, 128.6, 134.7, 155.2, 160.7. IR: 3301, 2966, 1732, 1176, 1093, 696 cm $^{-1}$. Exact mass calcd for $C_{13}H_{18}NO_3S$ requires m/z 300.1269, found m/z 300.1260 (MH^+, FAB).

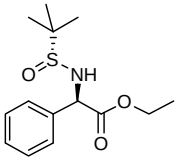
General Procedure for the Addition of Arylboronic Acids to *N*-*tert*-Butanesulfinyl Imines. Reactions were set up in a glovebox. To a vial containing a

stir-vane and the appropriate arylboronic acid (0.500 mmol, 2.0 equiv) was added the appropriate sulfinyl imine (0.250 mmol, 1.0 equiv) in 1.0 mL of dioxane. 1,2-Bis(diphenylphosphino)benzene (6.2 mg, 0.014 mmol, 0.055 equiv) was dissolved in 1.0 mL of dioxane and added to a vial containing acetylacetonatobis(cyclooctene)rhodium (5.3 mg, 0.013 mmol, 0.050 equiv), and the resulting mixture of catalyst and ligand was added to the sulfinyl imine mixture. The reaction vial was capped, removed from the glovebox, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 70 ˚C (aluminum block temperature) and stirred for 14-19 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (4 mL). The organic layer was washed with brine (2 mL) and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc:hexanes mixtures and were visualized with CMA stain.

General Procedure for the Preparation of (+) and (-) α-Methoxy-α-trifluoromethylphenylacetamides (MTPA amides) from *N*-sulfinyl arylglycine esters. Cleavage of the sulfinyl group was carried out according to the literature procedure.[36] Specifically, the *N*-sulfinyl arylglycine esters were treated with a 1:1 mixture of MeOH and 4 M HCl in dioxane (0.06 M). The reaction mixture was stirred at rt, concentrated, and the desired product was precipitated with diethyl ether. The resulting amine hydrochloride (1.0 equiv) was dissolved in CH_2Cl_2 (0.1 M) and Hunig's base (4.0 equiv) was added dropwise. >99% ee (+) or >99% (-) MTPA

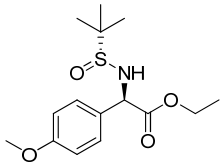
chloride (~ 2.0 equiv) was added to the reaction mixture, and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with 1 N sodium bisulfate and diluted with Et_2O. The organic layer was removed, and the remaining aqueous layer was extracted with Et_2O (2x). The combined organic layers were dried over Na_2SO_4, concentrated, and filtered through a short plug of silica gel with EtOAc eluent.

General Procedure for Epimerizations to Obtain an Authentic Mixture of Diastereomers. *N*-Sulfinyl arylglycines (1.0 equiv) were dissolved in CH_2Cl_2 (0.75 M) and NEt_3 (7.0 equiv) was added dropwise. The resulting mixture was stirred for 1-24 h at room temperature or 30 ˚C. The reaction mixture was quenched with 1 N sodium bisulfate and diluted with EtOAc. The organic layer was removed and the remaining aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine (1 x), dried over Na_2SO_4, and concentrated. The obtained product was analyzed without further purification.

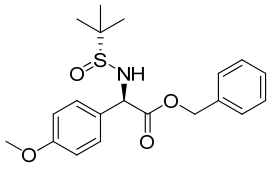


***N*-sulfinyl arylglycine ether ester 2.8**. The general procedure was followed with stirring for 19 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (66.1 mg, 93% yield). 97:3 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min,

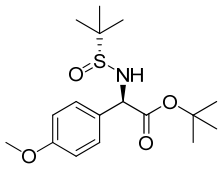
20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 29.33 min, minor diasteromer t_R = 28.84 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.2, 3H), 1.24 (s, 9H), 4.11 - 4.25 (m, 2H), 4.60 (d, *J* = 4.0, 1H), 5.06 (d, *J* = 4.4, 1H), 7.31-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 55.9, 60.4, 62.1, 127.7, 128.4, 128.6, 137.2, 171.4. Spectroscopic data corresponds to that reported in literature.[18]



***N*-sulfinyl 4-methoxyarylglycine ethyl ester 2.20a**. The general procedure was followed with stirring for 19 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (70.0 mg, 89% yield). 98:2 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 33.49 min, minor diasteromer t_R = 32.95 min).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 2.8, 3H), 1.22 (s, 9H), 3.80 (s, 3H), 4.13- 4.27 (m, 2H), 4.5 (d, *J* = 4 Hz, 1 H), 5.15 (d, *J* = 4 Hz, 1H), 6.88 (d, *J* = 9 Hz, 2H), 7.34 (d, *J* = 9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5. 55.2, 55.8, 59.7, 62.0, 113.9, 128.9, 129.2, 159.6, 171.5. IR: 3281, 3202, 2966, 1733, 1070 cm $^{-1}$. Exact mass calcd for $C_{15}H_{24}NO_4S$ requires m/z 314.1426, found m/z 314.1435 (MH^+, FAB).

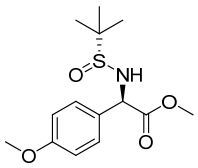


***N*-sulfinyl 4-methoxyarylglycine benzyl ester 2.21a**. The general procedure was followed with stirring for 18 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a white solid (80.0 mg, 85% yield). mp 76-78 ˚C. 98:2 dr. The MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 99:1 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; (*R*)-MTPA derivative of major diasteromer t_R = 10.95 min, minor diasteromer t_R = 9.69 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 3.80 (s, 3H), 4.54 (d, *J* = 3.9 Hz, 1H), 5.08 (d, *J* = 4.0 Hz, 1 H), 5.09 – 5.19 (dd, *J* = 12.3 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 2H), 7.27 (m, 2H), 7.28-7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 55.2, 55.9, 59.8, 67.5, 114.0, 127.9, 128.3, 128.5, 128.9, 129.1, 135.1, 159.7, 171.4. IR: 3301, 2965, 1734, 1068, 735 cm $^{-1}$. Exact mass calcd for $C_{20}H_{26}NO_4S$ requires m/z 376.1582, found m/z 376.1580 (MH^+, FAB).



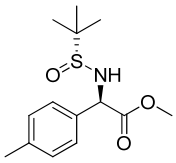
***N*-sulfinyl 4-methoxyarylglycine *tert*-butyl ester 2.22a**. The general procedure was followed with stirring for 19 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a white solid (66.0 mg, 78% yield). mp 67-69 ˚C. 98:2 dr. The

MTPA derivatives of this compound were prepared according to the general procedure and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*R*)-MTPA derivative of major diastereomer δ =-68.29, minor diasteromer δ = -68.01. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.38 (s, 9H), 3.81 (s, 3H), 4.53 (d, *J* = 3.6 Hz, 1H), 4.91 (d, *J* = 4.0 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 27.7, 55.2, 55.7, 60.1, 82.7, 113.8, 128.8, 129.8, 159.4, 170.6. IR: 3230, 2966, 1731, 1055 cm^{-1}. Exact mass calcd for $C_{17}H_{28}NO_4S$ requires m/z 342.1739, found m/z 342.1727 (MH^+, FAB).

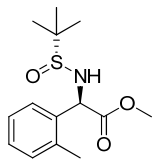


***N*-sulfinyl 4-methoxyarylglycine methyl ester 2.19a.** The general procedure was followed with stirring for 18 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (67.0 mg, 90% yield). 99:1 dr. The MTPA derivatives of **2.19a** were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 32.25 min, minor diasteromer t_R = 32.74 min). $[\alpha]^{25}_D$ = -127.0 (c =1.0, EtOH) as the free amine after sulfinyl group removal. Lit. value : 84% ee, $[\alpha]^{25}_D$ = -117.3 (c =1.0, EtOH).[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ1.23 (s, 9H), 3.72 (s, 3H), 3.81 (s, 3H), 4.55 (s, 1H), 5.04 (d, *J* = 2.6 Hz, 1 H), 6.89 (d, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, MeOD): δ 21.5, 51.7, 54.3, 55.8, 60.4, 113.7, 128.5, 128.8, 159.4, 172.0. IR: 3292, 2957, 1737,

1063 cm $^{-1}$. Exact mass calcd for $C_{14}H_{22}NO_4S$ requires m/z 300.1269, found m/z 300.1260 (MH^+, FAB).

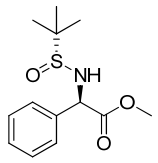


***N*-sulfinyl arylglycine methyl ester 2.19b**. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (64.0 mg, 90% yield). 98:2 dr. The MTPA derivatives of **2.19b** were prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 30.18 min, minor diasteromer t_R = 29.59 min).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 2.35 (s, 3H), 3.72 (s, 3H), 4.55 (d, *J* = 4.0 Hz, 1H), 4.5 (d, *J* = 4.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 22.6. 53.0, 56.0, 60.1, 127.7, 129.5, 134.1, 138.4, 172.1. IR: 3282, 2955, 1739, 1066 cm $^{-1}$. Exact mass calcd for $C_{14}H_{22}NO_3S$ requires m/z 284.1320, found 284.1325 (MH^+, FAB).



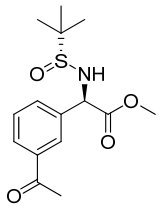
***N*-sulfinyl arylglycine methyl ester 2.19c**. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (43.0 mg, 61% yield). 99:1 dr. The MTPA derivatives of **2.19c** were

prepared according to the general procedure and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 29.34 min, minor diasteromer t_R = 28.72 min).[1]H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 2.48 (s, 3H), 3.78 (s, 3H), 4.56 (d, *J* = 3.4 Hz, 1H), 5.27 (d, *J* = 4.9 Hz, 1 H), 7.19-7.27 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 22.5, 53.0, 55.8, 57.4, 126.3, 128.2, 128.4, 130.9, 135.2, 136.8, 172.2. IR: 3284, 3199, 2966, 1736, 1067 cm $^{-1}$. Exact mass calcd for $C_{14}H_{22}NO_3S$ requires m/z 284.1320, found m/z 284.1322 (MH^+, FAB).

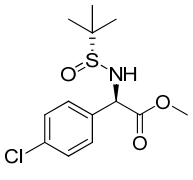


***N*-sulfinyl arylglycine methyl ester 2.19d**. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (53.0 mg, 79% yield). 99:1 dr. An authentic mixture of diastereomers of **2.19d** were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 18.24 min, minor diasteromer t_R = 13.54 min). $[\alpha]^{25}_D$ = -135.2 (c =1.0, MeOH) as the amine hydrochloride salt after sulfinyl group cleavage. Lit. value: $[\alpha]^{25}_D$ = -132.0 (c =1.0, MeOH).[12] [1]H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 3.72 (s, 3H), 4.58 (d, *J* = 4.0 Hz, 1H), 5.08 (d, *J* = 4.3 Hz, 1 H), 7.33-7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 53.0, 55.9, 60.3,

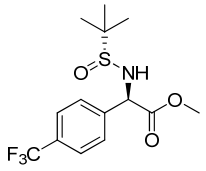
127.7, 128.5, 128.7, 137.0, 171.8. IR: 3197, 2966, 1739, 1066, 698 cm $^{-1}$. Exact mass calcd for $C_{13}H_{20}NO_3S$ requires m/z 270.1164, found m/z 270.1161 (MH^+, FAB).



***N*-sulfinyl arylglycine methyl ester 2.19e**. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (68.0 mg, 87% yield). 99:1 dr. An authentic mixture of diastereomers of **2.19e** were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 90:10 hexanes: iPrOH, 1.0 mL/min, λ= 254 nm; major diastereomer t_R = 22.96 min, minor diasteromer t_R = 20.21 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 9H), 2.61 (s, 3H), 3.74 (s, 3H), 4.66 (d, *J* = 3.5 Hz, 1H), 5.17 (d, *J* = 3.8 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 26.6, 53.2, 56.1, 59.9, 127.6, 128.5, 129.0, 132.4, 137.5, 137.7, 171.3 197.4. IR: 3198, 2966, 1740, 1684, 1067, 691 cm $^{-1}$. Exact mass calcd for $C_{15}H_{22}NO_4S$ requires m/z 312.1269, found m/z 312.1270 (MH^+, FAB).

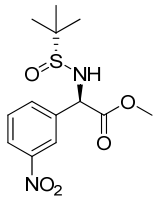


***N*-sulfinyl arylglycine methyl ester 2.19f**. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (50:50 EtOAc:hexanes) as a yellow oil (62.0 mg, 82% yield). 99:1 dr. An authentic mixture of diastereomers of **2.19f** were prepared according to the general procedure and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 17.95 min, minor diasteromer t_R = 12.08 min). $[\alpha]^{25}_D$ = -122.3 (c =1.0, MeOH) as the free amine after sulfinyl group cleavage. Lit. value : $[\alpha]^{25}_D$ = -129.0 (c =1.0, MeOH).[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 9H), 3.73 (s, 3H), 4.58 (d, *J* = 3.5 Hz, 1H), 5.06 (d, *J* = 3.8 Hz, 1 H), 7.28-7.36 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 53.2, 56.0, 59.6, 128.9, 129.2, 134.4, 135.5, 171.4. IR: 3285, 2956, 1741, 1075 cm $^{-1}$. Exact mass calcd for $C_{13}H_{19}ClNO_3S$ requires m/z 304.0774, found m/z 304.0779 (MH^+, FAB).

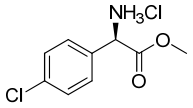


***N*-sulfinyl arylglycine methyl ester 2.19g**. The general procedure was followed with stirring for 14 h. The product was isolated by chromatography (40:60 EtOAc:hexanes) as a yellow oil (62.5 mg, 74% yield). 98.5:1.5 dr. An authentic mixture of diastereomers of **2.19g** were prepared according to the general procedure with stirring for 1 h and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 18.96 min, minor diasteromer t_R = 12.36 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H),

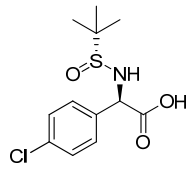
3.73 (s, 3H), 4.64 (d, J = 3.7 Hz, 1H), 5.15 (d, J = 3.9 Hz, 1 H), 7.51 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 53.5, 56.4, 60.0, 125.4 (q, J = 272 Hz) 125.9 (q, J = 3.7 Hz), 128.4 (2 overlapping C's), 130.8 (q, J = 32 Hz), 141.2, 171.3. ^{19}F NMR (376 MHz, $CDCl_3$) -61.87. IR: 3286, 2959, 1743, 1326, 1067 cm $^{-1}$. Exact mass calcd for $C_{14}H_{19}F_3NO_3S$ requires m/z 338.1038, found m/z 338.1046 (MH^+, FAB).



***N*-sulfinyl arylglycine methyl ester 2.19h**. The general procedure was followed with stirring for 16 h. The product was isolated by chromatography (40:60 EtOAc:hexanes) as a yellow oil (53.9 mg, 69% yield). 99:1 dr. An authentic mixture of diastereomers of **2.19h** were prepared according to the general procedure with stirring for 1 h and the diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 93:7 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 22.84 min, minor diasteromer t_R = 17.56 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 3.76 (s, 3H), 4.71 (d, J = 3.0 Hz, 1H), 5.22 (d, J = 3.5 Hz, 1 H), 7.57 (t, J = 7.9 Hz, 1H), 7.75 (d, J = 7.7 Hz , 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.29(s, 1 H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 53.7, 56.4, 59.5, 122.9, 123.7, 129.9, 134.2, 139.3, 148.6, 171.7. IR: 3295, 2988, 2870, 1740, 1529, 1349, 1066 cm $^{-1}$. Exact mass calcd for $C_{13}H_{18}N_2O_5S$ requires m/z 315.1015, found m/z 315.1010 (MH^+, FAB).

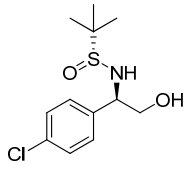


4-chloro phenylglycine methyl ester hydrochloride 2.23. *N*-sulfinyl arylglycine derivative **2.19f** (29.0 mg, 0.096 mmol, 1.0 equiv) was taken up in MeOH (0.640 mL, 0.15 M) and was treated with 4.0 M HCl in dioxane (0.120 mL, 5.0 equiv. HCl) at room temperature for 3 h. The reaction mixture was concentrated *en vacuo*, and the amine hydrochloride was precipitated with dry diethyl ether.[1] The precipitate was collected by filtration and washed with diethyl ether to yield the amine hydrochloride (21.4 mg, 95%) as a white solid. mp 169-171 ˚C. 98% ee. The MTPA derivatives of **2.23** were prepared according to the general procedure with stirring for 1 H at -78 ˚C, and the diastereomeric ratio was determined by GC analysis (Agilent Ultra II column, 100-300 ˚C, 5 deg/min, 20 psi; (*R*)-MTPA derivative of major diastereomer t_R = 31.37 min, minor diasteromer t_R = 30.67 min).^{1}H NMR (400 MHz, MeOD): δ 3.82 (s, 3H), 5.27 (s, 1H), 7.47- 7.53 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 54.1, 56.8, 130.7, 131.0, 132.0, 137.3, 169.7. IR: 2988, 2869, 1737, 1234, 1138, 765 cm $^{-1}$. Exact mass calcd for $C_9H_{11}ClNO_2$ requires m/z 200.0478, found m/z 200.0482 (MH^+, FAB).

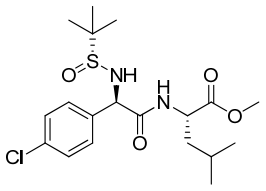


***N*-sulfinyl arylglycine 2.24** To a round bottomed flask containing LiOH (34.2 mg, 0.990 mmol, 10 equiv) was added distilled H_2O (5.0 mL, 2.0 M), and the resulting solution was cooled to 0 ˚C. A solution of **2.19f** (30.0 mg, 0.099 mmol, 1.0 equiv) in

dioxane (5.0 mL, 0.02 M) was cannulated into the reaction flask. The resulting solution was stirred at 0˚ C for 5.5 h. The reaction mixture was then concentrated to remove the dioxane, and the remaining material was diluted with distilled H_2O (3 mL) and EtOAc (3 mL) and placed in a seperatory funnel. 1 N $NaHSO_4$ (2 mL) was added and the aqueous layer was extracted with EtOAc (5 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated with no further purification (26.1 mg, 91%) as a white solid. mp 142-144 ˚C. 99:1 dr. To determine the diastereomeric purity of **2.24**, the product **2.24** was treated with diazomethane to afford the *N*-sulfinyl arylglycine methyl ester **2.19f**. An authentic mixture of diastereomers was made by stirring **2.19f** with NEt_3 according to the general procedure for 1.5 h at 30 ˚C followed by column chromatography (1:1 EtOAc:hexanes). The diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 95:5 hexanes: iPrOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 17.81 min, minor diasteromer t_R = 11.83 min). ^{1}H NMR (400 MHz, MeOD): δ 1.23 (s, 9H), 5.03 (s, 1H), 7.36-7.43 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 22.9, 61.3, 129.8, 130.6, 135.2, 137.7, 173.6. IR: 3261, 2988, 2870, 1721, 1254, 1007, 887 cm $^{-1}$**.** Exact mass calcd for $C_{12}H_{16}ClNO_3S$ requires m/z 290.0618, found m/z 290.0622 (MH^+, FAB).

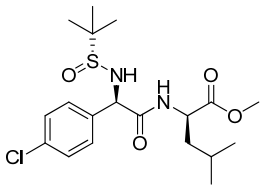


Alcohol 2.25. To a Kontes vial containing a stir vane was added **2.19f** (30.0 mg, 0.099 mmol, 1.0 equiv) in MeOH (0.250 mL, 0.4 M). The resulting solution was cooled to 0 °C and $NaBH_4$ was added in one portion (19.1 mg, 0.50 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with EtOAc (3 mL) and was washed with distilled water. The aqueous layer was extracted with EtOAc (3 x), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated with no further purification (22.0 mg, 81%) as an off-white solid. mp 96-98 °C. 99:1 dr. To determine the diastereomeric purity of **2.25**, epimerized **2.19f** was reduced with $NaBH_4$ according to the procedure presented above. The diastereomeric ratio was determined by HPLC analysis (HPLC, silica column, 90:10 hexanes: EtOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 7.95 min, minor diasteromer t_R = 11.24 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H), 3.60 (m, 1H), 3.89 (m, 1 H), 4.28 (m, 1 H), 4.52 (m, 1H), 7.27-7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 56.1, 61.1, 67.2, 128.9, 129.0, 133.9, 137.6. IR: 3277, 2924, 1039, 1012, 825 cm $^{-1}$**.** Exact mass calcd for $C_{12}H_{18}ClNO_2S$ requires m/z 276.0825, found m/z 276.0820 (MH^+, FAB).



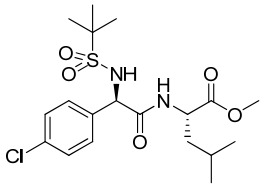
***N*-sulfinyl dipeptide 2.26**. To a vial containing a stir-vane was added **2.24** (25.8 mg, 0.089 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 M) and the resulting suspension was cooled to 0 ˚C. Proton sponge was subsequently added in one portion (57.4 mg, 0.27 mmol, 3.0

equiv.) followed by addition of HOAT (15.8 mg, 0.12 mmol, 1.3 equiv). L-Leucine methyl ester was added to the reaction mixture (48.6 mg, 0.27 mmol, 3.0 equiv), followed by the addition of EDC (22.2 mg, 0.12 mmol, 1.3 equiv) and the reaction mixture was allowed to stir at 0 ˚C for 1 h and was then warmed to rt and stirred for an additional 2 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with 1 N $NaHSO_4$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL), and the combined organics were then washed with 1 N $NaHCO_3$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL) and combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by column chromatography (12% EtOAc: hexanes – 100% EtOAc) as a viscous clear oil (30.7 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.933 (d, J = 5.1 Hz, 6H), 1.24 (s, 9H), 1.62 (m, 3H), 3.70 (s, 3H), 4.22 (d, J = 4.2 Hz, 1H) 4.62 (m, 1H), 5.03 (d, J = 4.3 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.34 (m, 4H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.7, 22.8, 24.9, 41.1, 51.4, 52.6, 56.2, 60.8, 129.4, 129.7, 134.8, 136.6, 169.9, 173.1. IR: 3267, 2988, 2956, 2870, 1740, 1679, 1144, 1049, 827 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_4S$ requires m/z 423.1697, found m/z 423.1712 (MLi^+, FAB).



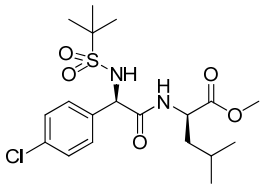
***N*-sulfinyl dipeptide 2.27**. To a vial containing a stir-vane was added **2.24** (22.6 mg, 0.078 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) and the resulting suspension was cooled to 0 ˚C. Proton sponge was subsequently added in one portion (50.3 mg, 0.24 mmol, 3.0

equiv.) followed by addition of HOAT (13.8 mg, 0.10 mmol, 1.3 equiv). D-Leucine methyl ester was added to the reaction mixture (42.6 mg, 0.24 mmol, 3.0 equiv), followed by the addition of EDC (19.5 mg, 0.10 mmol, 1.3 equiv) and the reaction mixture was allowed to stir at 0 ˚C for 1 h and was then warmed to rt and stirred for an additional 2 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with 1 N $NaHSO_4$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL), and the combined organics were then washed with 1 N $NaHCO_3$. The aqueous layer was back-extracted with EtOAc (3 x 5 mL) and combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by column chromatography (12% EtOAc: hexanes – 100% EtOAc) as a white solid (15.4 mg, 78 %). mp 102-104 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6.2 Hz, 6H), 1.21 (s, 9H), 1.45-1.62 (m, 3H), 3.66 (s, 3H), 4.55 (m,1H), 4.89 (d, *J* = 2.3 Hz, 1H), 4.95 (d, *J* = 2.6 Hz, 1H), 6.04 (d, *J* = 8.0 Hz, 1H), 7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.7, 22.8, 25.0, 41.2, 51.4, 52.5, 56.1, 60.3, 129.5, 130.0, 135.1, 136.0, 169.9, 172.8. IR: 3272, 3067, 2957, 2871, 2870, 1744, 1663, 1201, 1060, 866 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_4S$ requires m/z 417.1615, found m/z 417.1616 (MH^+, FAB).

