Synthesis and Applications of *tert*-Butanesulfinamide

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Contents

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1. Introduction

Amines are present in a large majority of drugs and drug candidates. Consequently, the asymmetric synthesis of amine containing compounds represents an extremely important endeavor in the discovery and production of new pharmaceutical agents. Over the past decade, an ever increasing collection of methods based upon the chiral amine reagent *tert*-butanesulfinamide (**1**) have become some of the most extensively used synthetic approaches for both the discovery and production of drug candidates. Moreover, *tert*-butanesulfinamide is increasingly being applied across many additional research areas, including the development of agrochemicals, natural product synthesis, and the preparation of chemical tools for a wide range of biological investigations.

A number of factors have led to the popularity of *tert*-butanesulfinamide (**1**). From a practical standpoint, either enantiomer of **1** is inexpensive to prepare on a large scale in enantiomerically pure form. Indeed, greater than 75 chemical suppliers currently market **1** in many cases at reasonable prices (<$1/g for bulk quantities).[1] More importantly, the synthesis steps used to prepare amines from **1** are typically robust, straightforward, and broad in scope (Scheme 1).

There are several distinguishing characteristics of this chemistry: (1) The direct condensation of **1** with a wide range of aldehydes and ketones proceeds in high yields under mild conditions to give stable *N*-*tert*-butanesulfinyl aldimines **2** and ketimines **3**, respectively, that are much less hydrolytically labile or prone to tautomerization than most *N*-alkyl, aryl, acyl, or carbamoyl imines. (2) *N*-*tert*-Butanesulfinyl imines **2** and **3**, despite their stability, are significantly more electrophilic than typical *N*-alkyl or aryl imines, which can be explained by the significant positive charge on sulfur. This enhanced electrophilicity enables clean and high yield additions of a very wide range of diverse nucleophiles, including organo-magnesium, lithium, zinc, silicon, indium, cerium, and boron reagents, stabilized carbanions exemplified by enolates, and noncarbon nucleophiles such as phosphorus, boron, tin, and silicon species as well as numerous hydride reagents. Moreover, additions to α-heteroatom substituted imines **2** and **3** typically proceed in high yield, and when an α-stereocenter is present, without epimerization. (3) The *tert*-

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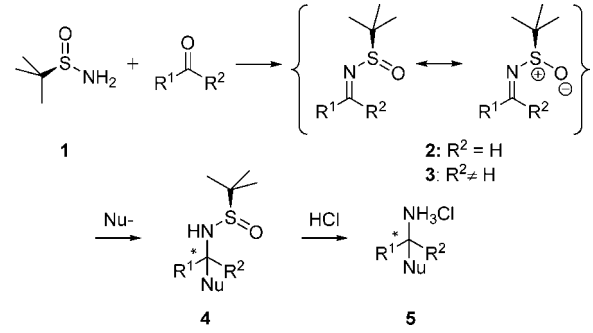
Melissa Herbage obtained a B.A. in chemistry in 2004 from Northwestern University under the mentorship of Professor Karl Scheidt. She then received her Ph.D. in 2009 from the University of California, Berkeley, working in the laboratories of Professor Jonathan Ellman. Her graduate work focused on the development of new methods for the asymmetric synthesis of α-amino acid derivatives from *N-tert*-butanesulfinyl imines. She is currently conducting postdoctoral research in the laboratories of Professor Barry Trost at Stanford University.

Jonathan Ellman earned his B.S. degree from MIT in 1984 and his Ph.D. degree at Harvard University in 1989, working under the direction of Professor David Evans. He carried out postdoctoral research with Professor Peter Schultz at the University of California at Berkeley. In 1992 he was appointed to the faculty at the University of California at Berkeley, where he is currently Professor of Chemistry. He holds a joint appointment in the Department of Cellular and Molecular Pharmacology at the University of California at San Francisco. Among his previous honors are election as a fellow of the American Association for the Advancement of Science, a Sloan Foundation Fellowship, an American Chemical Society Cope Scholar Award, a Tetrahedron Young Investigator Award, a Society of Biomolecular Screening Achievement Award, and the Scheele Award, selected by the Swedish Academy of Pharmaceutical Sciences. His laboratory is engaged in the design of chemical tools for biological studies and in the development of selective, practical, and general synthetic methods in the areas of C−H bond functionalization and the asymmetric synthesis of amine-containing compounds.

Scheme 1. General Sequence for the Synthesis of Amines from *tert*-Butanesulfinamide (1)



butanesulfinyl group is not only chiral but also capable of metal coordination, resulting in high diastereoselectivities for the addition of many different nucleophiles to imines **2** and **3**. (4) The *tert*-butanesulfinyl group in addition products **4** serves as an extremely versatile protecting group that parallels the reactivity of carbamoyl protecting groups in attenuating the nucleophilicity of the protected amine. The *N-tert*-butanesulfinyl group is also stable to a wide range of reaction conditions, including strong bases, nucleophiles, and a variety of transition metal catalyzed processes such as olefin metathesis and Pd-mediated cross-coupling. (5) Convenient and high yielding cleavage of the *N-tert*-butanesulfinyl group can be accomplished by simple treatment with methanolic HCl to provide the amine hydrochloride products **5** after precipitation with ethereal solvents, often in nearly quantitative yields and in analytically pure form.

As detailed in this review, numerous researchers in both academics and industry have contributed innovative and useful new methods based on **1** and have applied these methods to efficient syntheses of drug candidates and natural products, often in the context of densely functionalized structures. While many of these contributions rely on nucleophilic additions to *N-tert*-butanesulfinyl imines **2** and **3**, a number of alternative approaches to convergently assemble complex molecules with multiple stereocenters have also been developed. Particularly notable are methods to reductively couple *N-tert*-butanesulfinyl imines **2** and **3** with carbonyl compounds, imines, and electron deficient alkenes in high yield and with excellent diastereoselectivity. Another general strategy for the convergent assembly of amines with two or more stereocenters proceeds via the diastereoselective addition of *N-tert*-butanesulfinyl metalloenamines to electrophiles such as aldehydes, imines, Michael acceptors, and alkylating agents to produce *N-tert*-butanesulfinyl imine products to which nucleophiles can then readily be added. Finally, for the purpose of asymmetric catalysis, *tert*-butanesulfinamide is increasingly being incorporated within chiral ligand and organocatalyst frameworks due to the opportunities provided by the distinctive presentation of chirality in the context of metal coordination or substrate hydrogen bonding interactions.

While this review specifically focuses on the chemistry and applications of *tert*-butanesulfinamide (**1**), other sulfinamides such as *p*-toluenesulfinamide and 2,4,6-triisopropylbenzenesulfinamide have very useful and often complementary properties. The methods and applications of other sulfinamides have been carefully reviewed elsewhere.[2−4] Several insightful reviews have also appeared on various aspects of *tert*-butanesulfinamide chemistry.[2,4,5]

2. Synthesis of tert-Butanesulfinamide

A variety of innovative methods have been developed for the preparation of enantiomerically pure *tert*-butanesulfinamide. Currently, the large majority of chemical suppliers produce enantiomerically pure **1** by the highly practical two-step procedure of catalytic enantioselective oxidation of inexpensive *tert*-butyl disulfide to the thiosulfinate ester **8** followed by amide displacement (see Scheme 4). This process has in fact been utilized to prepare enantiomerically pure **1** in ton quantities. At least one chemical supplier produces enantiomerically pure **1** using the three-step process that relies on *N*-tosyl norephedrine (**18**) as a chiral auxiliary (see Scheme 7). Procedures based upon the chiral auxiliary **18** have proven to be particularly versatile for the synthesis of other sulfinamides as well as sulfoxides.