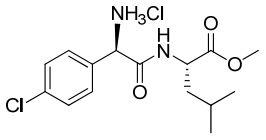


***N*-sulfonyl dipeptide 2.28**. A vial was charged with **2.26** (17.0 mg, 0.041 mmol, 1.0 equiv.) in CH_2Cl_2 (0.12 mL, 0.33 M). CH_3CN (0.12 mL, 0.33 M) and H_2O (0.19 mL,

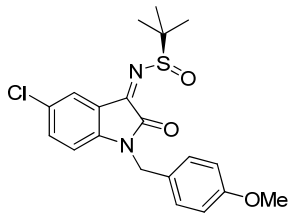
0.22M) were subsequently added to the reaction vial. The reaction mixture was cooled to 0˚C and $NaIO_4$ was added (13.1 mg, 0.061 mmol, 1.5 equiv) followed by a catalytic amount of $RuCl_3$ (0.06 mg, 0.0003 mmol). The reaction mixture was stirred at 0 ˚C for 1 h and then warmed to rt and stirred for an additional 30 minutes. The reaction mixture was diluted with EtOAc (4 mL) and washed with brine. The aqueous layer was extracted with EtOAc (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated after trituration with 95% hexanes:isopropanol as a white solid (14.4 mg, 81%). dr 99:1. An authentic mixture of diastereomers was prepared by mixing **2.28** with **2.29**. The diastereomeric ratio was determined by HPLC analysis of the crude product (HPLC, silica column, 97:3 hexanes: EtOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 15.60 min, minor diasteromer t_R = 12.59 min).^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, *J* = 6.6 Hz, 6H), 1.28 (s, 9H), 1.42 (m, 1H), 1.55 (m, 2H), 3.74 (s, 3H), 4.60 (m, 1H), 5.11 (d, *J* = 6.6 Hz, 1H), 5.54 (d, *J* = 6.5 Hz, 1H), 6.07 (d, J = 8.3 Hz, 1H), 7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.8, 24.2, 24.9, 41.4, 51.4, 52.7, 60.2 (2 overlapping carbons), 128.9, 129.5, 134.9, 136.9, 169.2, 172.9. IR: 3324, 3261, 1728, 1651, 1305, 1136, 1120, 1090, 1015 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_5S$ requires m/z 433.1564, found m/z 433.1559 (MH^+, FAB).



***N*-sulfonyl dipeptide 2.29**. A vial was charged with **2.27** (17.4 mg, 0.042 mmol, 1.0 equiv) in CH_2Cl_2 (0.13 mL, 0.33M). CH_3CN (0.13 mL, 0.33M) and H_2O (0.19 mL, 0.22M) were subsequently added to the reaction vial. The reaction mixture was cooled to 0 ˚C and $NaIO_4$ was added (13.4 mg, 0.063 mmol, 1.5 equiv) followed by a catalytic amount of $RuCl_3$ (0.06 mg, 0.0003 mmol). The reaction mixture was stirred at 0 ˚C for 1 h and then warmed to rt and stirred for an additional 30 minutes. The reaction mixture was diluted with EtOAc (4 mL) and washed with brine. The aqueous layer was extracted with EtOAc (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated after trituration with 95% hexanes:isopropanol as a white solid (12.6 mg, 70%). dr 99:1. An authentic mixture of diastereomers was prepared by mixing **2.28** with **2.29**. The diastereomeric ratio was determined by HPLC analysis of the crude product (HPLC, silica column, 97:3 hexanes: EtOH, 1.0 mL/min, λ= 230 nm; major diastereomer t_R = 12.68 min, minor diasteromer t_R = 15.65 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (m, 6H), 1.27 (s, 9H), 1.50-1.65 (m, 3H), 3.66 (s, 3H), 4.62 (m, 1H), 5.10 (d, *J* = 6.7 Hz, 1H), 5.44 (d, *J* = 6.5 Hz, 1H), 5.91 (d, J = 4.3 Hz), 7.31 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.9, 24.1, 25.0, 41.4, 51.5, 52.6, 60.1, 60.2, 129.1, 129.5, 135.0, 136.3, 169.5, 172.7. IR: 3282, 2951, 1739, 1651, 1303, 1133, 1091, 684 cm $^{-1}$. Exact mass calcd for $C_{19}H_{29}ClN_2O_5S$ requires m/z 433.1564, found m/z 433.1555 (MH^+, FAB).

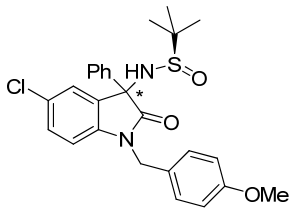


Cleavage of the sulfinyl group to yield dipeptide hydrochloride 2.30. Dipeptide **2.26** (17.4 mg, 0.042 mmol, 1.0 equiv) was taken up in dioxane (0.280 mL) and MeOH (0.280 mL) and was treated with 4.0 M HCl in dioxane (0.280 mL, 27.0equiv HCl). The reaction mixture was allowed to stir at rt for 3 h. The reaction mixture was concentrated *in vacuo*, and the amine hydrochloride was washed with a 2:1 mixture of pentane:dry diethyl ether (3x). The precipitate was collected by filtration and dried overnight *in vacuo* to yield the amine hydrochloride (13.6 mg, 93%) as a white solid. mp 53-55 ˚C. ^{1}H NMR (400 MHz, MeOD): δ 0.76 (m, 6H), 1.24 (m, 1H), 1.55 (m, 2H), 3.72 (s, 1H), 5.04 (s, 1H), 7.48- 7.54 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 21.3, 23.1, 25.9, 41.1, 52.3, 52.9, 57.1, 130.5, 131.0, 133.2, 137.2, 168.6, 174.1. IR: 2957, 1733, 1678, 1494, 1437, 1014 cm $^{-1}$. Excat mass calcd for $C_{15}H_{21}ClN_2O_3$ requires m/z 313.1319, found m/z 313.1320 (MH^+, FAB).



***N*-tert-Butanesulfinyl-1-(p-Methoxybenzyl)-5-chloroisatin imine 2.34**. To 1-(p-Methoxybenzyl)-5-chloroisatin[28] (0.359 g, 1.19 mmol, 1.0 equiv) dissolved in 2.7 mL of THF was added *tert*-butanesulfinamide (0.178 g, 1.47 mmol, 1.2 equiv), followed by $Ti(OEt)_4$ (5-15% isopropanol, 0.6 mL, ~2.37 mmol, ~2.0 equiv). The reaction mixture was stirred overnight. After diluting with an equal volume of EtOAc, the reaction was quenched with 0.3 mL of brine. The resulting mixture was stirred for 5 min and then was filtered through a pad of Celite, which was rinsed with EtOAc. The

filtrate was washed with brine, dried with Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (98/2 CH_2Cl_2/EtOAc to 95/5 CH_2Cl_2/EtOAc) to provide the desired product as a red solid (0.299 g, 63%). ^{1}H NMR (400 MHz): δ 1.44 (s, 9H), 3.78 (s, 3H), 4.80 (d, *J* = 15.4 Hz, 1H), 4.90 (d, *J*=15.5 Hz, 1H), δ 6.67 (d, 1H, *J*= 8.4 Hz, 1H), δ 6.86 (d, *J*=8.7 Hz, 2H), δ 7.22-7.32 (m, 5H). ^{13}C NMR (400 MHz): δ 23.5, 43.7, 55.4, 61.6, 111.2, 114.4, 117.5, 126.5, 128.9, 129.0, 131.9, 134.8, 146.3, 157.7, 157.7, 159.5. IR (neat): 2961, 1735, 1601, 1514, 1470, 1335, 1249, 1178, 1089, 1033, 808 cm^{-1}. Exact mass calcd for $C_{20}H_{21}ClN_2O_3S$ requires m/z 405.1039, found m/z 405.1032 (MH^+, FAB).



(*R*)-*N*-*tert*-Butanesulfinyl-5-chloro-1-(4-methoxybenzyl)-2-oxo-3-phenylindolin-3-yl 2.35. A solution of imine **2.34** (79.3 mg, 0.198 mmol, 1 equiv), phenylboronic acid (45.7 mg, 0.370 mmol, 2 equiv), BF_4[Rh(COD)(MeCN)$_2$] (3.6 mg, 0.009 mmol, 0.05 equiv), and potassium fluoride (3.2 mg, 0.11 mmol, 0.5 equiv) in 1:1 toluene and water (1 mL) was stirred for 24 h at 70 ºC. The reaction mixture was then diluted with EtOAc and washed with 2 mL of brine. The brine was back-extracted with EtOAc (2 x 2 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by reverse phase column chromatography (95/5 H_2O/MeCN to 5/95 H_2O/MeCN) to yield the desired product as a white solid (0.013 g, 13% yield). mp 74-76 ˚C. 82:18 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 3.79

(s, 3H), 4.74 (br, 1H), 4.87 (d, *J* = 15.4 Hz, 1H), 5.07 (d, *J*= 15.5Hz, 1H), 6.70 (d, *J*= 9.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.15-7.18 (m, 2H), 7.32-7.41 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 44.4, 53.6, 55.5, 66.8, 111.6, 114.5, 125.9, 126.9, 127.1, 127.2, 128.6, 128.7, 128.9, 129.3, 130.1, 130.2, 139.5, 141.7, 159.4. IR (neat): 1725, 1609, 1514, 1483 cm^{-1}. Exact mass calcd for $C_{26}H_{27}ClN_2O_3S$ requires m/z 483.1509, found m/z 483.1507 (MH^+, FAB).

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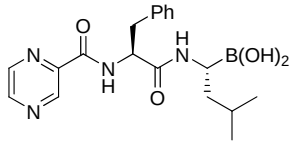
Chapter 3. The Asymmetric Copper-Catalyzed Synthesis of α-Amino Boronate Esters From *N-tert*-Butanesulfinyl Imines

The copper-catalyzed addition of bis(pinacolato)diboron to N-tert-*butanesulfinyl imines is described. This chemistry is amenable to a variety of alkyl and aryl* N-tert-*butanesulfinyl imines and provides rapid access to use of a number of chiral α-amino boronate esters, a biologically relevant scaffold that is difficult to access by other means. The utility of this methodology was demonstrated by the efficient synthesis of bortezomib (Velcade®), the first FDA approved proteasome inhibitor drug. The majority of this work was published in a communication* (Beenen, M. A.; An, C.; Ellman, J. A. Asymmetric Copper-Catalyzed Synthesis of α-Amino Boronate Esters From *N-tert*-Butanesulfinyl Imines. *J. Am. Chem. Soc.* **2008***, 130,* 6910-6911).

Exploration of the further functionalization of the α-amino boronate products is also described. This includes the homologation of the α-amino boronate ester products as well as the conversion of the boronate ester to the potassium trifluoroborate salt. The application of this methodology for the enantioselective synthesis of α-amino boronate esters is also addressed.

Introduction

α-Amino boronic acids have emerged as key mechanism-based pharmacophores for serine protease inhibition and have been incorporated into inhibitors of numerous therapeutically important proteases, including thrombin,[1] elastase,[2] and dipeptidyl protease IV.[3] Indeed, bortezomib, a boronic acid dipeptide marketed as Velcade®, is a highly potent reversible inhibitor of the 26S proteasome[4] and was the first FDA approved proteasome inhibitor drug (Figure 3.1). Currently, bortezomib is in clinical use for the treatment of multiple myeloma and mantle cell lymphoma.



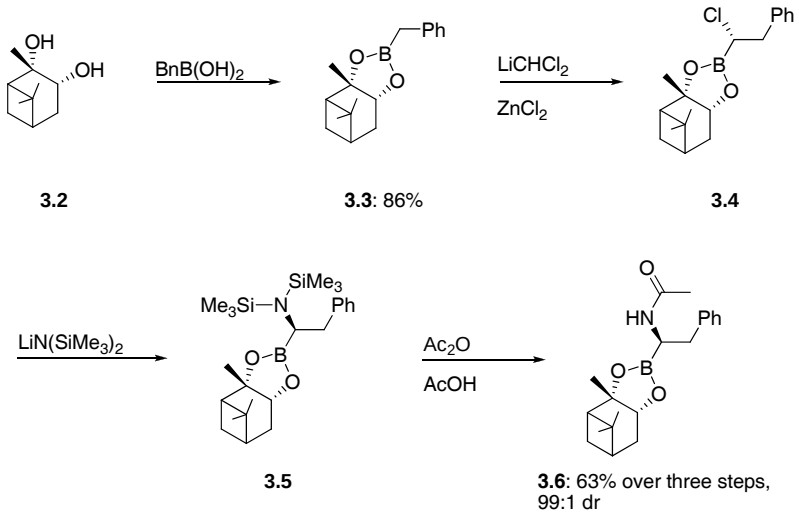
3.1: bortezomib

Figure 3.1. Structure of Bortezomib (Velcade ®).

Despite the clear biological importance of α-amino boronic acids, few methods are currently available for their asymmetric synthesis. In fact, the only reported syntheses of enantiomerically enriched α-amino boronic acids have relied on Matteson's protocol (Scheme 3.1).[3] This method utilizes a chiral pinanediol boronate ester **3.3** in a homologation reaction to prepare the α-amino boronic acid **3.6**. Reaction of the chiral boronate ester **3.3** with dichloromethyl-lithium forms the dichloromethyl borate complex which in the presence of zinc chloride rearranges to the α-chloro boronate ester **3.4** in high diasteromeric purity. Addition of the Lewis acid in the homologation transformation is critical to prevent epimerization of the α-chloro boronate ester.[5] In addition, rigorous exclusion of water and careful control of the Lewis acid stoichiometry are required to achieve consistent results.[6] The α-chloro boronate ester

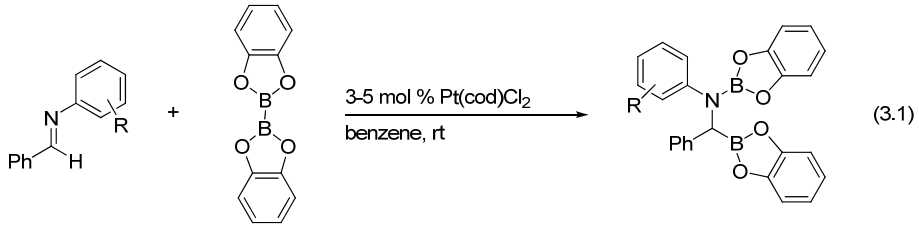
intermediate has the chlorine in a favorable position for displacement with lithium hexamethyldisilylazide, yielding the desired product **3.6** after acetylation in good yield and high diastereomeric ratio. While Matteson's chemistry has been extensively used in both academia and industry,[1-3, 7] few alkyl boronic acids are commercially available thus limiting the scope of the reaction with respect to the α-amino boronic acid side chain. In addition, amine displacement of the α-chloro substituent is limited to relatively unhindered systems due to the steric limitations inherent to S_N2 reactions.

Scheme 3.1. Homologation Reaction to Synthesize α-Amino Boronate Esters



An alternative approach for the synthesis of α-heteroatom boronic acids is the direct addition of boron to carbonyl compounds. However, few reports have been published in the literature on the addition of boron to a carbon-heteroatom double bond. Baker and coworkers demonstrated a platinum-catalyzed addition of bis(catecholato)diboron (B_2cat_2) across the double bond of a very limited number of aryl aldimines **3.7** (eq 3.1).[8] This reaction provided the racemic α-amino boronate esters **3.8** in 66-95% yield as determined by ^1H NMR. However, diboration of aliphatic aldimines was not

successful. Moreover, *N*-aryl groups do not serve as convenient protecting groups, which further limits the utility of this chemistry.

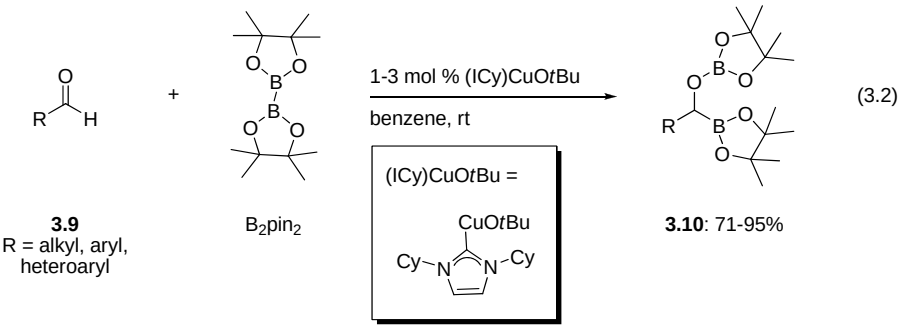


3.7
R = 2,6-Me,
2,6-*i*Pr, 4-OMe

B_2cat_2

3.8: 66-95 %

The copper-catalyzed addition of bispinacolatodiboron (B_2pin_2) across the double bond of aldehydes was reported by Sadighi and coworkers (eq 3.2).[9] For this transformation a catalytic amount of the copper imidazolium catalyst (1,3-dicyclohexylimidazol-2-ylidene)copper(I) *tert*-butoxide ((ICy)CuO*t*Bu) was utilized, providing a number of diboration products **3.10** derived from alkyl, aryl, and heteroaryl aldehydes in good isolated yields (71-95%) under mild conditions. An isolated example of the addition of a boryl anion to an aldehyde has also been described.[10]



3.9
R = alkyl, aryl,
heteroaryl

B_2pin_2

3.10: 71-95%

Encouraged by these preliminary reports, we envisioned that a direct approach for the asymmetric synthesis of diverse α-amino boronic acids could be achieved using *N*-*tert*-butanesulfinyl aldimines.[11] This chapter will describe the development of the

highly diastereoselective copper-catalyzed addition of bis(pinacolato)diboron to *N*-*tert*-butanesulfinyl aldimines. The utility of this methodology is further demonstrated by the concise asymmetric synthesis of bortezomib. Further functionalization of the α-amino boronate esters and initial results towards the enantioselective synthesis of α-amino boronate esters will also be addressed.

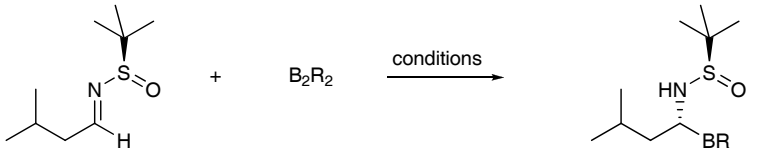
Synthesis of α-Amino Boronate Esters From *N*-*tert*-Butanesulfinyl Imines

Reaction Optimization

The platinum-catalyzed diborylation of *N*-*tert*-butanesulfinyl aldimine **3.11a** with bis(catecholato)diboron (B_2cat_2) was first examined according to the procedure developed by Baker and coworkers.[8] Unfortunately, no reaction was observed using this catalyst system (Table 3.1, entry 1). The addition of bis(pinacolato)diboron (B_2pin_2) across **3.11a** using a catalytic amount of (1,3-dicyclohexylimidazol-2-ylidene)copper(I) *tert*-butoxide ((ICy)CuO*t*Bu) under the reaction conditions optimized by Sadighi and coworkers was also evaluated.[9] Gratifyingly, the addition of B_2pin_2 to *tert*-butanesulfinyl aldimines with Sadighi's catalyst proceeded in 78% yield (Table 3.1, entry 2). A very high diastereomeric ratio of >98:2 was achieved, as determined by ^{19}F NMR analysis of the corresponding (+)- and (-)-MTPA amides prepared by acidic deprotection of the *N*-sulfinyl group followed by treatment with either (+)- or (-)-MTPACl.[12] A control reaction was performed to demonstrate that in the absence of catalyst no reaction was observed (Table 3.1, entry 3). The effect of temperature on the reaction was also probed. Carrying out the reaction at lower temperatures required extended times for reaction completion (entry 4), and at higher temperatures a lower yield was observed (entry 5). A number of solvents were also

screened. Reactions performed in toluene, dioxane or THF as the solvent (entries 6-8) proceeded with lower yields, but with comparable diastereoselectivity to those run with benzene (entry 2).

Table 3.1. Reaction optimization for the synthesis of α-amino boronate esters



3.11a **3.12a**

entry	B_2R_2	catalyst[a]	temp (° C)	solvent	yield (%)[b]	dr[c]
1	B_2cat_2	$Pt(cod)Cl_2$	rt	C_6H_6	NR	-
2	B_2pin_2	(ICy)CuO*t*Bu	rt	C_6H_6	78%	>98:2
3	B_2pin_2	none	rt	C_6H_6	NR	-
4[d]	B_2pin_2	(ICy)CuO*t*Bu	10	C_6H_6	71%	>98:2
5	B_2pin_2	(ICy)CuO*t*Bu	50	C_6H_6	54%	97:3
6	B_2pin_2	(ICy)CuO*t*Bu	rt	toluene	69%	>98:2
7	B_2pin_2	(ICy)CuO*t*Bu	rt	dioxane	62%	98:2
8	B_2pin_2	(ICy)CuO*t*Bu	rt	THF	50%	99:1

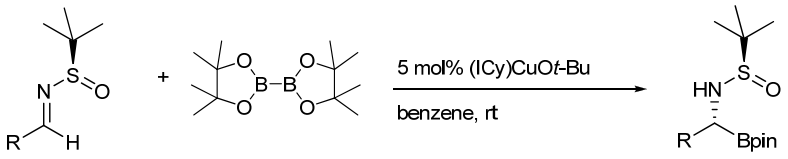
[a] 5 mol% catalyst was used. [b] Yields were determined by ^1H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. [c] Diastereomeric ratio was determined by ^{19}F NMR of the corresponding (*R*) and (*S*)-MTPA amides. [d]The reaction time was extended to 30 h.