2.1. Synthesis of Racemic *tert*-Butanesulfinamide

Racemic *tert*-butanesulfinamide has been used for the synthesis of a large number of amines, either because the desired amine product is achiral,[6−11] the racemic rather than enantiomerically pure product is desired,[12] or the sulfinyl group is not the stereocontrolling element in the addition step.[13] It is therefore important that practical methods for the synthesis of racemic *tert*-butanesulfinamide are available. In one approach, treatment of inexpensive *tert*-butyl disulfide (**6**) with H_2O_2 followed by Cl_2, according to the procedure of Prinzbach,[14] provides *tert*-butanesulfinyl chloride (**7**), which upon reaction with ammonium hydroxide provides (±)-**1** in 93% overall yield (Scheme 2).[15]

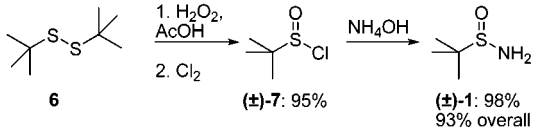
2.2. Synthesis of Enantiomerically Pure *tert*-Butanesulfinamide

The synthesis and isolation of enantiomerically pure *tert*-butanesulfinamide (**1**) was first reported by Ellman and co-workers in 1997.[16] Since then, several different approaches to the synthesis of this compound have been reported, including enantioselective oxidation, resolution of racemic material, diastereoselective synthesis utilizing stoichiometric chiral auxiliaries, and catalytic enantioselective sulfinyl transfer.

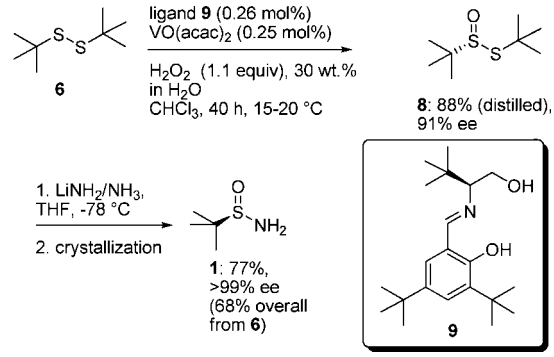
2.2.1. Enantioselective Oxidation

The two-step synthesis of enantiomerically pure *tert*-butanesulfinamide via catalytic asymmetric oxidation of *tert*-butyl disulfide (**6**), followed by nucleophilic displacement with lithium amide (Scheme 3), was initially reported by

Scheme 2. Synthesis of (±)-*tert*-Butanesulfinamide



Scheme 3. Original Synthesis of *tert*-Butanesulfinamide[15]

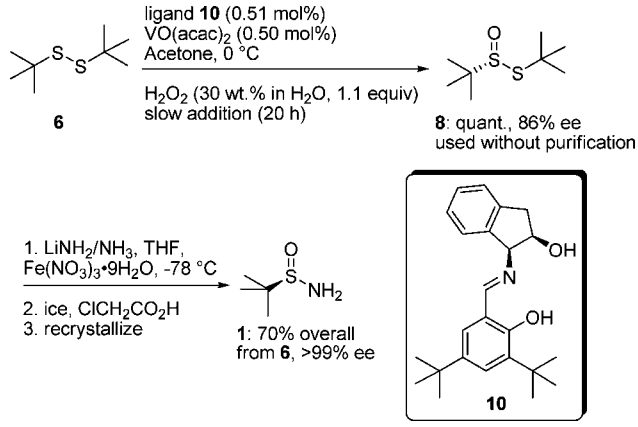


Ellman and co-workers in a 1997 Communication[16] and described in more detail in the subsequent full paper.[15] The starting material, *tert*-butyl disulfide (**6**), which is a petroleum byproduct, is available in large quantities at low cost. The catalytic oxidation reaction, developed on the basis of work by Bolm and co-workers on oxidation of thioethers,[17] utilizes low catalyst loading of Schiff base−vanadium catalyst complexes. Schiff base ligands such as **9** were easily prepared, allowing for extensive catalyst screening to optimize reaction conversion and enantioselectivity. Aqueous hydrogen peroxide, the stoichiometric oxidant, is inexpensive and easy to handle. Addition of lithium amide to the oxidation product **8** after bulb-to-bulb distillation proceeded cleanly with inversion of configuration. Recrystallization of the crude product provided enantiomerically pure **1** in 68% overall yield for the two-step process from *tert*-butyl disulfide (**6**).