Exploration of the Reaction Scope

With optimal reaction conditions identified, the scope of the methodology was investigated by the borylation of various *N*- *tert*-butanesulfinyl aldimines (Table 3.2). Additions to unbranched aliphatic aldimines proceeded in good yields and with high diastereoselectivities to provide the *N*-*tert*-butanesulfinyl-α-amino boronate esters corresponding to leucine, phenylalanine, and homophenylalanine, respectively (entries 1-3). The addition reaction is not sensitive to sterics as demonstrated by the syntheses of the analogues of valine, α-cyclohexylglycine (entries 4 and 5), and most dramatically, *tert*-leucine (entry 6). Addition of B_2pin_2 to *N*-*tert*-butanesulfinyl aromatic aldimines could also be achieved to produce the boronate ester analogues of arylglycines. However, for these substrates further optimization of the reaction conditions was necessary. The best yields for the arylglycine adducts were obtained when the temperature was lowered to 0 °C, the reaction times were increased, and the catalyst loading and equivalents of B_2pin_2 were increased (entries 7-11). Both electron-donating (entry 8) and electron-deficient (entries 9-11) substituents were tolerated on the aryl ring. While yields, as determined by ^{1}H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard, were good (66-79%), isolation of the pure material was nontrivial. Although compounds **3.11g-j** were isolated after column chromatography in 52-61% yield, for the *p*-trifluoromethyl substituted adduct **3.12k**, protodeborylation upon purification was especially problematic and clean material was not obtained. The success of the method for functionalized α-amino boronic acid analogues was demonstrated by the preparation of the α-amino boronate ester corresponding to *O*-TBDPS protected serine (entry 12). Encouraged by the ability of the methodology to tolerate an α-silyloxy functional

group, the α-chloro-substituted *N-tert*-butanesulfinyl imines **3.11m**[13] and **3.11n**[14] were also surveyed as coupling partners for the copper-catalyzed borylation reaction. Nucleophilic addition of Grignard reagents,[14] organocerium reagents,[15] and hydrides[16] to α-chloro *N-tert*-butanesulfinyl aldimines have been employed for the synthesis of *N-tert*-butanesulfinyl aziridines. Successful addition of the boronate ester to either **3.11m** or **3.11n** followed by ring-closure would constitute an efficient route towards chiral aziridine boronate esters. Unfortunately, the presence of the halide on the imine precursor was incompatible with the developed methodology (entries 13-14). Notably, all α-*N-tert*-butanesulfinylamino boronate ester products were obtained with excellent diastereoselectivity (96:4 to >99:1).

Table 3.2. Synthesis of Functionalized α-Amino Boronate Esters



3.11 **3.12**

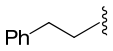
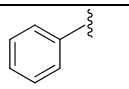
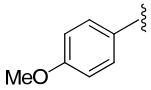
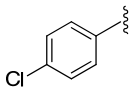
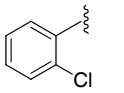
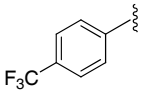
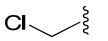
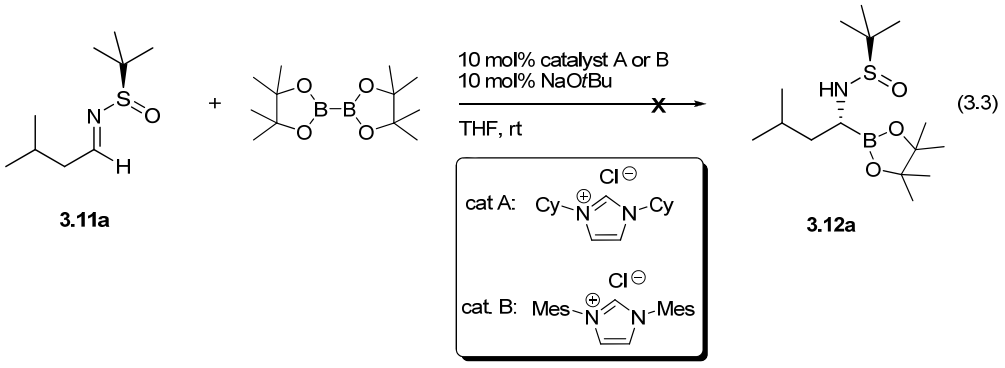
entry	imine	R	product	yield (%)[b]	Dr
1	**3.11a**		**3.12a**	74	>98:2[c]
2	**3.11b**		**3.12b**	59	>98:2[c]
3	**3.11c**		**3.12c**	70	99:1[c]
4[a]	**3.11d**		**3.12d**	88	>98:2[d]
5	**3.11e**		**3.12e**	81	97:3[d]
6	**3.11f**		**3.12f**	75	96:4[d]

Table 3.2 (Continued)

7[e]	**3.11g**		**3.12g**	(66[f]) 54	99:1[c]
8[e]	**3.11h**		**3.12h**	(74[f]) 57	>98:2[c]
9[e]	**3.11i**		**3.12i**	(77[f]) 61	99:1[c]
10[e]	**3.11j**		**3.12j**	(79[f]) 52	>97:3[g]
11[e]	**3.11k**		**3.12k**	(66[f])	-
12	**3.11l**		**3.12l**	75	>99:1[c]
13	**3.11m**		**3.12m**	-	-
14	**3.11n**		**3.12n**	-	-

[a] Absolute configuration was determined by x-ray crystallography. [b] Isolated yields after silica gel chromatography. [c] Diastereomeric ratio was determined by ^{19}F NMR of the corresponding (*R*) and (*S*)-MTPA amides. [d] Determined by ^{1}H and ^{13}C NMR after preparation of an authentic mixture of diasteromers. [e] Reaction was run in toluene at 0 °C for 48 h with 2.0 equiv of B_2pin_2 and 10 mol% catalyst. [f] Yields were determined by ^{1}H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. [g] No minor diastereomer detected in ^{1}H and ^{13}C NMR.

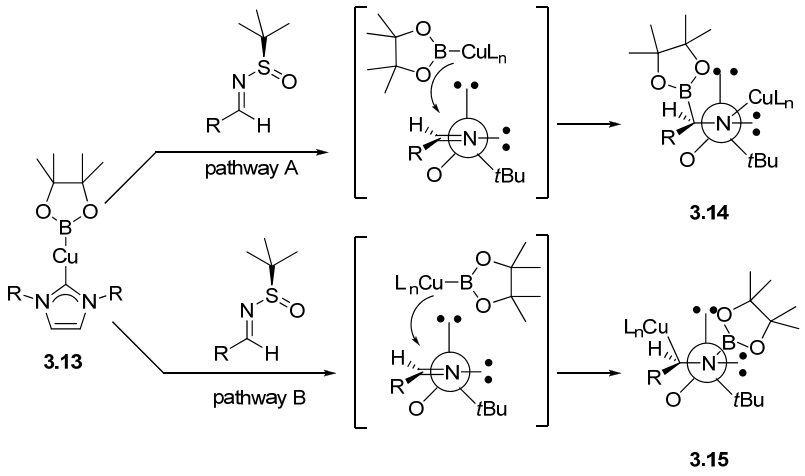
Recently, Hoveyda and coworkers published an interesting study of the metal-free 1,4-addition of bis(pinacolato)diboron to cyclic and acyclic α,β-unsaturated ketones and esters catalyzed by readily available *N*-heterocyclic carbenes.[17] Their reaction conditions were employed with either imidazolium salt catalyst A or B for additions to *N*-*tert*-butanesulfinyl imine **3.11a**, but none of the desired product **3.12a** was produced (eq 3.3). This result correlates with Hoveyda and coworkers' observations that addition of the boronate ester to cyclohexenone in the presence of benzaldehyde resulting only conjugate addition without any aldehyde diboration being observed.



Rationale for the Observed Sense of Induction

The absolute configuration of the α-amino boronate ester products was determined by X-ray structural analysis of **3.12d**. The sense of induction can best be understood by considering Sadighi's preliminary investigations on the copper-catalyzed diborylation of aldehydes with B_2pin_2 where he demonstrated that **3.13** is generated upon mixing a copper NHC complex with B_2pin_2 (Scheme 3.2). From **3.13** two pathways for the stereo-determining step are possible, and neither could be conclusively ruled out by Sadighi and coworkers in their mechanistic studies.[9] In pathway A direct boron-carbon bond formation occurs, while in pathway B an organocopper intermediate is first generated, which is expected to undergo transmetallation with retention of configuration to give the boronate ester product. Recently in the literature, DFT calculations have been conducted which suggest that pathway A is the most plausible.[18] For both pathways, the sense of induction is consistent with an open transition state with the reagent delivered from the least hindered face.[19]

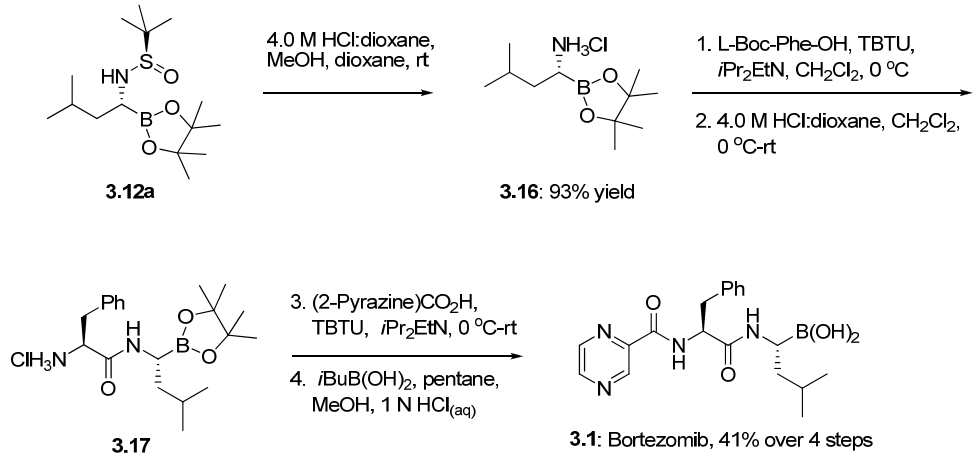
Scheme 3.2 Rationale for the Observed Sense of Induction



Synthesis of Bortezomib (Velcade ®)

Upon establishing broad substrate scope, we sought to demonstrate the utility of the *N*-*tert*-butanesulfinyl α-amino boronate esters by utilizing **3.12a** in the efficient synthesis of bortezomib **3.1**. Selective removal of the *N*-*tert*-butanesufinyl group under acidic conditions afforded the amine hydrochloride **3.16** in 93% yield (Scheme 3.3). *N*-Boc-L-phenylalanine was coupled with **3.16** using *N,N,N′,N′*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) according to the procedure by Millenium Pharmaceuticals,[12] and without purification, treatment with HCl then provided the amine hydrochloride **3.17**. Coupling of 2-pyrazinecarboxylic acid to crude **3.17** provided the penultimate intermediate, the pinacol boronate of bortezomib. This unpurified material was subsequently hydrolyzed under biphasic conditions utilizing *iso*-butylboronic acid as a pinacol sequestering agent.[12] Purification by reverse phase chromatography produced analytically pure bortezomib, **3.1**, in an overall yield of 41% from **3.16** for the four step process.

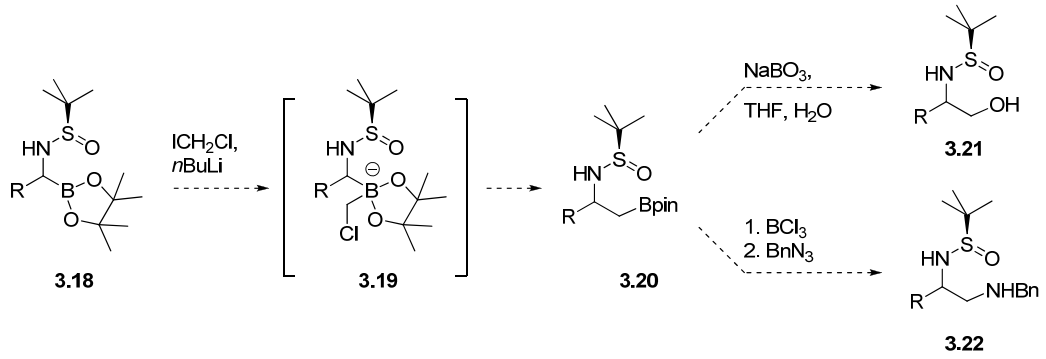
Scheme 3.3. Synthesis of Bortezomib



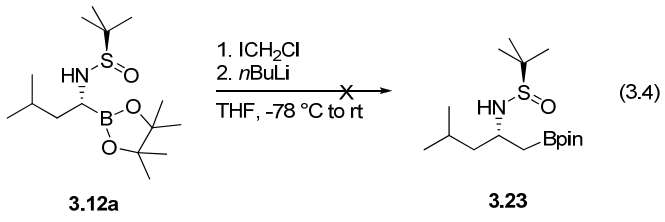
Further Functionalization of the α-Amino Boronate Esters

Boronate esters are highly versatile intermediates and the carbon-boron bond can be converted to a carbon-oxygen,[20] a carbon-nitrogen,[21, 22] or a carbon-carbon[22, 23] bond by various synthetic procedures including metal-catalyzed cross-coupling reactions. Homologation of the α-amino boronate ester products by insertion of a methylene group between the stereogenic center and the boronate ester followed by manipulation of the carbon-boron bond would provide a new route to 1,2-amino alcohols (**3.21**) or 1,2-diamines (**3.22**, Scheme 3.4). Formation of the borate complex **3.19** using the conditions developed by Matteson and Sadhu for the homologation of aryl or alkyl pinacol or pinanediol boronate esters,[24] followed by rearrangement would provide the versatile intermediate **3.20**. Upon further synthetic manipulations **3.20** could be converted to either a 1,2-amino alcohol (**3.21**) or a 1,2-diamine (**3.22**).

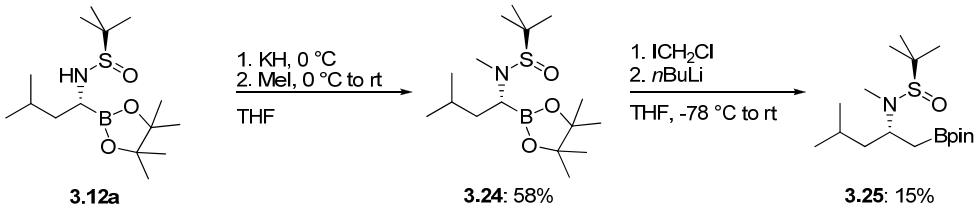
Scheme. 3.4. Homologation of *N*-*tert*-butanesulfinyl α-Amino Boronate Esters



Preliminary studies were conducted in an effort to develop a route towards the direct synthesis of 1,2-amino alcohols or 1,2-diamines from a *N*-*tert*-butanesulfinyl α-amino boronate ester **3.12a**. Unfortunately, direct homologation of **3.12a** by treatment with (chloromethyl)lithium, prepared by mixing *n*BuLi and iodochloromethane at -78 °C following the protocol of Matteson and Sadhu was unsuccessful (eq 3.4). However, when amine **3.24**, prepared by deprotonation of **3.12a** and addition of MeI, was subjected to these reaction conditions **3.25** was isolated in 15% yield along with unreacted starting material (Scheme 3.5). Although a number of optimization studies were conducted to improve the conversion of this reaction, superior results were not achieved.

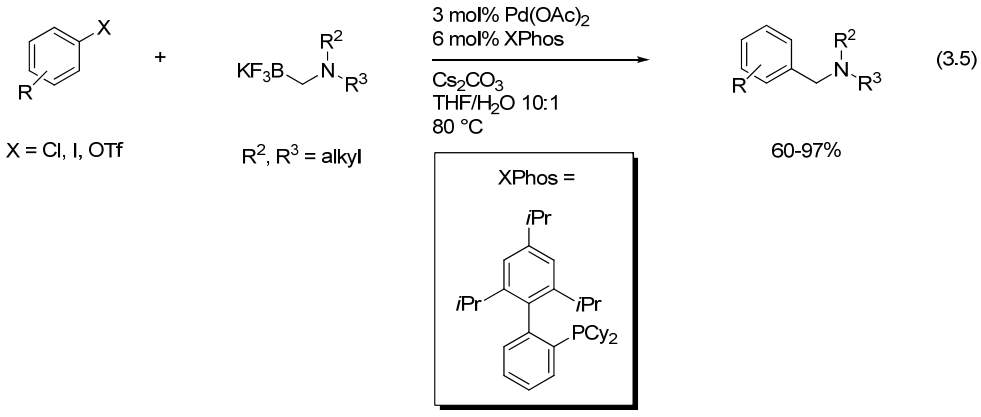


Scheme 3.5 Homologation of **3.12a**



3.12a **3.24**: 58% **3.25**: 15%

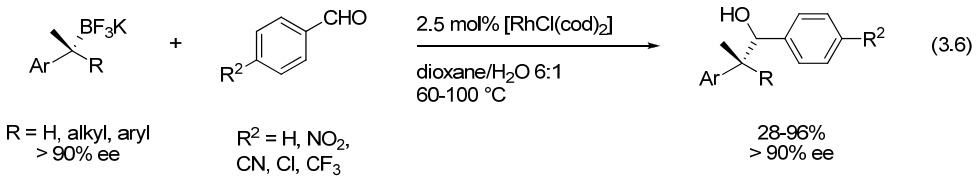
Trifluoroborates, which are readily prepared from boronate esters, are useful alternatives to boronate esters and boronic acids due to their enhanced stability to air and water as well as their increased reactivity in many organic transformations.[25] Trifluoroborates are particularly useful in metal-catalyzed cross-coupling reactions because they are less prone to protodeborylation than the corresponding boronic acids. Recently, Molander and coworkers reported the Suzuki coupling of *N,N*-dialkylaminomethyltrifluoroborates with aryl bromides (eq 3.5)[26] providing exciting precedent for the possibility of conducting cross-coupling reactions on the analogous trifluoroborate derivatives of the α-amino boronate esters.



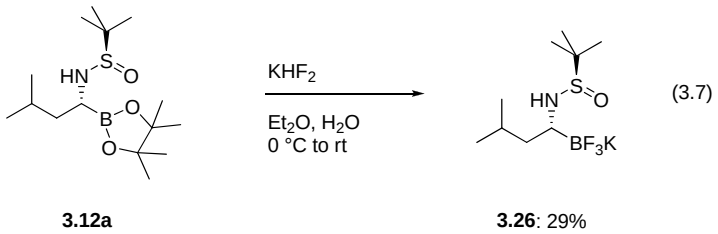
(3.5)

Furthermore, Aggarwal and Ros reported the 1,2-addition of chiral secondary and tertiary alkyl portassium trifluoroborates to aldehydes, a transformation that proceeded with complete stereoretention at the chiral center (eq 3.6).[27] If applicable to our

system, this process would provide rapid access to 1,2-amino alcohols. Thus the α-amino boronate ester products obtained from the addition of bis(pinacolato)diboron to *N-tert*-butanesulfinyl imines could serve as useful intermediates for the synthesis of a number of valuable molecules.



Investigations into the conversion of the boronate ester of the α-amino boronate ester products to the potassium trifluoroborate salt were conducted. The pinacol boronate ester of α-amino boronate adduct **3.12a** was converted to the trifluoroborate salt **3.26** upon treatment with KHF_2 in Et_2O and H_2O (eq 3.7). Separation from the pinacol byproduct was not trivial and required sublimation of the pinacol from the crude mixture at 60 °C under vacuum[28] followed by precipitation of the trifluoroborate from pentane and Et_2O. The final isolated yield was low (29%) and the reaction was not optimized. However, this potassium trifluoroborate product **3.26** could potentially serve as a useful substrate for cross-coupling reactions or 1,2-additions into aldehydes.

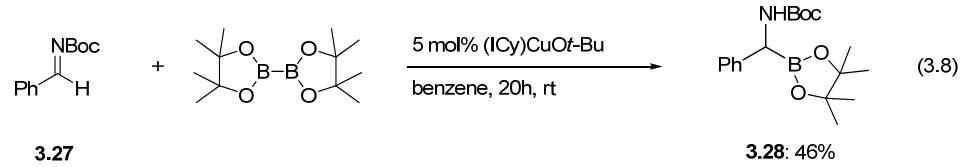


3.12a **3.26**: 29%

Enantioselective Synthesis of α-Amino Boronate Esters

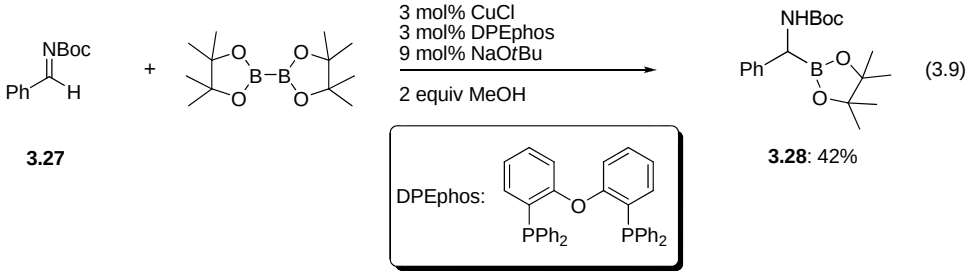
The use of aryl *N*-Boc imines as substrates for the enantioselective synthesis of α-amino boronate esters was also explored. The copper-catalyzed addition of

bis(pinacolato)diboron to *N*-Boc-aryl imine **3.27** was conducted under the optimized reaction conditions, providing α-amino boronate ester **3.28** in 46% yield (eq 3.8). Although the use of chiral imidazolium catalysts for the copper-catalyzed borylation of alkenes has been elegantly developed by Hoveyda and coworkers,[29] we decided to investigate the borylation of aryl *N*-Boc imines with chiral phosphine ligands due in large part to the number of commercially accessible ligands available for screening.

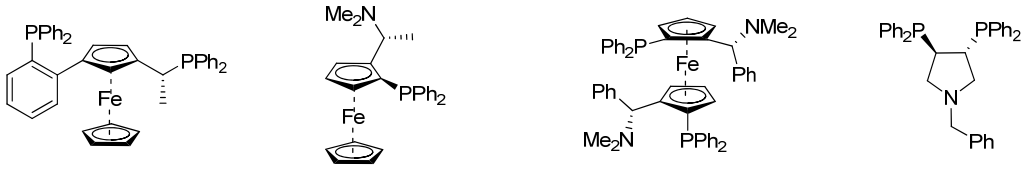


3.27 **3.28**: 46%

Yun and coworkers developed a 1,4-addition of bis(pinacolato)diboron to α,β-unsaturated carbonyl compounds using methanol as an additive and a copper catalyst derived from a copper salt and the diphosphine ligand DPEphos.[30] Following their reaction conditions, addition of bis(pinacolato)diboron to **3.27** was conducted in the presence of two equivalents of MeOH, providing racemic **3.28** in 42% yield (eq 3.9). A brief survey of other alcohol additives was conducted including *t*BuOH, *i*PrOH, and no added alcohol, but results were comparable to that obtained with MeOH. The analogous reaction with the *N*-*tert*-butanesulfinyl imine **3.11g** was also explored, but the α-amino boronate ester **3.12g** was produced in poor yield (13 % yield as determined by ^{1}H NMR).



Yun and Lee also reported the catalytic enantioselective addition of bis(pinacolato)diboron to acyclic α,β-unsaturated carbonyl compounds using the chiral phosphine ligand **3.31**.[31] However, attempts to render the transformation asymmetric using substrate **3.27** under several conditions ultimately failed. A screen of commercially available chiral phosphine ligands, including **3.31** did not give enantioselectivity in excess of 33% (Figure 3.2). Moderate yields were typically obtained in addition to the poor enantioselectivities. While the chiral phosphine ligands tested to date have proven to be ineffective for enantioselective catalytic additions to achiral imines, chiral imidazolium salts represent promising ligand precursors worthy of future investigation.



3.29: 46%, 33% ee

3.30: 50%, 12% ee

3.31: 54%, 0% ee

3.32: 35%, 0% ee

Figure 3.2. Chiral Ligands Surveyed For Reaction 3.9

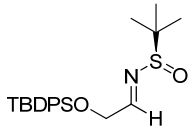
Conclusion

In conclusion, the first asymmetric addition of boron to a carbon heteroatom double bond was demonstrated, enabling the practical production of highly enantioriched α-

amino boronic acid derivatives from readily accessible *N*-*tert*-butanesulfinyl imine inputs using a very inexpensive Cu/ligand catalyst system. This transformation proceeded in good yields and with very high diastereoselectivities for both hindered and unhindered *N*-*tert*-butanesulfinyl imine substrates. Moreover, the *N*-*tert*-butanesulfinyl α-amino boronate pinacol ester products are ideal substrates for direct incorporation into α-amino boronic acid based protease inhibitors, as demonstrated by the efficient synthesis of bortezomib, a potent proteasome inhibitor approved for the treatment of cancer. Furthermore, homologation of an α-amino boronate ester was achieved and conversion of a boronate ester to a potassium trifluoroborate salt was also demonstrated. Studies were conducted in an attempt to render the synthesis of α-amino boronate esters enantioselective, but ultimately, further evaluation of chiral catalyst systems will be necessary to successfully achieve this goal.

General Procedure Methods. Bis(pinacolato)diboron was purchased from Acros and used without further purification. *tert*-Butanesulfinamide was obtained from Allychem and used without further purification. Benzaldehyde, hydrocinnamaldehyde, trimethylacetaldehdye, isovaleroaldehyde, phenylacetaldehyde, cyclohexane-carboxaldehyde, p-anisaldehyde, 4-chlorobenzaldehye, 2-chlorobenzaldehye, 4-(trifluoromethyl)benzaldehyde and 2,5-dihydroxy-1,4-dioxane were purchased from commercial sources and used without further purification. [(*t*-Butyldiphenylsilyl)oxy]acetaldehyde was synthesized according to literature procedure.[32] The starting materials 1,3-dicyclohexylimidazolium chloride,[33] [1.3-dicyclohexylimidazol-2-ylidene]copper (I) chloride,[9] and [1.3-dicyclohexylimidazol-

2-ylidene]copper (I) *tert*-butoxide[9] were synthesized according to literature procedures. The starting imines **3.11a**,[34] **3.11b**,[35] **3.11c**,[36] **3.11d**,[35] **3.11e**,[37] **3.11f**,[38] **3.11g**,[37] **3.11h**,[39] **3.11i**,[39] **3.11j**,[40] and **3.11k**,[39] **3.11m**,[13] and **3.11n**[14] were synthesized according to literature procedures. Boc-Phenylalanine and TBTU were purchased from NovaBiochem and used without further purification. 2-Pyrazinecarboxylic acid was purchased from Aldrich and was recrystallized from H_2O before use. (2-methylpropyl)boronic acid and sodium *tert*-butoxide were purchased from Aldrich and used without further purification. Puratrem copper(I) chloride was purchased from Strem and stored in a glovebox. 4.0 M HCl (solution in 1,4-dioxane) was purchased from Aldrich. Anhydrous THF, CH_2Cl_2, 1,4-dioxane, benzene, and toluene were obtained from Seca Solvent Systems by GlassContour and were dried over alumina under a nitrogen atmosphere. Methanol and DIPEA were freshly distilled over CaH_2 prior to use. Column chromatography was carried out using Merck 60Å 230-240 mesh silica gel. Reverse phase column chromatography was performed using a C_{18}HS packed column on a Biotage SP1 system (Charlottesville, VA). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer and only partial data are listed. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded in ppm and referenced to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. Mass spectra were obtained from the Microanalytical Laboratory at the University of California, Berkeley.



***N*-tert-Butanesulfinyl-[(*t*-butyldiphenylsilyl)oxy]acetamide 3.11l.** To [(*t*-butyldiphenylsilyl)oxy]acetaldehyde[1] (2.5 g, 8.4 mmol, 1.0 equiv) dissolved in 20 mL of THF was added *tert*-butanesulfinamide (1.2 g, 10 mmol, 1.2 equiv), followed by $Ti(OEt)_4$ (5-15% isopropanol, 4.0 mL, ~16.5 mmol, ~2.0 equiv). The reaction mixture was stirred overnight. After diluting with an equal volume of EtOAc, the reaction was quenched with 10 mL of brine. The resulting mixture was stirred for 5 min and then was filtered through a pad of Celite, which was rinsed with EtOAc. The filtrate was washed with brine, dried with Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (100/0 CH_2Cl_2/EtOAc to 95/5 CH_2Cl_2/EtOAc) to provide **3.11l** as a colorless oil (2.5 g, 74%). ^{1}H NMR (400 MHz): δ 1.06 (s, 9H), δ 1.17 (s, 9H), δ 4.53 (d, 2H, *J*= 2.6), δ 7.35-7.44 (m, 6H), δ 7.64-7.65 (m, 4H), δ 8.08 (t, 1H, *J*=2.9). ^{13}C NMR (400 MHz): 19.3, 22.4, 26.8, 56.9, 66.2, 127.9, 130.1, 132.8, 135.6, 168.2. Exact mass calcd for $C_{22}H_{32}BNO_2SSi$ requires m/z 402.1923, found m/z 402.1915 (MH^+, FAB).

General Procedure for the Addition of Bis(pinacolato)diboron to alkyl *N-tert*-Butanesulfinyl Imines. Reactions were set up in a glovebox. To a scintillation vial containing a stir bar and bis(pinacolato)diboron (0.254 g, 1.00 mmol, 1.0 equiv) in 4.0 mL of benzene was added the appropriate sulfinyl imine (1.00 mmol, 1.0 equiv) in 4.0 mL of benzene. (ICy)CuO*t*Bu (18.3 mg, 0.050 mmol, 0.050 equiv) was dissolved in 3.0 mL of benzene and added to the reaction vial. The reaction vial was capped, and the mixture was stirred in the glovebox for 20-48 h. The reaction mixture was removed from the glovebox and diluted with EtOAc (10 mL). The organic layer was

washed with 1 N $NaHCO_3$ (10 mL) and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layer was then washed with brine (10 mL), and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by *rapid* silica gel chromatography on deactivated silica gel (35% w/w) using EtOAc:CH_2Cl_2 mixtures and were visualized with CMA stain.

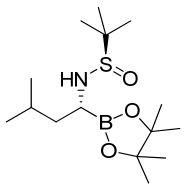
General Procedure for the Addition of Bis(pinacolato)diboron to aryl *N-tert*-Butanesulfinyl Imines. Reactions were set up in a glovebox. To a Schlenk tube containing a stir bar and bis(pinacolato)diboron (0.508 g, 2.00 mmol, 2.0 equiv) in 2.0 mL of toluene was added the appropriate sulfinyl imine (1.00 mmol, 1.0 equiv) in 2.0 mL of toluene. (ICy)CuO*t*Bu (36.6 mg, 0.100 mmol, 0.10= equiv) was dissolved in 2.0 mL of toluene and added to the reaction vessel. The Schlenk tube was sealed, and the mixture was placed in a pre-cooled bath at 0 °C, and the reaction mixture was stirred at that temperature for 28-48 h. The reaction mixture was removed from the Schlenk flask and diluted with EtOAc (10 mL). The reaction mixture was then directly concentrated under reduced pressure. The products were isolated by *rapid* silica gel chromatography on deactivated silica gel (35% w/w) using EtOAc:CH_2Cl_2 mixtures and were visualized with CMA stain.

General Procedure to Obtain an Authentic Mixture of Diastereomers. Method A: The sulfinyl protected α-amino boronic ester was dissolved in dioxane (0.2 M) in an oven-dried vial equipped with a Teflon coated stir bar under nitrogen. Freshly distilled MeOH (10 equiv) was added to the solution, followed by the drop-wise addition of 4.0

M HCl in dioxane (1 equiv). The reaction mixture was stirred at rt for 45 min to 1 h before it was directly concentrated under reduced pressure. The resulting amine hydrochloride salt was triturated with a 2:1 mixture of hexanes to Et_2O. The amine hydrochloride (1.0 equiv) was then dissolved in THF (0.19 M) and cooled to – 78 °C. DIPEA (4.0 equiv) was then added followed by the addition of *tert*-butanesulfinyl chloride.[41] The resulting mixture was stirred for 1.5 h at – 78 °C. The reaction was quenched with DIPEA (5.3 equiv) and MeOH (9.2 equiv) at – 78 °C and stirred for 5 min. The reaction mixture was then diluted with EtOAc and washed with 1 N $NaHSO_4$. The aqueous layer was extracted with EtOAc (2x). The organic layer was then washed with brine, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography on deactivated silica gel (35% w/w) using EtOAc:CH_2Cl_2 mixtures and were visualized with CMA stain.

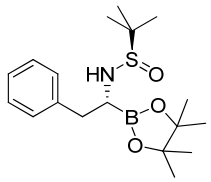
Determination of Diastereomeric Purity by Preparation of both (*R*)- and (*S*)-MTPA Amide Diastereomers. Method B: The sulfinyl protected α-amino boronic esters were dissolved in dioxane (0.2 M) in an oven-dried vial equipped with a Teflon coated stir bar under nitrogen. Freshly distilled MeOH (10 equiv) was added to the solution, followed by the drop-wise addition of 4.0 M HCl in dioxane (1 equiv). The reaction mixture was stirred at rt for 45 min to 1 h before it was directly concentrated under reduced pressure. The resulting amine hydrochloride salt was triturated with a 2:1 mixture of hexanes to Et_2O. The amine hydrochloride (1.0 equiv) was then

dissolved in CH_2Cl_2 (0.19 M) and cooled to 0 °C. DIPEA (4.0 equiv) was then added followed by the addition of >99% ee (+) or >99% (-) MTPA chloride (~ 2.0 equiv), and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with EtOAc and then washed with 1 N sodium bisulfate. The organic layer was then washed with 1 N $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. Diastereomeric ratios were determined by ^{19}F NMR of the unpurified material.

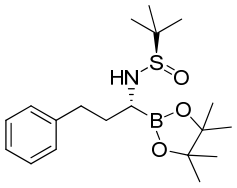


Pinacol *(R)*-1-*N*-sulfinyl-3-methylbutane-1-boronate (3.12a). The general procedure for alkyl imines was followed using 0.189 g (1.00 mmol) of imine with stirring for 22 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (10-20% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (20% EtOAc: CH_2Cl_2) to yield the desired product as a clear oil that solidified to a white solid under 25 °C (0.236 g, 74% yield). >98:2 dr. Both (*R*)- and (*S*)-MTPA amides were prepared according to general procedure B, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*R*)-MTPA derivative of major diastereomer δ =-68.18, minor diastereomer δ =-68.27. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (d *J* = 6.6 Hz, 6H), 1.17 (s, 9H), 1.23 (s, 6H), 1.24 (s, 6H), 1.53 (m, 2H), 1.68 (m, 1H), 3.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 22.7,

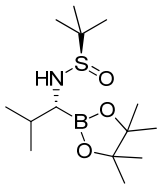
22.9, 24.6, 25.1, 25.7, 41.2, 42.6, 56.1, 84.0. IR (neat): 3225, 2955, 1466, 1365, 1337, 1133, 1062, 849 cm^{-1}**.** Exact mass calcd for $C_{15}H_{33}BNO_3S$ requires m/z 318.2274, found m/z 318.2279 (MH^+, FAB).



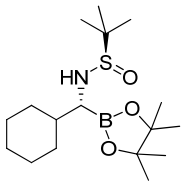
Pinacol *(R)*-1-*N*-sulfinyl—phenylmethane-1-boronate (3.12b). The general procedure for alkyl imines was followed using 0.221g (0.987 mmol) of imine with stirring for 23 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (10-15-30% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (20% EtOAc: CH_2Cl_2) to yield the desired product as a yellow solid (0.213 g, 61% yield). mp 66-68 ˚C. >98:2 dr. The authentic mixture of diastereomers of this compound was prepared according to general procedure A, and no minor diastereomer was detected by ^{13}C NMR. ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 15H), 1.12 (s, 6H), 2.92 (m, 2H), 3.12 (d, J_1 = 6.4 Hz, 1H), 3.27 (dt, J_1 = 7.0 Hz, J_2= 6.9Hz, 1H), 7.12-7.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.4, 24.8, 39.2, 43.9 (br), 56.0, 84.0, 126.5, 128.3, 129.4, 138.2. IR (neat): 3259, 2980, 1454, 1370, 1336, 1142, 1065, 697 cm^{-1}. Exact mass calcd for $C_{18}H_{31}BNO_3S$ requires m/z 352.2118, found m/z 352.2112 (MH^+, FAB).



Pinacol *(R)*-1-*N*-sulfinyl-phenylethyl-1-boronate (3.12c). The general procedure for alkyl imines was followed using 0.238 g (1.00 mmol) of imine with stirring for 24 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (25-30% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (30% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.254 g, 70% yield). mp 75-78 ˚C. 99:1 dr. Both (*R*)- and (*S*)-MTPA amides were prepared according to general procedure B, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*R*)-MTPA derivative of major diastereomer δ =-68.12, minor diastereomer δ =-68.27. ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.27 (s, 6H), 1.28 (s, 6H), 2.03 (m, 2H), 2.62-2.80 (m, 2H), 3.10 (dt, J_1 = 6.7 Hz, $J_2 = J_3$ = 6.8 Hz, 1H), 3.28 (d, J = 6.7, 1H), 7.15-7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 24.4, 24.9, 33.0, 35.3, 42.8, 55.9, 84.0, 125.7, 128.2, 128.4, 141.7. IR (neat): 3201, 2975, 1455, 1327, 1144, 1052, 698 cm^{-1}. Exact mass calcd for $C_{19}H_{33}BNO_3S$ requires m/z 366.2274, found m/z 366.2269 (MH^+, FAB).

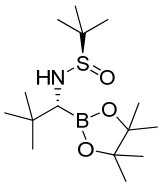


Pinacol *(R)*-1-*N*-sulfinyl-2-methylpropane-1-boronate (3.12d). The general procedure for alkyl imines was followed using 0.170 g (0.970 mmol) of imine with stirring for 22 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (15% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (15% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.259 g, 88% yield). Vapor diffusion with pentane/Et_2O yielded X-ray quality crystals. mp 71-75 ˚C. >98:2 dr. The authentic mixture of diastereomers of this compound was prepared according to general procedure A, and no minor diastereomer was detected by ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 7.0 Hz, 3H), 0.99 (d, J=6.9 Hz, 3H), 1.19 (s, 9H), 1.40 (s, 6H), 1.41 (s, 6H), 1.99 (m, 1H), 2.89 (dd, J_1 = 6.9 Hz, J_2 = 5.7 Hz, 1H), 3.29 (d, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 20.2, 22.7, 24.7, 25.3, 32.0, 50.0, 56.4, 84.1. IR (neat): 3316, 2957, 1465, 1370, 1330, 1141, 1068, 846 cm^{-1}. Exact mass calcd for $C_{14}H_{31}BNO_3S$ requires m/z 304.2118, found m/z 304.2123 (MH^+, FAB).



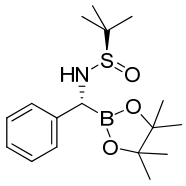
Pinacol *(R)*-1-*N*-sulfinyl-2-cyclohexyl-1-boronate (3.12e). The general procedure for alkyl imines was followed using 0.214g (0.994 mmol) of imine with stirring for 21 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (15% EtOAc: CH_2Cl_2). Mixed fractions

were combined and purified by a second column (containing 35% water w/w), eluting with (15- 20% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.279 g, 81% yield). mp 119-122 ˚C. 97:3 dr. An authentic mixture of diastereomers of this compound was prepared according to the general procedure A, and the minor diastereomer was detected in the ^{1}H NMR of the crude material. (400 MHz, $CDCl_3$): δ 1.04 (m, 3H), 1.17 (s, 9H), 1.22 (m, 1H), 1.24 (s, 6H), 1.26 (s, 6H), 1.40-1.80 (m, 7H), 2.88 (m, 1 H), 3.30 (d, J = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.5, 25.1, 26.2, 26.3, 26.4, 30.2, 30.5, 41.6, 49.2 (br), 56.1, 83.9 IR (neat): 3314, 2920, 1448, 1383, 1329, 1142, 1061, 835 cm^{-1}. Exact mass calcd for $C_{17}H_{35}BNO_3S$ requires m/z 344.2431, found m/z 344.2422 (MH^+, FAB).

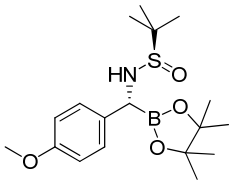


Pinacol *(R)*-1-*N*-sulfinyl-*t*-butyl-1-boronate (3.12f). The general procedure for alkyl imines was followed using 0.188 g (0.995 mmol) of imine with stirring for 22 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (5-15% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (15% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.238 g, 75% yield). mp 93-96 ˚C. 96:4 dr. The authentic mixture of diastereomers of this compound was prepared according to the general procedure A, and the diastereomeric ratio was determined by ^{1}H NMR of the crude material. ^{1}H NMR (400 MHz, $CDCl_3$):

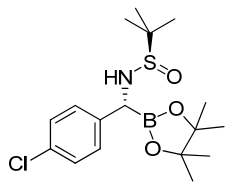
δ 0.99 (s, 9H), 1.19 (s, 9H), 1.24 (s, 6H), 1.25 (s, 6H), 2.76 (d, 1H), 3.35 (d, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 22.58, 20.2, 24.8, 25.2, 27.8, 34.2, 56.6, 84.0. IR (neat): 3348, 2956, 1466, 1364, 1331, 1139, 1061, 844 cm^{-1}**.** Exact mass calcd for $C_{15}H_{33}BNO_3S$ requires m/z 318.2274, found m/z 318.2282 (MH^+, FAB).



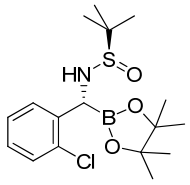
Pinacol *(R)*-1-*N*-sulfinyl-phenyl-1-boronate (3.12g). The general procedure for aryl imines was followed using 0.209 g (1.00 mmol) of imine with stirring for 48 h at 0 °C in toluene. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (5-15% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (15% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.182 g, 54% yield). mp 73-76 ˚C. 99:1 dr. Both (*R*)- and (*S*)-MTPA amides were prepared according to general procedure B, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*S*)-MTPA derivative of major diastereomer δ =-68.06, minor diasteromer δ = -68.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.08 (s, 6H), 1.24 (s, 9H), 3.58 (d, J = 4.4 Hz, 1H), 4.28 (d, J = 4.4 Hz, 1H), 7.2-7.4 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.2, 24.6, 47.3, 56.3, 84.2, 126.9, 127.4, 128.5, 139.9. IR (neat): 2978, 1454, 1336, 1139, 1056, 845, 701 cm^{-1}. Exact mass calcd for $C_{17}H_{29}BNO_3S$ requires m/z 338.1961, found m/z 338.1961 (MH^+, FAB).



Pinacol *(R)*-1-*N*-sulfinyl-4-methoxyphenyl-1-boronate (3.12h). The general procedure for aryl imines was followed using 0.238 g (0.990 mmol) of imine with stirring for 28 h at 0 °C in toluene. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (0-10% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (7% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.207 g, 57% yield**).** mp 97-101 ˚C**.** >98:2 dr. Both (*R*)- and (*S*)-MTPA amides were prepared according to general procedure B, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*S*)-MTPA derivative of major diastereomer δ =-68.37, minor diasteromer δ = -68.06. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H), 1.14 (s, 6H), 1.16 (s, 9H), 3.42 (d, *J* = 4.4 Hz, 1H), 3.71 (s, 3H), 4.12 (d, *J* = 4.4 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.2, 24.6, 46.7, 55.1, 56.2, 84.1, 113.9, 128.8, 131.8, 158.6. IR (neat): 2975, 1461, 1344, 1140, 1055, 843, 716 cm^{-1}. Exact mass calcd for $C_{18}H_{31}BNO_4S$ requires m/z 368.2066, found m/z 368.2067 (MH^+, FAB).

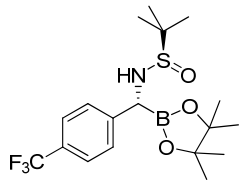


Pinacol *(R)*-1-*N*-sulfinyl-4-chlorophenyl-1-boronate (3.12i). The general procedure for aryl imines was followed using 0.233 g (0.960 mmol) of imine with stirring for 31 h at 0 °C in toluene. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (0-10% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (10% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.218 g, 61% yield). mp 102-105 ˚C. 99:1 dr. Both (*R*)- and (*S*)-MTPA amides were prepared according to general procedure B, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*S*)-MTPA derivative of major diastereomer δ =-68.31, minor diasteromer δ = -68.04. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 6H), 1.20 (s, 6H), 1.23 (s, 9H), 3.62 (d, *J* = 4.8 Hz, 1H), 4.23 (d, *J* = 4.9 Hz, 1H), 7.27-7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.2, 24.6, 46.7, 56.4, 84.4, 128.6, 128, 132.6, 138.6. IR (neat): 3197, 2980, 1487, 1347, 1140, 1066, 850, 694 cm^{-1}. Exact mass calcd for $C_{17}H_{28}BClNO_3S$ requires m/z 372.1577, found m/z 372.1571 (MH^+, FAB).



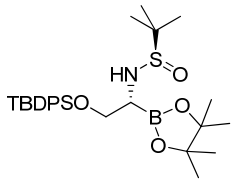
Pinacol *(R)*-1-*N*-sulfinyl-2-chlorophenyl-1-boronate (3.12j). The general procedure for aryl imines was followed using 0.240 g (0.990 mmol) of imine with stirring for 31 h at 0 °C in toluene. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (0-10% EtOAc:

CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (7% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.192 g, 52% yield). dr > 97:3. No minor diastereomer was observed in either the ^1H NMR or the ^{13}C NMR. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 15H), 1.24 (s, 6H), 13.89 (d, J = 3.6 Hz, 1H), 4.47 (d, J = 7.3 Hz, 1H), 7.15-7.19 (m, 1H), 7.23-7.27 (m, 1H), 7.33 (dd, J_1= 7 Hz, J_2= 1.3 Hz, 1H), 7.48 (dd, J_1= 6.0 Hz, J_2= 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.5, 24.6, 47.4, 56.4, 84.4, 127.1, 128.2, 129.5, 129.8, 132.9, 138.6. IR (neat): 3217, 2978, 1457, 1339, 1140, 1045, 848, 752 cm^{-1}. Exact mass calcd for $C_{17}H_{28}BClNO_3S$ requires m/z 372.1577, found m/z 372.1571 (MH^+, FAB).

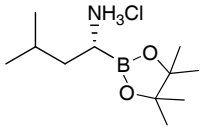


Pinacol *(R)*-1-*N*-sulfinyl-4-triflouromethylphenyl-1-boronate (3.12k). 66% ^1H NMR yield before purification with reference to 1,3,5-trimethoxybenzene as an internal standard. The material readily proto-deborylated using our standard purification method but reasonably pure material could be obtained by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (0-5% EtOAc: CH_2Cl_2). mp 129-135 ˚C. >95:5 dr. No minor diastereomer was observed in the unpurified material. ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 6H), 1.20 (s, 6H), 1.23 (s, 9H), 3.77 (d, J = 5.2 Hz, 1H), 4.33 (d, J = 5.3 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$):-61.83. ^{13}C

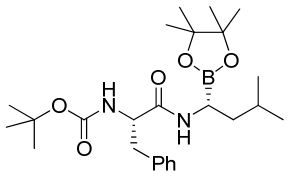
NMR (125 MHz, $CDCl_3$): δ 22.5, 24.2, 24.6, (C-B not shown), 56.5, 84.6, 125.2 (q, *J* = 272 Hz), 125.4 (q, *J* = 3.5 Hz), 127.5, 128.5 (q *J* = 32.3 Hz), 144.4. IR (neat): 2986, 1322, 1110, 1039, 849 cm^{-1}. LRMS for $C_{18}H_{27}BF_3NO_3S$ requires m/z 406, found m/z 406 (MH^+, FAB).