Despite the advantages, this route had a few shortcomings as originally published. First, difficulties were encountered in attempting to scale the oxidation reaction above 1 mol scale, because the biphasic reaction was particularly sensitive to vessel shape and stir rate. Both experimental[18] and calculation[19] studies have been undertaken to elucidate the mechanism of this oxidation, and of particular note is the dependence of the active catalyst species on the concentration of hydrogen peroxide, with high concentrations resulting in catalyst decomposition. This accounts for the sensitivity of the reaction to stirring under the biphasic conditions. Also, the optimal ligand **9** was derived from *tert*-leucinol, for which the (*R*) enantiomer is far more expensive than the (*S*) enantiomer. Ma and co-workers reported additional ligand screening but were not successful in identifying a superior ligand.[20] Finally, the side product from the nucleophilic displacement step is *tert*-butanethiol, which can be detected by smell in very low concentration and is the primary odorant added to natural gas, causing alarm if it is not efficiently trapped in the reaction workup. Subsequent work by Weix and Ellman addressed the concerns with both the oxidation step and the nucleophilic displacement step.[21,22]

Acetone was found to be a suitable solvent for carrying out the oxidation reaction under homogeneous reaction conditions, eliminating the scalability problems encountered in the biphasic system (Scheme 4).[21] Importantly, slow addition of the aqueous H_2O_2 peroxide to the reaction solution not only prevents exotherms but is also essential for minimizing catalyst death by maintaining a low H_2O_2 concentration. Moreover, these modified conditions enable the oxidation reaction to be performed at a very high concentration (2.3 M), further enhancing the practicality of the process. Schiff base ligand **10**, which was suboptimal

Scheme 4. Optimized Synthesis of *tert*-Butanesulfinamide[22]

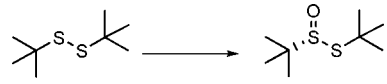


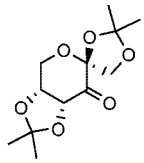
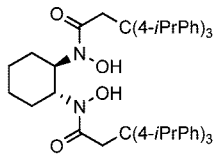
under the original reaction conditions, was found to be superior under the new conditions, providing nearly quantitative conversion of *tert*-butyl disulfide (**6**) to **8** with 86% ee. The high level of conversion eliminates the need for purification of intermediate **8**. Furthermore, optimal ligand **10** is derived in one step from *cis*-1-amino-2-indanol, for which both enantiomers are commercially available at significantly lower cost than that for *tert*-leucinol. This general procedure for enantioselective asymmetric oxidation of *tert*-butyl disulfide in the two-step synthesis of enantiomerically pure *tert*-butanesulfinamide has been employed by many chemical supply companies. Indeed, Allychem employs this procedure to prepare *tert*-butanesulfinamide on greater than ton scale production capacity.

To address the issue of *tert*-butanethiol release in the nucleophilic displacement step, a modified workup procedure was developed.[22] Because thiols are quite nucleophilic, the use of an electrophilic reagent for scavenging the side product was investigated. Addition of chloroacetic acid to the crude mixture (after evaporation of the ammonia but before extractive isolation of sulfinamide **1**) proved to be effective at completely eliminating the thiol odor from the final mixture. Trituration of the crude product followed by a single recrystallization from hexanes provided enantiomerically pure **1** in 70−72% overall yield from disulfide **6**.

Due to the success of the synthesis of enantiomerically pure *tert*-butanesulfinamide **1** via the thiosulfinate ester **8**, alternative approaches to this key chiral intermediate have been investigated (Table 1). Colonna and co-workers reported the enzymatic oxidation of disulfide **6** to thiosulfinate **8** in 90% conversion and with 97% ee, utilizing cyclohexanone monooxygenase (CYMO) (entry 1).[23] A catalytic amount of $NADP^+$ was used, while glucose-6-phosphate and glucose-6-phosphate dehydrogenase were used to regenerate the oxidant. Dzyuba and Klibanov reported the enantioselective oxidation of disulfide **6** to thiosulfinate **8** catalyzed by bovine serum albumin (BSA), with H_2O_2 as a stoichiometric oxidant, providing 66% conversion and 88% ee (entry 2).[24] Colonna, Malacria, and co-workers investigated the use of other oxidants with BSA but observed low conversion and enantioselectivity for these transformations.[25] However, they were more successful in the use of 30 mol % of fructose-derived ketone **11**, originally developed by Shi and co-workers for enantioselective epoxidation reactions,[26] as an organocatalyst for this oxidation reaction, obtaining quantitative conversion to thiosulfinate **8** in 75% ee under the optimized conditions (entry 3). Subsequently, Khiar, Fernandez, and co-workers reported the oxidation of **6** to **8** in 97% yield and 84% ee under similar conditions (entry 3).[27] Yamamoto and co-workers have also demonstrated that chiral molybdenum complexes developed for the enantioselective oxidation of sulfides can also be used to oxidize disulfide **6** to thiosulfinate **8** in 79% yield and 90% ee with trityl hydroperoxide as a stoichiometric oxidant (entry 4).[28]