Pinacol *(R)*-1-*N*-sulfinyl-(tert-butyl-diphenyl-silanyloxy)-ethyl-1-boronate (3.12l). The general procedure was followed using 0.398 g (0.992 mmol) of imine with stirring for 32 h. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (3-10% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (10% EtOAc: CH_2Cl_2) to yield the desired product as a clear oil (0.396 g, 75% yield). >99:1 dr. Both (*R*)- and (*S*)-MTPA amides were prepared according to general procedure B, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, $CDCl_3$): (*R*)-MTPA derivative of major diastereomer δ =-68.11, minor diasteromer δ = -68.28. ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.21 (s, 9H), 1.22 (s, 6H), 1.24 (s, 6H) 3.26 (m, 1H), 3.73 (d, *J* = 6.1 Hz, 1H), 3.91 (m, 2H), 7.35-7.43 (m, 6H), 7.69 (d, *J* = 6.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 22.7, 24.8, 25.2, 27.0, 45.6, 56.1, 65.8, 84.2, 127.8, 127.9, 129.7, 129.8, 133.2, 133.6, 135.7, 135.9. IR (neat): 2978, 1454, 1336, 1139, 1056, 845, 701 cm^{-1}. Exact mass calcd for $C_{28}H_{45}BNO_4SSi$ requires m/z 530.2932, found m/z 530.2922 (MH^+, FAB).

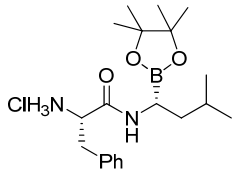


Pinacol 1-ammonium hydrochloride-3-methylbutane-1-boronate (3.16). Pinacol *(R)*-1-*N*-sulfinyl-3-methylbutane-1-boronate **3.12a** (0.306 g, 0.966 mmol, 1.00 equiv) was diluted with 1,4-dioxane (4.7 mL, 0.06 M) under a stream of nitrogen. Methanol (0.390 mL, 9.63 mmol, 10.0 equiv) was added at room temperature followed by the addition of 4.0 M HCl (solution in 1,4-dioxane) (0.240 mL, 0.960 mmol, 1.0 equiv). The resulting mixture was stirred at room temperature for 1 h before it was concentrated to dryness. The resulting solid was triturated with a 2:1 mixture of hexanes:Et_2O to obtain the desired product as a white solid (0.223 g, 93%). mp 185-188 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (m, 6H), 1.24 (s, 12H), 1.58 (m, 1H), 1.74 (m, 1H), 1.86 (m, 1H), 2.88 (br s, 1H), 8.18 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 22.7, 24.8, 25.2, 36.1 (br), 38.7, 85.1. IR (neat): 2962, 1350, 1253, 1137, 854, 674 cm^{-1}. Exact mass calcd for $C_{11}H_{25}BNO_2$ requires m/z 214.1978, found m/z 214.1974 (MH^+, FAB).



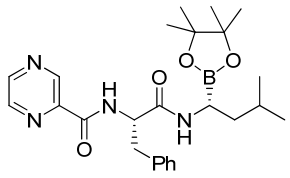
Pinacol *N*-Boc-L-phenylalanine-L-leucine boronate. A scintillation vial containing pinacol 1-ammonium hydrochloride-3-methylbutane-1-boronate **3.16** (0.148 g, 0.592 mmol, 1.00 equiv) was charged with CH_2Cl_2 (2.0 mL, 0.3 M) and cooled to 0 °C. Diisopropylethylamine (0.320 mL, 1.84 mmol, 3.1 equiv) was added dropwise to the

flask. Boc-L-phenylalanine (0.248 g, 0.933 mmol, 1.6 equiv) was then added to the flask. 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminiumtetrafluoroborate, TBTU (0.260 g, 0.810 mmol, 1.4 equiv), was then added to the reaction mixture. The reaction mixture was stirred at 0 °C for 7 h. The reaction mixture was then concentrated under reduced pressure maintaining an external bath temperature below 30 °C, and then 10 mL of EtOAc was added. The organic layer was washed with DI H_2O (2 x 10 mL), 1% phosphoric acid (2 x 10 mL), 2% K_2CO_3 (2 x 10 mL), and brine (2 x 10 mL). Each aqueous layer was back-extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure maintaining an external bath temperature below 30 °C. The desired product was isolated as a white foam and carried on to the next synthetic transformation without purification.



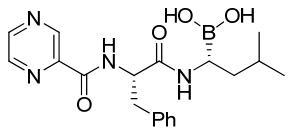
Pinacol L-phenylalanine-L-leucine boronate hydrochloride salt (3.17). CH_2Cl_2 (3.0 mL, 0.3 M) was charged to a scintillation vial containing pinacol *N*-Boc-L-phenylalanine-L-leucine boronate (0.592 mmol based on a theoretical yield of 100 %). The mixture was cooled to 0 °C. 4.0 M HCl (as a solution in 1,4-dioxane, 0.520 mL, 2.08 mmol, 3.5 equiv) was added dropwise over 10 min. The resulting solution was stirred at 0 °C for 1 h, and then the bath was removed and the reaction mixture was stirred for an additional 5 h. The reaction mixture was concentrated to dryness and the

resulting solid was washed with hexanes. The desired product was isolated as a white solid and was carried on to the next synthetic transformation without purification.



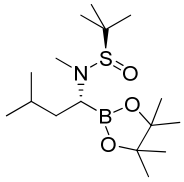
Pinacol *N*-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate. CH_2Cl_2 (1.2 mL, 0.5 M) was added to a scintillation vial containing pinacol *N*-Boc-L-phenylalanine-L-leucine boronate hydrochloride salt **3.17** (0.592 mmol based on a theoretical yield of 100 %). The mixture was cooled to 0 °C. Diisopropylethylamine (0.280 mL, 1.61 mmol, 2.7 equiv) was added dropwise to the flask, and the reaction mixture was stirred for 5 min. 2-Pyrazine carboxylic acid (0.101 g, 0.814 mmol, 1.4 equiv) was then added to the solution in one portion. 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate, TBTU (0.197 g, 0.614 mmol, 1.0 equiv), was then added to the reaction mixture. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to rt and was stirred for an additional 12 h. The reaction mixture was then concentrated under reduced pressure maintaining an external bath temperature below 30 °C and then 10 mL of EtOAc was added. The organic layer were washed with DI H_2O (2 x 10 mL), 1% phosphoric acid (2 x 10 mL), 2% K_2CO_3 (2 x 10 mL), and brine (2 x 10 mL). Each aqueous layer was back-extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure maintaining an external bath

temperature below 30 °C. The desired product was isolated as a pale yellow foam and carried on to the next synthetic transformation without purification.



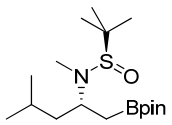
***N*-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride (3.1).** Distilled pentane (1.6 mL, 0.2M) and methanol (1.6 mL, 0.2M) were added to a scintillation vial containing pinacol *N*-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronate (0.592 mmol based on a theoretical yield of 100 %). 2-Methylpropaneboronic acid (0.25 g, 2.4 mmol, 7.4 equiv) was then added to the solution in one portion. 1 N $HCl_{(aq)}$ (1.2 mL, 0.28M) was added to the reaction mixture, and the resulting biphasic solution was stirred vigorously for 20 h. Stirring was then stopped and the biphasic mixture was allowed to separate, and the pentane layer was removed. The aqueous layer was transferred to a separatory funnel and was extracted with pentane (2 x 10 mL). The aqueous methanol layer was then concentrated under reduced pressure maintaining an external bath temperature of 34 °C. The resulting film was diluted with CH_2Cl_2, transferred to a separatory funnel, and 2 N $NaOH_{(aq)}$ (1.2 mL) was added and the aqueous layer was extracted with the CH_2Cl_2 (3 x 10 mL). 1 N $HCl_{(aq.)}$ was added to the aqueous layer until the pH of the solution was 6. CH_2Cl_2 was then added to the seperatory funnel and the desired *N*-(2-Pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic anhydride was extracted into the organic layer (3 x 10 mL of CH_2Cl_2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by reverse phase

HPFC (30:70:0.1 CH_3CN:H_2O:formic acid-80:20:0.1), and the desired fractions were concentrated to remove the acetonitrile. Water was removed by lyophilization to provide the desired product as a white solid (93.4 mg, 0.243 mmol, 41% over four steps). ^{1}H NMR (400 MHz, 4:1 CD_3CN:D_2O): δ 0.78 (m, 6H), 1.23 (m, 1H), 1.32-1.40 (m, 2H), 2.91 (m, 1H), 3.06 (m, 1H), 3.19 (m, 1H), 4.78 (m, 1H), 7.20 (m, 5H), 8.62 (s, 1H), 8.73 (s, 1H), 9.10 (s, 1H). ^{13}C NMR (100 MHz, 4:1 CD_3CN:D_2O): δ 22.0, 23.6, 26.0, 38.6, 40.3, 40.3 (br), 54.9, 127.9, 129.5, 130.4, 137.7, 144.5, 144.7, 145.1, 148.7, 164.5, 172.5. IR (neat): 3338, 1633, 1525, 1378, 1245, 1020 cm^{-1}**.** Anal. Calcd for $C_{19}H_{25}BN_4O_4$: C, 59.39; H, 6.56; N, 14.58. Found: C, 59.49; H, 6.27; N, 14.30.



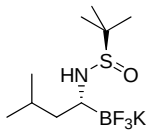
Pinacol *(R)*-1-*N*-sulfinyl-*N*-methyl 3-methylbutane-1-boronate (3.18). A flame-dried round bottom flask equipped with a stir bar was charged with amine **3.12a** (0.26g, 0.83 mmol, 1.0 equiv) and 8.5 mL of THF. The mixture was cooled to 0 °C and KH (0.08g, 2.1 mmol, 2.5 equiv) was added in one portion. The heterogenous mixture was stirred at 0 °C for 20 to 30 min before addition of MeI (0.20 mL, 4.2 mmol, 5.0 equiv). The reaction mixture was allowed to warm to rt and was stirred at that temperature for 12 h. The reaction mixture was diluted with EtOAc and washed with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on

deactivated silica gel (containing 35% water w/w), eluting with (3% EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.16 g, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 3.3 Hz, 3H), 0.93 (d, *J* = 3.3 Hz, 3H), 1.16 (s, 9H), 1.25 (s, 12H), 1.40 (m, 1H), 1.54 (m, 2H), 2.56 (s, 3H), 3.02 (app. t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.9, 23.5, 24.7, 24.8, 27.7, 37.7, C-B not observed, 58.5, 83.6. Exact mass calcd for $C_{16}H_{34}BNO_3S$ requires m/z 332.2431, found m/z 332.2437 (MH^+, FAB).



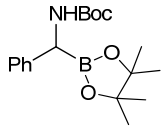
Pinacol *(R)*-1-*N*-sulfinyl-*N*-methyl 3-methylpentane-2-boronate (3.19). An oven-dried vial with a Teflon coated screw cap equipped with a stir bar was charged with amine **3.18** (0.05g, 0.15 mmol, 1.0 equiv) and 0.8 mL of THF. The mixture was cooled to -78 °C. Iodochloromethane (0.07 mL, 0.96 mmol, 6.4 equiv) was added, and the resulting reaction mixture was stirred at -78 °C for 10 min. *n*BuLi (0.6 mL, 0.84 mmol, 5.6 equiv) was added dropwise slowly over 50 min. The reaction mixture was allowed to warm to rt slowly in the dry ice/acetone bath. The reaction mixture was concentrated and then diluted with EtOAc. The organic layer was then washed with 1 N NH_4Cl (5 mL), and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (3% EtOAc: CH_2Cl_2) to afford **3.19** as a white solid (7.6 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d,

J = 6.6 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 1.12 (m, 2H), 1.17 (s, 9H), 1.23 (s, 6H), 1.24 (s, 6H), 1.53 (m, 1H), 1.70 (m, 2H), 2.45 (s, 3H), 3.50 (m, 1H). Exact mass calcd for $C_{17}H_{36}BNO_3S$ requires m/z 346.2587, found m/z 346.2594 (MH^+, FAB)



Potassium *(R)*-1-*N*-sulfinyl-3-methylbutane-1-trifluoroborate (3.20). The procedure was adapted according to a protocol developed by Molander and Ito.[42] To a precooled mixture of compound **3.12a** (0.152 g, 0.480 mmol, 1.0 equiv) in 1.0 mL Et_2O at 0 °C was added KHF_2 (0.231 g, 2.96 mmol, 6.2 equiv) in one portion followed by the dropwise addition of 0.6 mL of water. The ice bath was removed and the reaction mixture was stirred for 4 h. The liquid was decanted from the resulting suspension, acetone was added to the reaction flask, and the liquid was poured off (2 x 10 mL) and combined. The acetone solution was concentrated under reduced pressure to yield a mixture of potassium trifluoroborate salt and pinacol. The crude product was rinsed with pentane and heated at 60 °C under vacuum to remove most of the pinacol byproduct. The crude product was then precipitated from pentane followed by a subsequent precipitation with 90:10 pentane:Et_2O to afford **3.20** as a white solid (0.041 g, 29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 1.15 (s, 9H), 1.54 (m, 1H), 1.72 (m, 1H), 2.44 (br m, 1 H), 3.01 (br, 1H), 3.93 (d, J = 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 22.9, 23.8, 24.4, C-B not observed, 39.3, 55.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ -145.3 IR (neat): 3315, 2981,

2953, 1475, 1364, 1092, 928, 742, 602. Exact mass calcd for $C_9H_{20}BF_3KNOS$ requires m/z 336.0579, found m/z 336.0587 ($M+K^+$, ESI).



Pinacol *N*-Boc-Phenyl-1-Boronate 3.22. The reaction was performed in a glovebox. CuCl (3.0 mg, 0.03 mmol, 3 mol%), NaO*t*Bu (8.8 mg, 0.09 mmol, 9 mol%), and DPEPhos (16.4 mg, 0.03 mmol, 3 mol%) were placed into a scintillation vial containing a stir bar, and 0.8 mL of THF was added. The reaction mixture was stirred for 30 min at room temperature, and then a solution of bis(pinacolato)diboron (0.280 g, 1.1 mmol, 1.1 equiv) in 0.6 mL of THF was added. The reaction mixture was stirred for an additional 5 min, and then a solution of imine **3.21** (prepared from the α-amido sulfone precursor according to literature procedure,[43] 0.202 g, 0.984 mmol. 1.0 equiv) in 0.6 mL of THF was added followed by the addition of MeOH (0.080 mL, 1.97 mmol, 2.0 equiv). The reaction mixture was stirred for 48 h. The reaction mixture was removed from the glovebox and diluted with EtOAc (10 mL). The organic layer was washed with 1 N $NaHCO_3$ (10 mL) and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layer was then washed with brine (10 mL), and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on deactivated silica gel (containing 35% water w/w), eluting with (10-25% EtOAc: CH_2Cl_2). Mixed fractions were combined and purified by a second column (containing 35% water w/w), eluting with (20%

EtOAc: CH_2Cl_2) to yield the desired product as a white solid (0.135 g, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 6H), 1.19 (s, 6H), 1.45 (s, 9H), 4.20 (d, J = 4.7 Hz, 1H), 5.22 (br, 1H), 7.15-7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 28.3, 44.3, 80.2, 83.6, 126.1, 126.5, 128.3, 140.3, 157.1. Exact mass calcd for $C_{18}H_{28}BNO_4$ requires m/z 334.2173, found m/z 334.2184 (MH^+, ESI).

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Appendix 3.1: X-Ray Crystal Data for **3.12d**

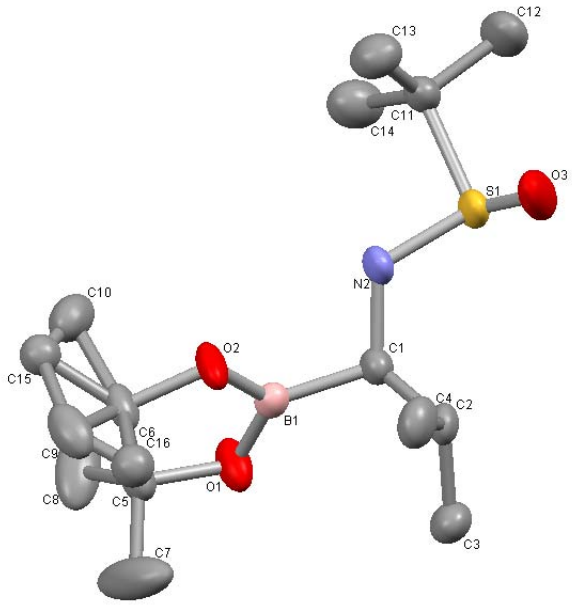


Figure A3.1. Ortep Diagram of **3.12d**. Hydrogen atoms have been omitted for clarity.

Table A3.1. Crystal and data collection parameters for **3.12d**

A. Crystal Data

Empirical Formula	$C_{14}SO_3NH_{30}B$
Formula Weight	303.27
Crystal Color, Habit	Colorless, tabular
Crystal Dimensions	0.10 X 0.22 X 0.39 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 15.674(1)Å
	b = 17.967(1) Å
	c = 6.3228(4) Å
	V = 1780.5(5) $Å^3$
Space Group	$P2_12_12$ (#18)
Z value	4
Dcalc	1.131 g/cm^3
F_{000}	664.00
μ(MoKα)	1.88 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker APEX CCD
Radiation	MoKα (λ= 0.71069Å)

	graphite monochromated
Detector Position	60.00 mm
Exposure Time	1.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
2_max	52.8°
No. of Reflections Measured	Total: 10144
	Unique: 3648 (R_{int} = 0.023)
	Corrections Lorentz-polarization
	Absorption (T_{max} = 1.00 T_{min} = 0.85)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ \omega\ (|Fo| - |Fc|)^2$
Least Squares Weights	$\omega = 1/\sigma^2(Fo) = [\sigma_c^2(F_o) + p^2/4\ F_o^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00_(I))	3001
No. Variables	190
Reflection/Parameter Ratio	15.79
Residuals: R; Rw; Rall	0.043 ; 0.051; 0.052
Goodness of Fit Indicator	2.03
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.25 e–/ Å^3
Minimum peak in Final Diff. Map	-0.21 e–/ Å^3

Table A3.2. Positional parameters and B(eq) for **3.12d** at -95 °C

atom	x	y	z	B(eq)
S1	0.66019(4)	-0.18315(3)	0.1354(1)	3.67(1)
O1	0.7797(1)	-0.01410(8)	0.7091(3)	3.71(4)
O2	0.7765(1)	0.03216(8)	0.3795(3)	3.92(4)
O3	0.7068(1)	-0.2138(1)	-0.0505(4)	5.72(5)
N2	0.7029(1)	-0.10425(9)	0.2208(4)	3.41(5)
C1	0.7608(1)	-0.1101(1)	0.4065(4)	2.59(5)
C2	0.8464(1)	-0.1495(1)	0.3567(4)	2.83(5)
C3	0.8945(2)	-0.1657(1)	0.5606(4)	3.67(6)
C4	0.9008(2)	-0.1063(1)	0.2008(4)	3.92(6)
C5	0.7940(2)	0.0655(1)	0.7362(4)	2.83(5)
C6	0.7835(2)	0.0970(1)	0.5095(3)	2.93(5)
C7	0.8820(2)	0.0739(2)	0.8232(7)	8.2(1)
C8	0.7290(3)	0.0936(2)	0.8892(5)	6.21(9)
C9	0.8425(3)	0.1553(2)	0.4329(6)	4.2(1)

C10	0.6878(3)	0.1280(3)	0.4789(7)	4.4(1)
C11	0.5594(1)	-0.1459(1)	0.0290(4)	3.00(5)
C12	0.5129(2)	-0.2141(2)	-0.0562(6)	5.32(8)
C13	0.5758(2)	-0.0902(2)	-0.1431(5)	4.33(6)
C14	0.5099(2)	-0.1130(2)	0.2106(5)	5.07(8)
C15	0.7367(5)	0.1619(4)	0.471(1)	3.0(2)
C16	0.8844(5)	0.1102(5)	0.428(1)	3.3(2)
B1	0.7727(2)	-0.0289(1)	0.5011(4)	2.36(5)
H1	0.7324	-0.1390	0.5105	3.0824
H2	0.8332	-0.1960	0.2934	3.3923
H3	0.8611	-0.1971	0.6483	4.3903
H4	0.9470	0.1899	0.5281	4.3903
H5	0.9061	-0.1204	0.6324	4.3903
H6	0.9501	-0.1345	0.1658	4.7104
H7	0.8687	-0.0971	0.0755	4.7104
H8	0.9175	-0.0603	0.2617	4.7104
H9	0.8873	0.0481	0.9534	9.8258
H10	0.9225	0.0528	0.7245	9.8258
H11	0.8956	0.1248	0.8424	9.8258
H12	0.7372	0.1454	0.9103	7.4262
H13	0.6736	0.0849	0.8344	7.4262
H14	0.7354	0.0682	1.0201	7.4262
H15	0.8989	0.1353	0.4262	4.4453
H16	0.8258	0.1713	0.2965	4.4453
H17	0.8420	0.1961	0.5280	4.4453
H18	0.6821	0.1728	0.5573	4.5258
H19	0.6787	0.1379	0.3331	4.5258
H20	0.6488	0.0922	0.5276	4.5258
H21	0.4574	-0.2002	-0.1017	6.3959
H22	0.5438	-0.2340	-0.1727	6.3959
H23	0.5087	-0.2505	0.0519	6.3959
H24	0.6099	-0.0508	-0.0891	5.1829
H25	0.6054	-0.1138	-0.2565	5.1829
H26	0.5233	-0.0709	-0.1932	5.1829
H27	0.5375	-0.0694	0.2604	6.0652
H28	0.4536	-0.1007	0.1649	6.0652
H29	0.5062	-0.1484	0.3225	6.0652
H30	0.7236	-0.0660	0.1159	5.4263
H31	0.7674	0.1846	0.3198	5.4263
H32	0.7702	0.2055	0.5457	5.4263
H33	0.6915	0.1774	0.4902	5.4263
H34	0.8731	0.1301	0.2915	5.4263
H35	0.8946	0.1564	0.4964	5.4263
H36	0.9178	0.0666	0.4437	5.4263

Table A3.3. Intramolecular Bond Angles (°) Involving the non-H Atoms in in **3.12d**

atom	atom	atom	angle	atom	atom	atom	angle
O3	S1	N2	112.0(1)	C5	C6	C15	121.4(4)
O3	S1	C11	105.4(1)	C5	C6	C16	103.5(3)
N2	S1	C11	98.9(1)	C9	C6	C10	107.3(3)
C5	O1	B1	108.7(2)	C9	C6	C15	71.3(4)
C6	O2	B1	109.9(2)	C9	C6	C16	37.9(3)
S1	N2	C1	116.3(1)	C10	C6	C15	37.2(3)
N2	C1	C2	113.6(2)	C10	C6	C16	142.2(3)
N2	C1	B1	107.7(2)	C15	C6	C16	108.8(4)
C2	C1	B1	113.3(2)	C6	C9	C15	52.1(3)
C1	C2	C3	110.1(2)	C6	C9	C16	81.6(5)
C1	C2	C4	112.6(2)	C15	C9	C16	132.9(6)
C3	C2	C4	111.7(2)	C6	C10	C15	59.5(5)
O1	C5	C6	103.4(2)	S1	C11	C12	104.3(2)
O1	C5	C7	106.5(2)	S1	C11	C13	111.1(2)
O1	C5	C8	107.6(2)	S1	C11	C14	107.8(2)
C6	C5	C7	113.8(2)	C12	C11	C13	111.2(2)
C6	C5	C8	113.8(2)	C12	C11	C14	109.8(2)
C7	C5	C8	111.0(3)	C13	C11	C14	112.3(2)
O2	C6	C5	104.1(2)	C6	C15	C9	56.5(3)
O2	C6	C9	115.8(2)	C6	C15	C10	83.3(6)
O2	C6	C10	98.2(2)	C9	C15	C10	137.3(7)
O2	C6	C15	122.6(4)	C6	C16	C9	60.5(4)
O2	C6	C16	90.6(3)	O1	B1	O2	113.3(2)
C5	C6	C9	119.6(3)	O1	B1	C1	123.9(2)
C5	C6	C10	109.7(2)	O2	B1	C1	122.8(2)

Table A3.4. Intramolecular Bond Angles (°) Involving the H-Atoms in in **3.12d**

atom	atom	atom	angle	atom	atom	atom	angle
S1	N2	H30	119.86	C5	C8	H12	109.27
C1	N2	H30	111.81	C5	C8	H13	109.45
N2	C1	H1	107.36	C5	C8	H14	109.28
C2	C1	H1	107.33	H12	C8	H13	109.67
B1	C1	H1	107.29	H12	C8	H14	109.51
C1	C2	H2	107.39	H13	C8	H14	109.64
C3	C2	H2	107.30	C6	C9	H15	109.14
C4	C2	H2	107.41	C6	C9	H16	109.92
C2	C3	H3	109.67	C6	C9	H17	109.62

C2	C3	H4	109.39	C6	C9	H34	104.26
C2	C3	H5	109.59	C6	C9	H35	115.66
H3	C3	H4	109.36	C15	C9	H15	161.27
H3	C3	H5	109.62	C15	C9	H16	80.53
H4	C3	H5	109.19	C15	C9	H17	81.17
C2	C4	H6	109.64	C15	C9	H34	124.78
C2	C4	H7	109.47	C15	C9	H35	145.21
C2	C4	H8	109.75	C16	C9	H15	28.88
H6	C4	H7	109.19	C16	C9	H16	112.54
H6	C4	H8	109.47	C16	C9	H17	128.66
H7	C4	H8	109.30	C16	C9	H34	52.32
C5	C7	H9	110.59	C16	C9	H35	57.69
C5	C7	H10	109.26	H15	C9	H16	109.26
C5	C7	H11	110.61	H15	C9	H17	109.03
H9	C7	H10	108.17	H15	C9	H34	53.97
H9	C7	H11	109.87	H15	C9	H35	36.60
H10	C7	H11	108.26	H16	C9	H17	109.85
H16	C9	H34	60.60	C11	C13	H25	109.45
H16	C9	H35	130.03	C11	C13	H26	109.68
H17	C9	H34	145.86	H24	C13	H25	109.15
H17	C9	H35	73.19	H24	C13	H26	109.61
H34	C9	H35	88.64	H25	C13	H26	109.45
C6	C10	H18	108.53	C11	C14	H27	110.01
C6	C10	H19	108.68	C11	C14	H28	109.64
C6	C10	H20	109.21	C11	C14	H29	109.61
C6	C10	H33	105.81	H27	C14	H28	109.26
C15	C10	H18	64.79	H27	C14	H29	109.38
C15	C10	H19	87.18	H28	C14	H29	108.92
C15	C10	H20	161.99	C6	C15	H18	119.94
C15	C10	H33	48.28	C6	C15	H31	102.85
H18	C10	H19	109.55	C6	C15	H32	106.25
H18	C10	H20	110.36	C6	C15	H33	138.96
H18	C10	H33	28.52	C9	C15	H18	154.96
H19	C10	H20	110.46	C9	C15	H31	59.41
H19	C10	H33	84.38	C9	C15	H32	68.01
H20	C10	H33	134.27	C9	C15	H33	162.88
C11	C12	H21	109.48	C10	C15	H18	56.15
C11	C12	H22	109.42	C10	C15	H31	126.35
C11	C12	H23	109.45	C10	C15	H32	145.79
H21	C12	H22	109.33	C10	C15	H33	59.79
H21	C12	H23	109.69	H18	C15	H31	136.18
H22	C12	H23	109.45	H18	C15	H32	91.96
C11	C13	H24	109.49	H18	C15	H33	24.10

H31	C15	H32	84.33
H31	C15	H33	112.99
H32	C15	H33	96.82
C6	C16	H15	123.85
C6	C16	H34	98.96
C6	C16	H35	98.18
C6	C16	H36	111.83
C9	C16	H15	65.90
C9	C16	H34	67.45
C9	C16	H35	54.10
C9	C16	H36	170.68
H15	C16	H34	74.13
H15	C16	H35	32.23
H15	C16	H36	119.41
H34	C16	H35	96.55
H34	C16	H36	120.65
H35	C16	H36	125.62

Table A3.5. Intramolecular Distances Involving Non-H Atoms (Å) in **3.12d**

atom	atom	distance	atom	atom	distance
S1	O3	1.490(2)	C5	C7	1.492(4)
S1	N2	1.658(2)	C5	C8	1.493(4)
S1	C11	1.843(2)	C6	C9	1.479(5)
O1	C5	1.459(3)	C6	C10	1.612(5)
O1	B1	1.346(3)	C6	C15	1.399(7)
O2	C6	1.430(3)	C6	C16	1.681(8)
O2	B1	1.341(3)	C9	C15	1.679(9)
N2	C1	1.488(3)	C9	C16	1.044(8)
C1	C2	1.549(3)	C10	C15	0.981(8)
C1	B1	1.588(3)	C11	C12	1.523(3)
C2	C3	1.522(3)	C11	C13	1.500(4)
C2	C4	1.517(4)	C11	C14	1.507(4)
C5	C6	1.550(3)			

Table A3.6. Intramolecular Distances Involving the H Atoms (Å) for **3.12d**

atom	atom	distance	atom	atom	distance
N2	H30	1.008	C10	H19	0.949
C1	H1	0.949	C10	H20	0.940
C2	H2	0.949	C10	H33	0.892
C3	H3	0.948	C12	H21	0.949
C3	H4	0.953	C12	H22	0.952
C3	H5	0.950	C12	H23	0.948
C4	H6	0.951	C13	H24	0.951
C4	H7	0.953	C13	H25	0.953
C4	H8	0.949	C13	H26	0.948
C7	H9	0.948	C14	H27	0.949
C7	H10	0.967	C14	H28	0.954
C7	H11	0.947	C14	H29	0.953
C8	H12	0.950	C15	H18	1.035
C8	H13	0.948	C15	H31	1.145
C8	H14	0.950	C15	H32	1.055
C9	H15	0.956	C15	H33	0.770
C9	H16	0.947	C16	H15	0.506
C9	H17	0.949	C16	H34	0.952
C9	H34	1.110	C16	H35	0.950
C9	H35	0.911	C16	H36	0.947
C10	H18	0.950			

Table A3.7. Torsion or Conformational Angles (°) for **3.12d**

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
S1	N2	C1	C2	69.8(2)	N2	S1	C11	C13	60.1(2)
S1	N2	C1	B1	164.0(2)	N2	S1	C11	C14	-63.3(2)
O1	C5	C6	O2	-7.7(2)	N2	C1	C2	C3	169.8(2)
O1	C5	C6	C9	139.0(3)	N2	C1	C2	C4	64.8(2)
O1	C5	C6	C10	96.5(3)	C1	N2	S1	C11	150.1(2)
O1	C5	C6	C15	135.8(4)	C1	B1	O1	C5	177.2(2)
O1	C5	C6	C16	101.8(4)	C1	B1	O2	C6	177.4(2)
O1	B1	O2	C6	-2.5(3)	C3	C2	C1	B1	67.0(2)
O1	B1	C1	N2	143.7(2)	C4	C2	C1	B1	-58.4(3)
O1	B1	C1	C2	-89.8(3)	C5	C6	O2	B1	6.4(3)
O2	C6	C5	C7	107.4(3)	C5	C6	C9	C15	116.2(4)
O2	C6	C5	C8	124.1(2)	C5	C6	C9	C16	73.1(5)
O2	C6	C9	C15	117.9(4)	C5	C6	C10	C15	116.4(6)
O2	C6	C9	C16	-52.8(5)	C5	C6	C15	C9	113.9(3)

O2	C6	C10	C15	135.4(6)	C5	C6	C15	C10	-81.2(6)
O2	C6	C15	C9	109.3(3)	C5	C6	C16	C9	121.2(4)
O2	C6	C15	C10	55.6(7)	C6	C5	O1	B1	6.6(3)
O2	C6	C16	C9	134.2(4)	C6	C9	C15	C10	-22.4(9)
O2	B1	O1	C5	-3.0(3)	C6	C10	C15	C9	18.7(7)
O2	B1	C1	N2	-36.1(3)	C6	C15	C9	C16	12.5(8)
O2	B1	C1	C2	90.3(3)	C6	C16	C9	C15	-10.0(6)
O3	S1	N2	C1	-99.1(2)	C7	C5	O1	B1	113.6(3)
O3	S1	C11	C12	64.1(2)	C7	C5	C6	C9	-23.9(4)
O3	S1	C11	C13	-55.8(2)	C7	C5	C6	C10	148.4(3)
O3	S1	C11	C14	179.2(2)	C7	C5	C6	C15	109.0(5)
N2	S1	C11	C12	180.0(2)	C7	C5	C6	C16	13.3(4)
C8	C5	O1	B1	127.3(2)					
C8	C5	C6	C9	104.6(4)					
C8	C5	C6	C10	-19.9(3)					
C8	C5	C6	C15	19.4(5)					
C8	C5	C6	C16	141.8(4)					
C9	C6	O2	B1	139.9(3)					
C9	C6	C10	C15	-15.0(6)					
C9	C6	C15	C10	164.9(6)					
C9	C15	C6	C10	-164.9(6)					
C9	C15	C6	C16	-6.0(4)					
C9	C16	C6	C10	30.0(8)					
C9	C16	C6	C15	9.2(6)					
C10	C6	O2	B1	-106.3(2)					
C10	C6	C9	C15	9.5(4)					
C10	C6	C9	C16	-161.3(5)					
C10	C15	C6	C16	158.9(5)					
C10	C15	C9	C16	-10(1)					
C15	C6	O2	B1	-136.6(4)					
C15	C6	C9	C16	-170.8(6)					
C15	C9	C6	C16	170.8(6)					
C15	C10	C6	C16	-33.8(8)					
C16	C6	O2	B1	110.5(3)					

Table A3.8. Anisotropic Displacement Parameters for **3.12d** at -95 °C

atom	U11	U22	U33	U12	U13	U23
S1	0.0493(3)	0.0211(2)	0.0689(4)	-0.0002(3)	-0.0240(3)	-0.0079(3)
O1	0.083(1)	0.0267(8)	0.0311(9)	-0.0100(9)	0.0032(9)	0.0006(7)
O2	0.094(1)	0.0232(7)	0.0317(8)	-0.0001(8)	-0.0162(10)	-0.0064(8)
O3	0.059(1)	0.057(1)	0.102(2)	0.020(1)	-0.021(1)	-0.047(1)
N2	0.048(1)	0.0212(9)	0.060(1)	-0.0024(9)	-0.020(1)	-0.0083(9)

C1	0.038(1)	0.025(1)	0.036(1)	-0.0010(9)	-0.0062(10)	-0.0016(10)
C2	0.046(1)	0.0217(10)	0.040(1)	0.0048(10)	-0.003(1)	-0.0036(10)
C3	0.049(1)	0.039(1)	0.052(2)	0.007(1)	-0.010(1)	0.003(1)
C4	0.057(2)	0.041(1)	0.052(2)	0.013(1)	0.008(1)	-0.002(1)
C5	0.048(1)	0.024(1)	0.036(1)	-0.005(1)	-0.007(1)	-0.0002(9)
C6	0.061(1)	0.026(1)	0.025(1)	-0.007(1)	0.004(1)	-0.0058(10)
C7	0.090(2)	0.077(2)	0.144(4)	-0.041(2)	-0.071(3)	0.067(3)
C8	0.146(3)	0.051(2)	0.039(2)	0.019(2)	0.039(2)	0.009(2)
C9	0.084(3)	0.041(2)	0.034(2)	-0.021(2)	0.005(2)	0.002(2)
C10	0.064(3)	0.054(3)	0.048(3)	0.020(2)	-0.004(2)	-0.003(2)
C11	0.035(1)	0.030(1)	0.049(1)	-0.0029(10)	-0.011(1)	-0.004(1)
C12	0.056(2)	0.046(2)	0.100(3)	-0.008(1)	-0.029(2)	-0.008(2)
C13	0.050(2)	0.056(2)	0.058(2)	0.001(1)	-0.007(1)	0.011(2)
C14	0.051(2)	0.079(2)	0.063(2)	0.003(2)	-0.003(1)	-0.005(2)
B1	0.026(1)	0.026(1)	0.038(2)	-0.000(1)	-0.002(1)	0.001(1)

Table A3.9. Positional parameters for**3.12d** at -95 °C

atom	x	y	z
S1	0.66019(4)	-0.18315(3)	0.1354(1)
O1	0.7797(1)	-0.01410(8)	0.7091(3)
O2	0.7765(1)	0.03216(8)	0.3795(3)
O3	0.7068(1)	-0.2138(1)	-0.0505(4)
N2	0.7029(1)	-0.10425(9)	0.2208(4)
C1	0.7608(1)	-0.1101(1)	0.4065(4)
C2	0.8464(1)	-0.1495(1)	0.3567(4)
C3	0.8945(2)	-0.1657(1)	0.5606(4)
C4	0.9008(2)	-0.1063(1)	0.2008(4)
C5	0.7940(2)	0.0655(1)	0.7362(4)
C6	0.7835(2)	0.0970(1)	0.5095(3)
C7	0.8820(2)	0.0739(2)	0.8232(7)
C8	0.7290(3)	0.0936(2)	0.8892(5)
C9	0.8425(3)	0.1553(2)	0.4329(6)
C10	0.6878(3)	0.1280(3)	0.4789(7)
C11	0.5594(1)	-0.1459(1)	0.0290(4)
C12	0.5129(2)	-0.2141(2)	-0.0562(6)
C13	0.5758(2)	-0.0902(2)	-0.1431(5)
C14	0.5099(2)	-0.1130(2)	0.2106(5)
C15	0.7367(5)	0.1619(4)	0.471(1)
C16	0.8844(5)	0.1102(5)	0.428(1)
B1	0.7727(2)	-0.0289(1)	0.5011(4)
H1	0.7324	-0.139	0.5105
H2	0.8332	-0.196	0.2934
H3	0.8611	-0.1971	0.6483

H4	0.947	-0.1899	0.5281
H5	0.9061	-0.1204	0.6324
H6	0.9501	-0.1345	0.1658
H7	0.8687	-0.0971	0.0755
H8	0.9175	-0.0603	0.2617
H9	0.8873	0.0481	0.9534
H10	0.9225	0.0528	0.7245
H11	0.8956	0.1248	0.8424
H12	0.7372	0.1454	0.9103
H13	0.6736	0.0849	0.8344
H14	0.7354	0.0682	1.0201
H15	0.8989	0.1353	0.4262
H16	0.8258	0.1713	0.2965
H17	0.842	0.1961	0.528
H18	0.6821	0.1728	0.5573
H19	0.6787	0.1379	0.3331
H20	0.6488	0.0922	0.5276
H21	0.4574	-0.2002	-0.1017
H22	0.5438	-0.234	-0.1727
H23	0.5087	-0.2505	0.0519
H24	0.6099	-0.0508	-0.0891
H25	0.6054	-0.1138	-0.2565
H26	0.5233	-0.0709	-0.1932
H27	0.5375	-0.0694	0.2604
H28	0.4536	-0.1007	0.1649
H29	0.5062	-0.1484	0.3225
H30	0.7236	-0.066	0.1159
H31	0.7674	0.1846	0.3198
H32	0.7702	0.2055	0.5457
H33	0.6915	0.1774	0.4902
H34	0.8731	0.1301	0.2915
H35	0.8946	0.1564	0.4964
H36	0.9178	0.0666	0.4437

Table A3.10. Intermolecular Distances Involving the Non-H Atoms in **3.12d**

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O1	C13	3.599(3)	55601	C3	C16	3.703(8)	75502
O2	C8	3.374(4)	55401	C3	C15	3.723(7)	64604
O3	C9	3.461(5)	64504	C4	C16	3.662(8)	75502
O3	C15	3.583(8)	64504	C10	C14	3.542(6)	65502
O3	C8	3.746(4)	64604				

Table A3.11. Intermolecular Distances Involving the H Atoms in **3.12d**

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
S1	H17	3.039	64604	C1	H32	3.363	64604
S1	H32	3.043	64604	C2	H32	3.242	64604
S1	H12	3.486	64604	C2	H18	3.268	64604
S1	H11	3.563	64604	C2	H33	3.311	64604
O1	H30	2.874	55601	C2	H21	3.594	54503
O1	H24	3.023	55601	C3	H33	3.141	64604
O1	H7	3.088	55601	C3	H18	3.226	64604
O1	H25	3.274	55601	C3	H35	3.335	75502
O2	H14	2.449	55401	C3	H23	3.387	54603
O2	H9	3.218	55401	C3	H15	3.392	75502
O2	H12	3.65	55401	C3	H7	3.505	55601
O3	H31	2.529	64504	C3	H36	3.518	75502
O3	H16	2.635	64504	C3	H32	3.531	64604
O3	H12	2.82	64604	C3	H10	3.663	75502
O3	H3	3.094	55401	C4	H9	3.192	55401
O3	H1	3.11	55401	C4	H36	3.31	75502
O3	H34	3.428	64504	C4	H23	3.469	54503
O3	H32	3.469	64504	C4	H15	3.487	75502
O3	H17	3.509	64504	C4	H5	3.604	55401
O3	H32	3.525	64604	C4	H34	3.616	75502
O3	H11	3.567	64604	C4	H21	3.643	54503
O3	H19	3.677	64504	C4	H22	3.645	54503
N2	H14	3.387	55401	C5	H30	3.546	55601
N2	H25	3.646	55601	C5	H24	3.73	55601
N2	H32	3.748	64604	C6	H14	3.227	55401
C1	H25	3.238	55601	C7	H34	3.132	55601
C7	H7	3.467	55601	C10	H21	3.727	65602
C7	H16	3.577	55601	C12	H6	2.975	44503
C7	H6	3.578	75602	C12	H11	3.502	64604
C7	H5	3.631	75502	C12	H2	3.577	44503
C7	H23	3.677	65604	C12	H4	3.598	44503
C7	H8	3.715	55601	C12	H16	3.599	64504
C8	H19	3.022	55601	C12	H34	3.639	64504
C8	H24	3.199	55601	C13	H26	3.302	65502
C8	H30	3.208	55601	C13	H1	3.404	55401
C8	H31	3.232	55601	C13	H13	3.503	55401
C8	H16	3.298	55601	C13	H29	3.702	55401
C8	H28	3.354	65602	C14	H19	3.088	65502
C8	H34	3.464	55601	C14	H20	3.216	65502
C8	H21	3.494	65602	C14	H27	3.376	65502
C9	H22	3.137	65504	C14	H25	3.687	55601

C9	H4	3.411	75502	C15	H3	3.055	65604
C9	H14	3.475	55401	C15	H2	3.153	65604
C9	H9	3.659	55401	C15	H14	3.31	55401
C9	H6	3.682	75502	C15	H12	3.556	55401
C9	H12	3.697	55401	C15	H1	3.612	65604
C10	H28	3.016	65502	C15	H28	3.722	65502
C10	H14	3.182	55401	C16	H4	3.071	75502
C10	H29	3.218	65502	C16	H6	3.109	75502
C10	H3	3.333	65604	C16	H9	3.202	55401
C10	H2	3.49	65604	C16	H8	3.399	75502
C10	H12	3.691	55401	C16	H22	3.422	65504
C16	H5	3.534	75502	H3	H32	2.968	64604
C16	H14	3.56	55401	H3	H19	3.032	64604
C16	H11	3.716	55401	H3	H23	3.135	54603
B1	H25	3.399	55601	H3	H7	3.247	55601
B1	H14	3.554	55401	H3	H29	3.592	54603
B1	H24	3.658	55601	H3	H21	3.728	54603
H1	H25	2.518	55601	H3	H6	3.731	55601
H1	H32	2.817	64604	H4	H35	2.562	75502
H1	H17	3.192	64604	H4	H15	2.684	75502
H1	H31	3.347	64604	H4	H23	3.023	54603
H1	H33	3.508	64604	H4	H22	3.036	54503
H1	H24	3.551	55601	H4	H36	3.111	75502
H1	H18	3.662	64604	H4	H29	3.193	54603
H1	H16	3.734	64604	H4	H33	3.228	64604
H2	H18	2.55	64604	H4	H18	3.236	64604
H2	H32	2.606	64604	H4	H17	3.309	75502
H2	H33	2.683	64604	H4	H21	3.346	54503
H2	H21	2.956	54503	H4	H34	3.367	75502
H2	H12	3.315	64604	H4	H11	3.377	75502
H2	H17	3.545	64604	H4	H10	3.434	75502
H2	H22	3.614	54503	H5	H7	2.893	55601
H2	H31	3.616	64604	H5	H10	3.005	75502
H2	H23	3.641	54503	H5	H36	3.159	75502
H3	H33	2.556	64604	H5	H35	3.305	75502
H3	H18	2.759	64604	H5	H15	3.334	75502
H3	H31	2.936	64604	H5	H11	3.381	75502
H5	H6	3.452	55601	H9	H36	3.154	55601
H5	H23	3.458	54603	H9	H16	3.245	55601
H6	H23	2.648	54503	H9	H15	3.38	55601
H6	H22	2.782	54503	H9	H30	3.442	55601
H6	H15	2.882	75502	H10	H10	3.082	75502
H6	H34	2.884	75502	H10	H36	3.744	75502
H6	H36	2.977	75502	H11	H23	2.778	65604
H6	H21	3.001	54503	H11	H34	2.863	55601

H6	H11	3.171	75402	H11	H16	3.184	55601
H6	H35	3.232	75502	H11	H22	3.42	65604
H6	H9	3.271	75402	H11	H15	3.697	55601
H6	H16	3.668	75502	H12	H31	2.724	55601
H6	H9	3.679	55401	H12	H19	2.83	55601
H6	H10	3.731	75402	H12	H16	2.846	55601
H7	H9	2.736	55401	H12	H21	3.206	65602
H7	H10	3.59	55401	H12	H34	3.228	55601
H7	H23	3.601	54503	H12	H28	3.491	65602
H7	H14	3.648	55401	H13	H24	2.679	55601
H8	H9	2.796	55401	H13	H28	2.903	65602
H8	H36	2.829	75502	H13	H21	2.944	65602
H8	H15	3.343	75502	H13	H26	3.102	65602
H8	H8	3.373	75502	H13	H19	3.295	55601
H8	H34	3.519	75502	H13	H30	3.338	55601
H8	H9	3.634	75402	H13	H26	3.664	55601
H8	H35	3.723	75502	H14	H30	2.494	55601
H9	H34	2.606	55601	H14	H19	2.505	55601
H14	H31	2.866	55601	H22	H34	2.866	64504
H14	H16	2.913	55601	H22	H35	2.999	64504
H14	H34	2.973	55601	H22	H31	3.429	64504
H14	H24	2.986	55601	H22	H29	3.592	55401
H14	H28	3.156	65602	H23	H34	3.571	64504
H14	H20	3.512	55601	H23	H35	3.641	64604
H14	H33	3.627	55601	H24	H26	3.095	65502
H15	H22	2.981	65504	H24	H28	3.313	65502
H16	H22	2.772	65504	H25	H29	3.145	55401
H16	H23	3.683	65504	H25	H27	3.331	55401
H17	H22	3.134	65504	H26	H26	2.652	65502
H17	H23	3.668	65604	H26	H29	3.375	55401
H18	H21	3.109	65602	H26	H27	3.462	55401
H18	H29	3.332	65502	H27	H27	2.758	65502
H18	H28	3.516	65502	H27	H28	3.118	65502
H19	H28	2.425	65502	H28	H33	3.363	65502
H19	H29	2.905	65502	H29	H33	3.317	65502
H19	H27	3.634	65502	H36	H36	3.517	75502
H19	H21	3.656	65502				
H20	H28	2.804	65502				
H20	H29	2.933	65502				
H20	H26	3.246	65602				
H20	H27	3.397	65502				
H20	H21	3.468	65602				
H20	H24	3.583	55601				
H21	H33	3.504	65402				

Chapter 4. The Design, Synthesis, and Application of New Amino Acid Based *N*-*tert*-Butanesulfinyl Amide Organocatalysts

The synthesis of new N-tert-*butanesulfinyl amide organocatalysts and their application to the intermolecular aldol reaction is described. Urea organocatalysts containing an* N-*acyl* s*ulfinamide have recently been identified as potent, highly selective catalysts for the aza-Henry reaction as well as for the addition of thioacetic acid to nitroalkenes. In an effort to expand this burgeoning area of research, novel amino acid based organocatalysts were developed in which the carboxylic acid is replaced with an* N-*acyl sulfinamide moiety. A number of catalysts were prepared in one step from commercially available amino acid precursors and were tested for their activity in the intermolecular aldol reaction. Although the proline* tert-*butanesulfinyl amide catalysts performed better than the parent proline catalyst in the intermolecular aldol reaction, preliminary results indicate that the primary amine catalysts are not competitive with other amino acid derived catalysts reported in the literature. Further optimization is necessary to fully evaluate the potential for this new class of catalysts.*

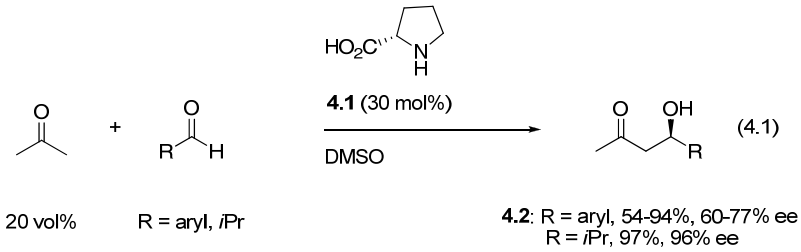
Authorship

This project was started by and conducted in collaboration with MaryAnn T. Robak. MaryAnn developed the synthesis of the proline *N-tert*-butanesulfinyl amide catalysts **4.9** and **4.21**. She also optimized the intermolecular aldol reaction between acetone and 4-nitrobenzaldehyde employing catalyst **4.9**. In collaboration, we prepared the panel of primary amine *N-tert*-butanesulfinyl amide catalysts **4.23a-h**. After preparation of a number of novel organocatalysts, my role in the project was to test these catalysts in the intermolecular aldol reaction using hydroxyacetone as a nucleophile.

Introduction

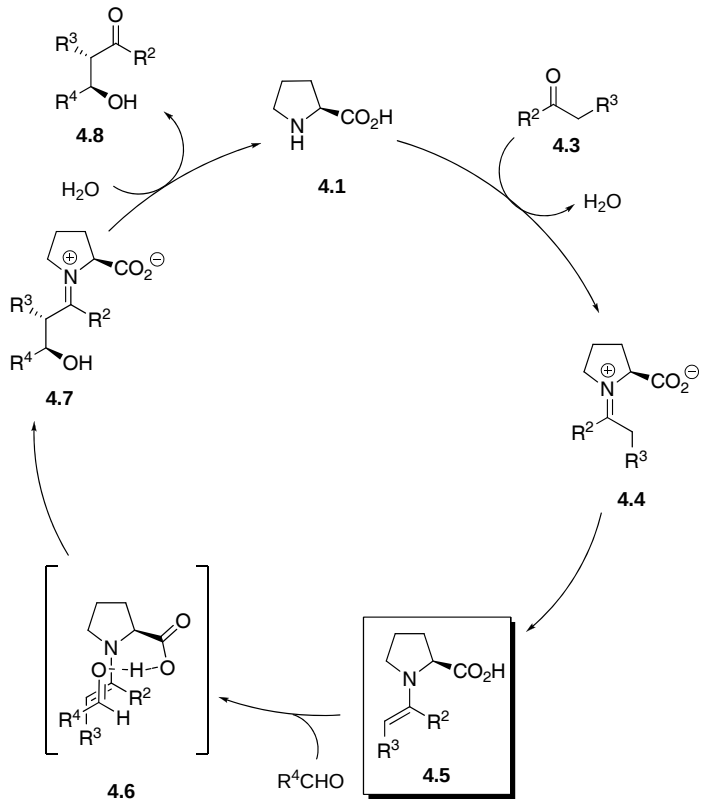
The field of enantioselective organocatalysis, particularly enamine catalysis utilizing amino-acid based catalysts, has been widely developed in the past decade.[1-3] Within this area of research, proline-catalyzed reactions have been extensively studied. Although an enantioselective proline-catalyzed intramolecular aldol reaction was initially disclosed in the 1970s by two industrial groups (the Hajos-Parrish-Eder-Sauer-Wiechert reaction),[4] this chemistry did not receive widespread attention until 2000 when List, Lerner, and Barbas reported an enantioselective intermolecular aldol reaction catalyzed by proline (**4.1**, eq 4.1).[5] The moderate enantioselectivities obtained with aryl aldehyde substrates (**4.2**, see eq 4.1) in the proline-catalyzed intermolecular aldol reaction has lead many researchers to study modified proline scaffolds in an effort to improve the stereocontrol in this reaction.[1] Additionally, primary amines

have been recently investigated and established as effective asymmetric organocatalysts.[2]



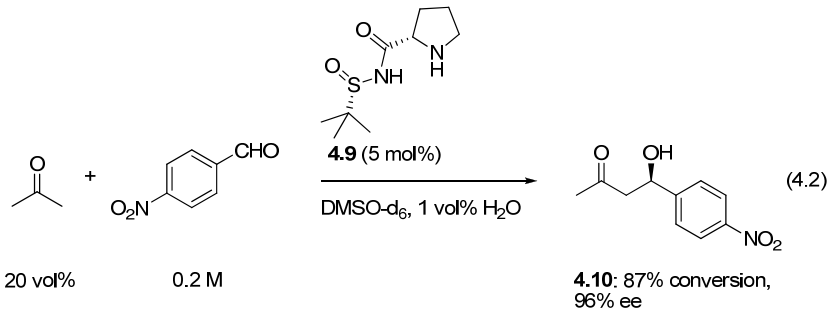
The proposed catalytic cycle for the proline-catalyzed aldol reaction (Scheme 4.1) involves condensation of the secondary amine with a ketone to form an iminium intermediate **4.4**, which is in equilibrium with the enamine **4.5**. Hydrogen bonding between the carboxylic acid hydrogen and the carbonyl oxygen of the aldehyde acceptor serves to activate the aldehyde as well as control the facial selectivity in the subsequnt stereodefining attack of the enamine on the aldehyde (**4.6**). Hydrolysis of the resulting imminium **4.7** provides the β-hydroxy ketone **4.8** and closes the catalytic cycle.

Scheme 4.1. Proposed Catalytic Cycle for Proline-Catalyzed Aldol Reaction



Recently, *N*-sulfinyl hydrogen-bonding urea organocatalysts, where the sulfinyl moiety in the catalyst scaffold serves as both an acidifying element and a chiral directing group, have been applied to the aza-Henry reaction[6] and the enantioselective addition of thioacetic acid to nitroalkenes.[7] Based on the success observed within this class of organocatalysis, it was envisioned that catalyst of structure **4.9** (eq 4.2), in which the carboxylic acid is replaced with an *N*-acyl sulfinamide moiety, could be applied as an amino acid derived organocatalyst. Based upon the measured pka of an *N*- *tert*-butanesulfinyl urea N-H as reported by Robak, Trincado, and Ellman in their seminal study on *N*-*tert*-butanesulfinyl urea organocatalysts,[6] we reasoned that *N*-acyl

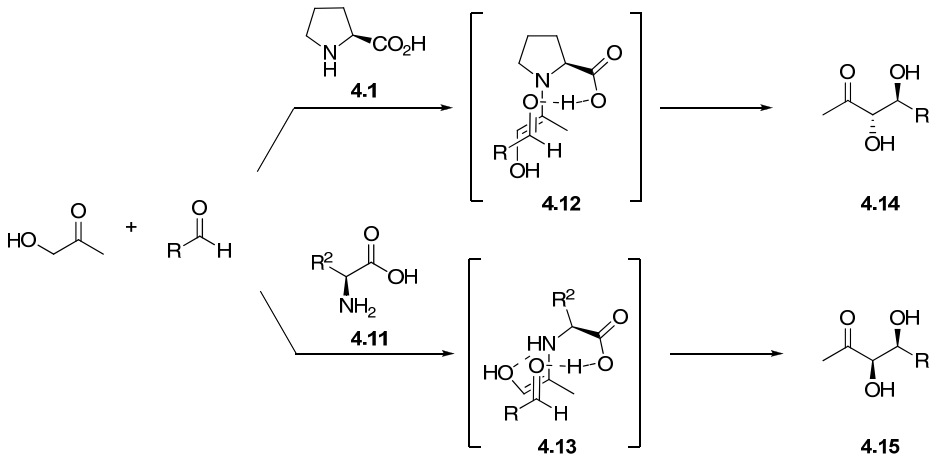
tert-butanesulfinamides could function as chiral carboxylic acid equivalents. In this scenario, the sulfinyl group serves both to add an element of chirality to the catalyst structure and to acidify the amide N-H bond, making it a stronger hydrogen bond donor to activate the aldehyde acceptor in the aldol reaction. A low loading of catalyst **4.9** was tested by MaryAnn Robak in a benchmark intermolecular aldol reaction between acetone and 4-nitrobenzaldehyde, providing **4.10** with 87% conversion and with high enantioselectivity (96%, eq 4.2). In contrast, using 30 mol% of the parent amino acid proline provides **4.10** in 68% yield and with 76% ee under comparable reaction conditions.[5] The diastereomer of **4.9** was also tested, providing **4.10** in 23% ee under the same conditions. Encouraged by these results, we sought to expand the scope of catalyst **4.9**. Moreover, due to the increasing number of reports on primary amino acid organocatalysts,[2] we also sought to develop new amino acid derived *N*-acyl *tert*-butanesulfinamide catalysts and test their application in other reactions.



In particular, the intermolecular aldol reaction using hydroxyacetone and amino acid organocatalysts was chosen to evaluate the performance of this new class of sulfinamide based organocatalysts (Scheme 4.2). Here, the proline-catalyzed reaction predominantly provides the *anti*-1,2-diol **4.14**[8] whereas with a primary amine catalyst

the *syn*-1,2-diol **4.15**[9] is generally formed. This switch in selectivity is attributed to the predominant *Z*-enamine for the primary amine catalyst in which an intramolecular H-bond between the amine and the alcohol functional group is present (**4.13**), while the *E*-enamine is favored when proline is used due to sterics (**4.12**). This chapter will describe the efficient synthesis and use of a number of *tert*-butanesulfinamide based organocatalysts in the intermolecular aldol reaction.

Scheme 4.2. Amino Acid Catalyzed Intermolecular Aldol Reaction with Hydroxyacetone



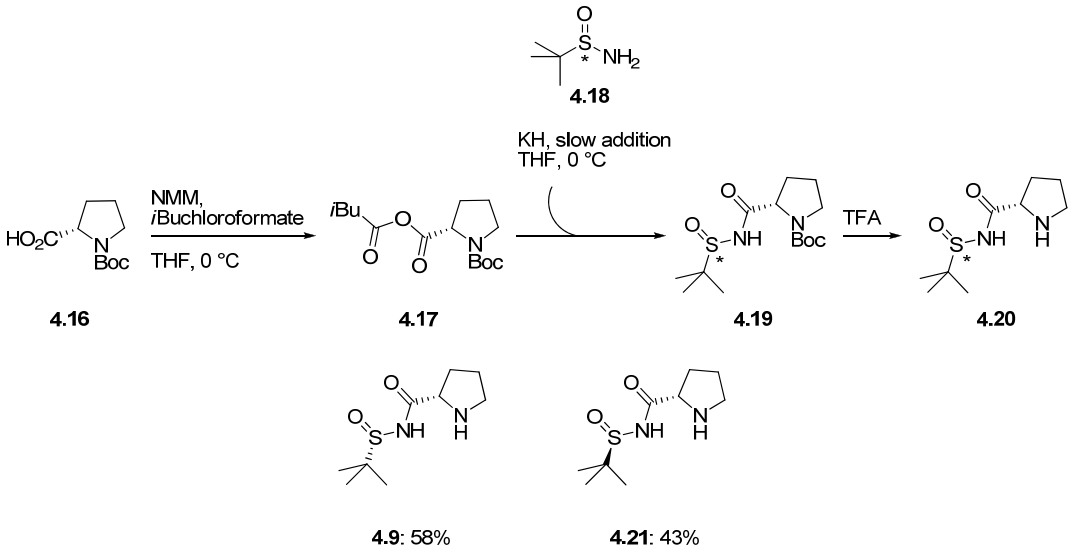
Synthesis of Amino Acid Based *N-tert*-Butanesulfinyl Amide Organocatalysts and Their Application in the Intermolecular Aldol Reaction

Catalyst Synthesis

Catalyst **4.9** and **4.21** were prepared via the common synthetic route outlined in Scheme 4.3 according to a procedure developed in the Ellman group.[10] The mixed anhydride **4.17**, generated from Boc-protected L-proline (**4.16**), was treated with

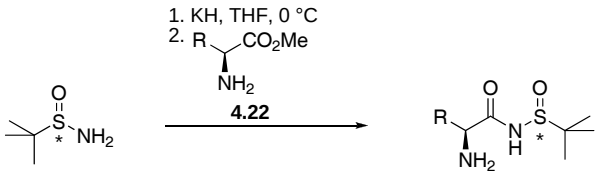
deprotonated (*R*)- or (*S*)-*tert*-butanesulfinamide (**4.18**), and the subsequent intermediate **4.19** was purified by recrystallization or column chromatography. Removal of the Boc-protecting group under acidic conditions yielded **4.9** and **4.21** in 58% and 43% yield over two steps, respectively.

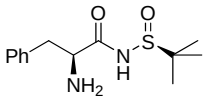
Scheme 4.3. Synthesis of the Proline *tert*-Butanesulfinyl Amide Catalysts **4.9** and **4.21**



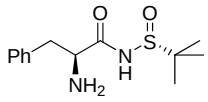
The panel of *N*-*tert*-butanesulfinyl amide organocatalysts **4.23a-h**, derived from phenylalanine, valine, *tert*-leucine, and *O*-*tert*-butyl-threonine, were synthesized in one step from the amino acid methyl esters (**4.22**) and deprotonated (*R*)- or (*S*)-*tert*-butanesulfinamide (Scheme 4.4). In most cases, a small amount of the minor diastereomer of each catalyst was observed by ^{1}H NMR analysis of the crude reaction mixture, but this impurity was readily removed by recrystallization. Isolated yields for products **4.23a-h** varied (13-62%), and the syntheses were not optimized.

Scheme 4.4. Synthesis of Amino Acid *tert*-Butanesulfinyl Amide Catalysts

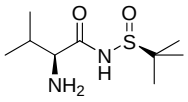




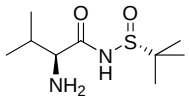
4.23a: 44%



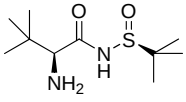
4.23b: 62%



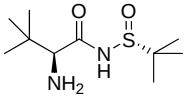
4.23c: 13%



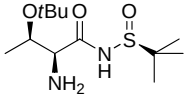
4.23d: 23%



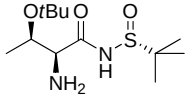
4.23e: 40%



4.23f: 24%



4.23g: 21%

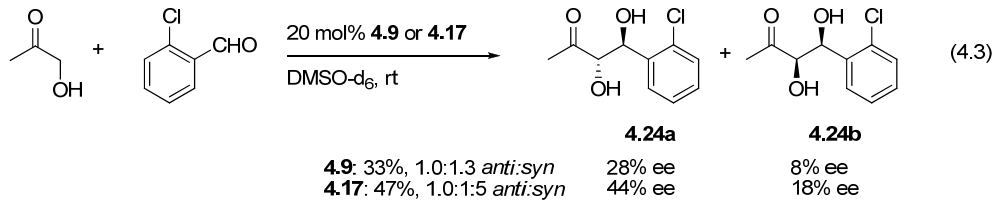


4.23h: 23%

Reaction Optimization

Initially, catalyst **4.9** and **4.21** were tested for their activity in the reaction between hydroxyacetone and 2-chlorobenzaldehyde (eq 4.3). While L-proline efficiently catalyzed the reaction between hydroxyacetone and α-branched alkyl aldehydes, providing the *anti*-1,2-diol with excellent diastereoselectivity and enantioselectivity, List and Notz reported that the transformation proceeded poorly with 2-chloro-benzaldehyde as the electrophile. In this case **4.24a** and **4.24b** were obtained in 95% yield, but with low diastereoselectivity (1.0:1.5 *anti:syn*) and moderate enatioselectivity of the *anti*-product (67%).[8] Unfortunately, under the reaction conditions reported by List and Notz neither the diastereoselectivity nor the enantioselectivity of the reaction were improved upon employing either catalyst **4.9** or

4.17. Several alternative solvents to DMSO were also screened, but superior results were not obtained.

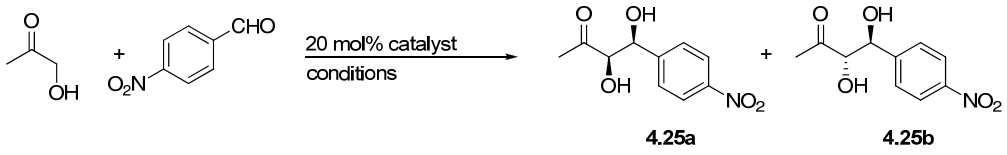


(4.3)

Encouraged by the growing number of reports of primary amine catalyzed intermolecular aldol reactions with α-hydroxy-ketones,[9, 11-13] we explored this transformation with our *N*-*tert*-butanesulfinyl amide organocatalysts **4.23** (Table 4.1). The reaction conditions reported by Barbas and coworkers for the *O*-*tert*-butyl threonine catalyzed aldol reaction between hydroxyacetone and electron-deficient aryl aldehydes were first evaluated with **4.23a** and **4.23b**, but moderate yields and poor diastereoselectivities and enantioselectivities were observed (entries 1-2). Barbas and coworkers also reported that an increase in diastereoselectivity and enantioselectivity was observed for some substrates when a 9:1 mixture of NMP:H_2O was used as the solvent system, but no marked improvement was noted when these reaction conditions were assayed (entries 3-4). In some cases, the addition of additives such as acids[13, 14] or alcohols[15] had proven fruitful in increasing catalyst turnover and enantioselectivity. When 10 mol% of TFA was premixed with catalysts **4.23a** or **4.23b** an increase in both diastereoselectivity and enantioselectivity was observed (compare entries 1-2 and 5-6). These conditions were also tried with catalysts **4.23g** and **4.23h**, the sulfinyl-modified version of the optimal catalyst previously reported by Barbas and coworkers.[16] Interestingly, a switch in selectivity was observed between **4.23g** and

4.23h (entries 7-8). Unfortunately, batch to batch variability of the hydroxyacetone lead to irreproducible results, therefore TBS-protected hydroxyacetone was investigated as the nucleophile.

Table 4.1. Reaction Optimization for the Intermolecular Aldol Reaction with Hydroxyacetone



entry	catalyst	solvent	additive	yield[a] (%)	dr[b] (**4.25a:b**)	ee (%)[c] (**a**)	ee[c] (%) (**b**)
1	**4.23a**	NMP, 1% H_2O	none	36	1:1	13	2
2	**4.23b**	NMP, 1% H_2O	none	67	1:1	12	6
3	**4.23a**	9:1 NMP:H_2O	none	58	1.4:1	0	0
4	**4.23b**	9:1 NMP:H_2O	none	55	1.3:1	8	12
5	**4.23a**	NMP, 1% H_2O	10 mol% TFA	19	2:1	28	24
6	**4.23b**	NMP, 1% H_2O	10 mol% TFA	60	1.6:1	50	56
7	**4.23g**	NMP, 1% H_2O	10 mol% TFA	64	3:1	-42	-45
8	**4.23h**	NMP, 1% H_2O	10 mol% TFA	83	1.7:1	63	73

[a] Yields were determined by ^{1}H NMR analysis of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. [b] Diastereomeric ratios were determined by ^{1}H NMR analysis. [c] Enantiomeric excesses were determined by HPLC, the absolute configuration was determined by chiral HPLC analysis of **4.25a** and **4.25b**, comparing with literature data.[9]

The TBS-protected hydroxyacetone **4.26** was prepared and purified according to literature procedure.[17] Catalysts **4.23a**-**4.23f** were screened in several different solvents (Table 4.2, entries 1-24). While some catalysts provided good diastereomeric ratios and enantioselectivities for the *syn*-product **4.27a**, yields were very low (entries 10, 16, and 24). Conversely, catalysts that provided a mixture of **4.27a** and **4.27b** in good yield generally gave moderate diastereomeric ratios or enantioselectivites (entries 6 and 13). Again, a switch in selectivity was observed between catalysts **4.23g** and **4.23h** (Table 4.2, entries 25-32), signifying a dominant role by the *tert*-butanesulfinyl group in the stereodefining step of the reaction. Indeed, adequate diastereoselectivities and good enantioselectivities favoring **4.27a** were observed when **4.23h** was employed in DMSO with 3% H_2O (entry 28) and when **4.23g** was used in H_2O or $CDCl_3$ (entries 29 and 31, respectively). Unfortunately, none of these results were superior to the direct aldol reaction between **4.26** and 4-nitrobenzaldehyde catalyzed by *O*-TBS-threonine in H_2O (91% yield, 7:1 *syn*:*anti*, 99% ee of **4.27a**).[11]

Table 4.2. Reaction Optimization for the Intermolecular Aldol Reaction with **4.26**

4.26 **4.27a** **4.27b**

entry	catalyst	solvent	yield	dr (**4.27a:b**)	ee (**a**)	ee (**b**)
1	4.23a	NMP, 3% H_2O	15	4:3:1.0	48	-6
2	4.23b	NMP, 3% H_2O	12	2.3:1.0	58	59

Table 4.2. Continued.

3	4.23a	DMSO, 3% H_2O	17	1.4:1.0	34	-4
4	4.23b	DMSO, 3% H_2O	10	2.8:1.0	59	47
5	4.23a	$CDCl_3$	65	1.8:1.0	15	24
6	4.23b	$CDCl_3$	74	3.0:1.0	70	58
7	4.23a	H_2O	22	3.2:1.0	47	44
8	4.23b	H_2O	59	2.3:1.0	75	77
9	4.23c	NMP, 3% H_2O	41	2.0:1.0	53	-40
10	4.23d	NMP, 3% H_2O	6	5.0:1.0	80	28
11	4.23c	DMSO, 3% H_2O	26	1.7:1.0	70	-39
12	4.23d	DMSO, 3% H_2O	25	2.1:1.0	78	0
13	4.23c	$CDCl_3$	69	2.4:1.0	39	32
14	4.23d	$CDCl_3$	58	2.2:1.0	51	43
15	4.23c	H_2O	14	4.1:1.0	68	35
16	4.23d	H_2O	19	2.9:1.0	84	62
17	4.23e	NMP, 3% H_2O	2	4.3:1.0	74	-14
18	4.23f	NMP, 3% H_2O	12	4.2:1.0	84	-24
19	4.23e	DMSO, 3% H_2O	16	1.6:1.0	63	-11
20	4.23f	DMSO, 3% H_2O	22	1.4:1.0	82	-33
21	4.23e	$CDCl_3$	22	3.1:1.0	58	34
22	4.23f	$CDCl_3$	26	3.6:1.0	69	26
23	4.23e	H_2O	19	4.5:1.0	73	24
24	4.23f	H_2O	36	3.8:1.0	87	38
25	4.23g	NMP, 3% H_2O	14	2.0:1.0	-76	-52
26	4.23h	NMP, 3% H_2O	66	2.3:1.0	64	30
27	4.23g	DMSO, 3% H_2O	24	2.8:1.0	-75	-38
28	4.23h	DMSO, 3% H_2O	64	3.9:1.0	87	75
29	4.23g	$CDCl_3$	71	1.7:1.0	-74	-84
30	4.23h	$CDCl_3$	66	1.8:1.0	23	29
31	4.23g	H_2O	62	2.9:1.0	-84	-84
32	4.23h	H_2O	58	2.1:1.0	61	33

[a] Yields were determined by ^{1}H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. [b] Diastereomeric ratios were determined by ^{1}H NMR. [c] Enantiomeric excesses were determined by HPLC, the absolute configuration was determined by chiral HPLC analysis of desilylated **4.27a** and **4.27b**, comparing with literature data.[9]

Conclusion

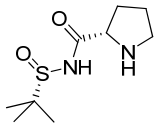
In conclusion, the efficient synthesis of a number of novel *tert*-butanesulfinamide-based organocatalysts was achieved and this new organocatalyst scaffold was applied

to the intermolecular aldol reaction. However, improvements in the diastereo- and enantioselectivity of the resulting products are still necessary and could be effected by further optimization of the reaction conditions or the addition of additives to the reaction mixture.

Experimental Procedure

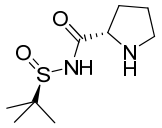
Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. *(R)-tert*-Butanesulfinamide and (*S*)-*tert*-butanesulfinamide were obtained from Allychem. Hydroxyacetone, technical grade 90%, was purified by column chromatography and distillation. Potassium hydride, 30 wt% dispersion in oil, was filtered under inert atmosphere, washed with pentane, and stored in a nitrogen-filled Vacuum Atmospheres inert atmosphere box. Unless otherwise noted, amino acid methyl esters were purchased as their hydrochloride salts and isolated in neutral form by extraction with CH_2Cl_2 from aqueous K_2CO_3. Anhydrous THF, CH_2Cl_2, benzene, and toluene were purchased from Fisher and obtained from a Seca Solvent Systems by GlassContour where they were dried over alumina under a nitrogen atmosphere. $CDCl_3$ was stored over K_2CO_3. Column chromatography was carried out using Merck 60Å 230-240 mesh silica gel. Reverse phase column chromatography was performed using a C_{18}HS packed column on a Biotage SP1 system (Charlottesville, VA). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer and only partial data are listed. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded in ppm and referenced to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. Mass spectra were

obtained from the Microanalytical Laboratory at the University of California, Berkeley.



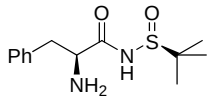
(S)-*N*-((*S*)-*tert*-butylsulfinyl)pyrrolidine-2-carboxamide 4.9. To a round bottom flask containing a stir bar and KH (1.2 g, 30 mmol, 3.0 equiv) in 20 mL of THF at 0 °C was slowly added a solution of (S)-*tert*-butanesulfinamide (1.2 g, 10 mmol, 1.0 equiv) in 10 mL of THF. The reaction mixture was stirred at 0 °C for 1 h. To another round bottom flask containing a stir bar and Boc-Pro-OH (2.2 g, 10 mmol, 1.0 equiv) in 40 mL of THF at 0 °C was added *N*-methylmorpholine (1.1 mL, 10 mmol, 1.0 equiv), and the reaction mixture was stirred for 5 min before *i*-butylchloroformate (1.3 mL, 10 mmol, 1.0 equiv) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture containing the mixed anhydride of Boc-Pro-OH was filtered and added dropwise over 20 min to the reaction mixture containing deprotonated *tert*-butanesulfinamide. The resulting reaction mixture was stirred for an additional 15 min, and the reaction was then quenched with 1.5 M K_2CO_3 (8 mL). The resulting mixture was concentrated to remove most of the THF, diluted with EtOAc and acidified with aqueous sodium bisulfate. The EtOAc layer was washed with brine, dried over sodium sulfate and concentrated to minimal volume of EtOAc. Hexanes were added and the product crystallized slowly overnight. The resulting material (1.9 g) was isolated by filtration and treated with TFA (5.0 mL) in 15 mL of CH_2Cl_2 for 4 h. The reaction mixture was concentrated, neutralized with

NH_4OH, and purified by reverse phase chromatography (NH_4OH, H_2O, MeCN, 0-30% MeCN:H_2O). The desired fractions were concentrated to remove any organic solvent and lyophilized to provide the desired product as a white powder (1.3 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.86 (m, 2H), 2.05 (m, 1H), 2.25 (m, 1H), 3.24-3.39 (m, 2H), 4.18 (m, 1H), 4.89 (b, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 25.5, 31.0, 47.1, 53.6, 61.4, 178.0. IR (neat): 3646, 3451, 3095, 2659, 1586, 1537, 1367, 1369, 1321, 811, 546 cm $^{-1}$. Exact mass calcd for $C_9H_{18}N_2O_2S$ requires m/z 219.1162, found m/z 219.1165 (MH^+, ESI).



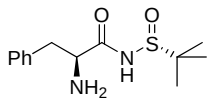
(*S*)-*N*-((*R*)-*tert*-butylsulfinyl)pyrrolidine-2-carboxamide 4.21. To a round bottom flask containing a stir bar and KH (0.61 g, 15 mmol, 3.0 equiv) in 5 mL of THF at 0 °C was slowly added a solution of (R)-*tert*-butanesulfinamide (0.61 g, 5.0 mmol, 1.0 equiv) in 10 mL of THF. The reaction mixture was stirred at 0 °C for 1 h. To another round bottom flask containing a stir bar and Boc-Pro-OH (1.1 g, 5.0 mmol, 1.0 equiv) in 20 mL of THF at 0 °C was added *N*-methylmorpholine (0.55 mL, 5.0 mmol, 1.0 equiv), and the reaction mixture was stirred for 5 min before *i*-butylchloroformate (0.65 mL, 5.0 mmol, 1.0 equiv) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 1 h. The reaction mixture containing the mixed anhydride of Boc-Pro-OH was filtered and added dropwise over 20 min to the reaction mixture containing deprotonated *tert*-butanesulfinamide. The resulting reaction mixture was stirred for 15 min, and the reaction was then quenched with 1.5 M K_2CO_3 (4 mL). The

resulting mixture was concentrated to remove most of the THF, diluted with EtOAc and acidified with aqueous sodium bisulfate. The EtOAc layer was washed with brine, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (50-100% EtOAc:hexanes). The resulting material was treated with TFA (2 mL) for 8 h. The reaction mixture was concentrated, neutralized with NH_4OH, and purified by reverse phase chromatography (NH_4OH, H_2O, MeCN, 0-30% MeCN:H_2O). The desired fractions were concentrated to remove any organic solvent and lyophilized to provide the desired product as a white powder (0.47 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 9H), 1.75 (m, 2H), 1.96 (m, 1H), 2.21 (m, 1H), 32.94 (m, 1H), 3.08 (m, 1H) 3.89 (m, 1H), 4.15 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 26.2, 30.8, 47.2, 56.1, 61.1, 176.5. IR (neat): 3651, 3368, 2981, 2888, 1566, 1298, 1270, 935, 599 cm $^{-1}$. Exact mass calcd for $C_9H_{18}N_2O_2S$ requires m/z 219.1162, found m/z 219.1162 (MH^+, ESI).



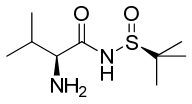
(*S*)-2-amino-*N*-((*S*)-*tert*-butylsulfinyl)-3-phenylpropanamide 4.23a. To a round bottom flask containing a stir bar and (*S*)-*tert*-butanesulfinamide (0.24 g, 2.0 mmol, 1.0 equiv) in 4 mL of THF was added KH (0.10 g, 2.4 mmol, 1.2 equiv). The reaction mixture was stirred at ambient temperature for 30 min. Phenylalanine methyl ester (0.36 g, 2.0 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with aqueous 1 M NH_4OAc (1.2 equiv), and the resulting mixture was diluted with a small amount of

H_2O. The mixture was concentrated to minimal volume and stirred for 10 h. The solids were collected by filtration and the product was purified by recrystallization from EtOH and was obtained as a white solid (0.24 g, 44%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.04 (s, 9H), 2.69 (dd, J_1 = 7.6, J_2 = 5.8 Hz, 1H), 2.85 (dd, J_1 = 6.4, J_2 = 6.9 Hz, 1H), 3.35 (br, 1 H), 3.66 (app t, J_1 = J_2 = 7.1 Hz, 1H), 4.72 (br, 2H), 7.17-7.27 (m, 5H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 21.7, 40.8, 55.4, 56.2, 126.2, 128.1, 129.3, 138.0, 176.4. IR (neat): 3176, 2587, 1544, 1287, 962, 702, 548 cm $^{-1}$. Exact mass calcd for $C_{13}H_{20}N_2O_2S$ requires m/z 269.1318, found m/z 221.1326 (MH^+, ESI).

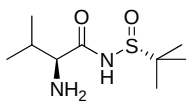


(*S*)-2-amino-*N*-((*R*)-*tert*-butylsulfinyl)-3-phenylpropanamide 4.23b. To a round bottom flask containing a stir bar and (*R*)-*tert*-butanesulfinamide (1.2 g, 10.0 mmol, 1.0 equiv) in 50 mL of THF was added KH (0.41 g, 10.2 mmol, 1.1 equiv). The reaction mixture was stirred at ambient temperature for 30 min. Phenylalanine methyl ester (1.8 g, 9.8 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with AcOH (0.613 g, 10.2 mmol, 1.1 equiv), and the resulting mixture was diluted with a small amount of THF (1-2 mL). The solids were collected by filtration, rinsing with THF. The product was purified by recrystallization from EtOH and H_2O and was obtained as a white solid (1.64 g, 62%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.13 (s, 9H), 2.50 (dd, J_1 = 8.0, J_2 =5.5 Hz, 1H), 2.95 (dd, J_1 = 8.5, J_2 = 5.1 Hz, 1H), 3.34 (br, 1 H), 3.58 (app t, J_1 = 7.6, J_2 = 5.3 Hz, 1H), 4.71 (br, 2H), 7.19-7.29 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ

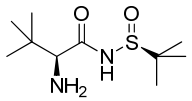
22.0, 40.2, 56.4, 56.7, 127.2, 128.9, 129.3, 136.6, 175.3. IR (neat): 3136, 2586, 1538, 1314, 1006, 703, 600 cm $^{-1}$. Exact mass calcd for $C_{13}H_{20}N_2O_2S$ requires m/z 269.1318, found m/z 221.1326 (MH^+, ESI).



(*S*)-2-amino-*N*-((*S*)-*tert*-butylsulfinyl)-3-methylbutanamide 4.23c. To a round bottom flask containing a stir bar and (*S*)-*tert*-butanesulfinamide (0.99 g, 8.2 mmol, 1.0 equiv) in 40 mL of THF was added KH (0.33 g, 8.3 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for 30 min. Valine methyl ester (1.1 g, 8.3 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 6 h. The reaction was quenched with AcOH (0.47 mL, 8.2 mmol, 1.0 equiv), and the resulting mixture was diluted with H_2O and 1.0 mL of DMSO. The mixture was concentrated to minimal volume with heat under vacuum, and the solid was collected by filtration. The product was purified by recrystallization from ~x mL of EtOH and isolated as a white solid (0.24 g, 13%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.27 (s, 9H), 2.34-2.42 (m, 1H), 3.31 (d, *J* = 3.6 Hz, 1H), 3.6 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 19.6, 22.1, 30.7, 56.5, 60.4, 175.6. IR (neat): 3343, 3278, 2980, 1557, 1516, 1468, 1313, 1020, 960, 821, 549 cm $^{-1}$. Exact mass calcd for $C_9H_{21}N_2O_2S$ requires m/z 221.1318, found m/z 221.1323 (MH^+, ESI).

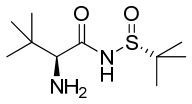


(*S*)-2-amino-*N*-((*R*)-*tert*-butylsulfinyl)-3-methylbutanamide 4.23d. To a round bottom flask containing a stir bar and (*R*)-*tert*-butanesulfinamide (0.49 g, 4.0 mmol, 1.0 equiv) in 20 mL of THF was added KH (0.16 g, 4.1 mmol, 1.1 equiv). The reaction mixture was stirred at ambient temperature for 30 min. Valine methyl ester (0.52 g, 4.0 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with AcOH (0.24 mL, 4.1 mmol, 1.1 equiv) and the resulting mixture was diluted with a mixture of EtOH, H_2O and 1.0 mL of DMSO. The mixture was concentrated to minimal volume with heat under vacuum, stirred overnight, and two crops of solids were collected. The solids were collected by filtration, rinsing with H_2O. The crude solid (0.62 g) was purified by recrystallization from 15 mL of EtOH with a hot filtration providing the desired product as a white solid (0.20 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.2 Hz, 3H), 1.26 (s, 9H), 2.23-2.34 (m, 1H), 3.68 (d, J = 3.7 Hz, 1H), 4.08 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.5, 22.1, 30.7, 56.2, 60.6, 175.6. IR (neat): 3116, 2970, 2879, 1554, 1443, 1336, 1017, 997, 829, 589 cm $^{-1}$. Exact mass calcd for $C_9H_{21}N_2O_2S$ requires m/z 221.1318, found m/z 221.1324 (MH^+, ESI).



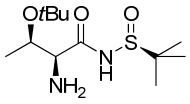
(*S*)-2-amino-*N*-((*S*)-*tert*-butylsulfinyl)-3,3-dimethylbutanamide 4.23e. To a round bottom flask containing a stir bar and (*S*)-*tert*-butanesulfinamide (1.2 g, 10.0 mmol, 1.0 equiv) in 50 mL of THF was added KH (0.41 g, 10.2 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for 30 mins. *tert*-Leucine methyl

ester[18] (1.5 g, 10.0 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with AcOH (0.61 g, 10.2 mmol, 1.0 equiv), and the resulting mixture was diluted with THF. The solids were collected by filtration and rinsed with THF. The product was isolated by recrystallization from EtOH and H_2O as a white solid (0.937 g, 40%). ^{1}H NMR (400 MHz, DMSO): δ 0.88 (s, 9H), 1.17 (s, 9H), 3.14 (s, 1H), 4.38 (br s, 3H). ^{13}C NMR (100 MHz, DMSO): δ 22.4, 26.8, 34.4, 55.7, 62.9, 176.9. IR (neat): 3361, 2980, 1529, 1271, 984, 814, 453 cm $^{-1}$. Exact mass calcd for $C_{10}H_{23}N_2O_2S$ requires m/z 235.1475, found m/z 235.1481 (MH^+, ESI).

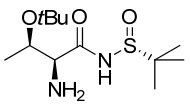


(*S*)-2-amino-*N*-((*R*)-*tert*-butylsulfinyl)-3,3-dimethylbutanamide 4.23f. To a round bottom flask containing a stir bar and (*R*)-*tert*-butanesulfinamide (1.0 g, 8.3 mmol, 1.1 equiv) in 40 mL of THF was added KH (0.33 g, 8.3 mmol, 1.1 equiv). The reaction mixture was stirred at ambient temperature for 30 min. *tert*-Leucine methyl ester[18] (1.1 g, 7.7 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with AcOH (0.47 mL, 8.2 mmol, 1.1 equiv), and the resulting mixture was diluted with H_2O. The mixture was concentrated to dryness under reduced pressure, and the resulting solid was triturated with Et_2O. The solids were purified by recrystallization from ~x mL of EtOH, and the product was isolated as a white solid (0.39 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.27 (s, 9H), 3.28 (s, 1H), 3.97 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1,

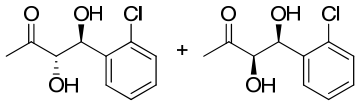
26.8, 34.3, 56.1, 64.6, 174.7. IR (neat): 3140, 2957, 2868, 1563, 1557, 1451, 1332, 1092, 993, 825, 590 cm $^{-1}$. Exact mass calcd for $C_{10}H_{23}N_2O_2S$ requires m/z 235.1475, found m/z 235.1482 (MH^+, ESI).



(2*S*,3*R*)-2-amino-3-*tert*-butoxy-*N*-((*S*)-*tert*-butylsulfinyl)butanamide 4.23g. To a round bottom flask containing a stir bar and (*S*)-*tert*-butanesulfinamide (0.84 g, 7.0 mmol, 1.0 equiv) in 35 mL of THF was added KH (0.28 g, 7.0 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for 30 min. *tert*-Butyl threonine methyl ester (1.3 g, 6.9 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with AcOH (0.42 g, 7.0 mmol, 1.0 equiv), and the resulting mixture was concentrated. The crude product was isolated by recrystallization from EtOH and H_2O with hot filtration and the solid was rinsed with H_2O to provide the desired product as a white solid (0.41 g, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (d, J = 6.4 Hz, 3H), 1.22 (s, 9H), 1.28 (s, 9H), 1.66 (br, 2H), 3.54 (d, J = 4.1 Hz, 1H), 4.10-4.13 (dq, J_1 = 4.1 J_2 = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 22.1, 28.3, 56.4 61.2, 67.5, 74.9, 174.4. IR (neat): 3410, 3110, 2975, 2697, 1576, 1557, 1436, 1358, 1355, 998, 962, 828, 547 cm $^{-1}$. Exact mass calcd for $C_{12}H_{26}N_2O_3S$ requires m/z 279.1737, found m/z 279.1745 (MH^+, ESI).



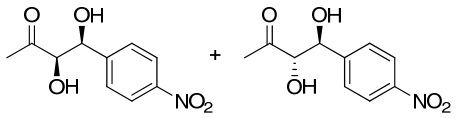
(2*S*,3*R*)-2-amino-3-*tert*-butoxy-*N*-((*R*)-*tert*-butylsulfinyl)butanamide 4.23h. To a round bottom flask containing a stir bar and (*R*)-*tert*-butanesulfinamide (0.84 g, 7.0 mmol, 1.0 equiv) in 35 mL of THF was added KH (0.28 g, 7.0 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for 30 min. *tert*-Butyl threonine methyl ester (1.3 g, 6.9 mmol, 1.0 equiv) was added to the reaction vessel, and the reaction mixture was stirred for 12-16 h. The reaction was quenched with AcOH (0.42 g, 7.0 mmol, 1.0 equiv), and the resulting mixture was concentrated. The crude product was isolated by recrystallization from EtOH and H_2O with hot filtration and the solid was rinsed with H_2O to provide the desired product as a white solid (0.45 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 9H), 1.17-1.18 (d, J = 6.2 Hz, 3H (overlap)), 1.28 (s, 9H), 3.27 (d, J = 2.6 Hz, 1H), 4.16-4.19 (dq, J_1 = 2.6, J_2 = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 22.3, 28.6, 55.9, 60.6, 67.8, 74.6, 175.3. IR (neat): 3122, 2980, 2866, 1565, 1452, 1361, 1330, 1018, 963, 817, 578 cm $^{-1}$. Exact mass calcd for $C_{12}H_{26}N_2O_3S$ requires m/z 279.1737, found m/z 279.1741 (MH^+, ESI).



4.24a **4.24b**

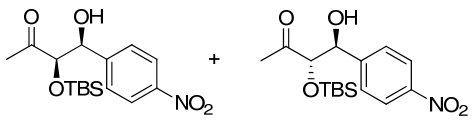
(3*S*,4*S*)-4-(2-Chlorophenyl)-3,4-dihydroxybutan-2-one 4.24a and (3*R*,4*S*)- 4-(2-Chlorophenyl)-3,4-dihydroxybutan-2-one 4.24b. The appropriate catalyst (4.3 mg, 0.02 mmol, 20 mol%) was weighed into a small vial equipped with a stir bar. Distilled DMSO-d_6 (0.8 mL) was added followed by the addition of freshly distilled hydroxyacetone (0.2 mL, 20 vol%), and the reaction mixture was transferred to an

oved-dried ^{1}H NMR tube and 2-Cl-benzaldehyde (0.01 mL, 0.1 mmol, 1.0 equiv) was added. The reaction mixture was kept at room temperature for 1 d. The spectroscopic data matched that reported in the literature.[8] The enantiomeric purity was determined by HPLC (Daicel Chiralpak AS-H, 90:10 hexanes:EtOH, 1 mL/min).[8]



4.25a **4.25b**

(3*R*,4*S*)-4-(4-Nitrophenyl)-3,4-dihydroxybutan-2-one 4.25a and (3*S*,4*S*)-4-(4-Nitrophenyl)-3,4-dihydroxybutan-2-one 4.25b. The appropriate catalyst (20 mol%) was weighed into a small vial equipped with a stir bar and 0.2 mL of the appropriate solvent was added. Hydroxyacetone (2 equiv) followed by 4-nitrobenzaldehyde (1 equiv) were added to the reaction vial. The reaction mixture was stirred at ambient temperature for 1-2 d. The reaction mixture was diluted with ethyl acetate (2 mL) and poured into half saturated NH_4Cl solution. The mixture was extracted with ethyl acetate and the organic layers were combined and washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography (30-80% EtOAc:hexanes) to afford the desired aldol product. The spectroscopic data matched that reported in the literature.[9]The enantiomeric purity was determined by HPLC (Daicel Chiralpak IA, 80:20 hexanes:EtOH, 1 mL/min).[9]



4.27a **4.27b**

(3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-4-(4-nitrophenyl)butan-2-one 4.27a and (3*S*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-4-(4-nitrophenyl)butan-2-one 4.27b. The appropriate catalyst (20 mol%) was weighed into a small vial equipped with a stir bar and 0.2 mL of the appropriate solvent was added. **4.26** (2 equiv) followed by 4-nitrobenzaldehyde (1 equiv) were added to the reaction vial. The reaction mixture was stirred at ambient temperature for 1-2 d. The reaction mixture was diluted with ethyl acetate (2 mL) and poured into a 1:1 mixture of an aqueous saturated NH_4Cl solution and H_2O. The mixture was extracted with ethyl acetate and the organic layers were combined and washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography (30-80% EtOAc:hexanes) to afford the desired aldol product. The spectroscopic data matched that reported in the literature.[11] The enantiomeric purity was determined by HPLC (Daicel Chiralpak IB, 95:5 hexanes:*i*PrOH, 1 mL/min).[11]

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