Table 1. Alternative Disulfide Oxidation Conditions



entry	catalyst	oxidant	conditions	conv (%)	ee (%)
1	CYMO (50 units)	$NADP^+$ (10 mol%) glucose-6-phosphate (5 equiv) glucose-6-phosphate dehydrogenase (100 units)	Tris-HCl buffer, pH 8.6 0.01 M **6**, 4 h, 25 °C	90	97
2	BSA (100 mg/mL)	H_2O_2 (1 equiv)	phosphate buffer, pH 7 0.01 M **6**, 67 h, 25 °C	66	88
3	 (**11**, 30 mol%)	Oxone (1.4 equiv)	aq.buffers (NBu_4HSO_4, K_2CO_3, $Na_2(EDTA)$) 0.07 M **6** in CH_3CN:DMM (1:2), 2-13 h, 0 °C	>97	75-84
4	 (2 mol%), $MoO_2(acac)_2$	trityl hydroperoxide	0.25 M **6**, CH_2Cl_2, 0 °C	79	90

2.2.2. Resolution of Racemic tert-Butylthiosulfinate

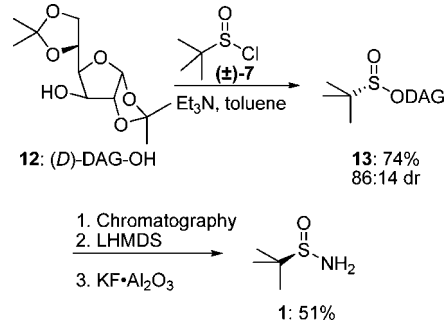
Deng and co-workers reported the classical resolution of racemic *tert*-butylthiosulfinate (**8**) by crystallization with enantiomerically pure (*R*)-BINOL.[29] Selective sequential crystallization of both diastereomeric complexes was accomplished. Enantiomerically pure thiosulfinate **8** was recovered from the crystals by vacuum distillation in 30% overall yield for the *R* enantiomer and 14% overall yield for the *S* enantiomer (based on the initial mass of (±)-**8**), and it is suggested that the BINOL may be recovered for reuse.

2.2.3. Diastereoselective Synthesis with Stoichiometric Chiral Auxiliaries

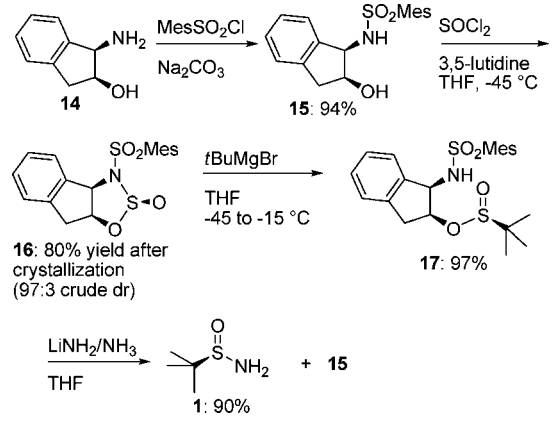
The synthesis of chiral sulfoxides, including *tert*-butyl sulfoxides, has been studied for decades.[30] The adaptation of methods originally designed for the synthesis of chiral sulfoxides to enable the synthesis of sulfinamides, including *tert*-butanesulfinamide (**1**), has been the subject of many studies. In one of the first such examples, the Ellman group initially explored the use of diacetone-D-glucose (DAG) as a chiral auxiliary for the synthesis of enantiomerically pure *tert*-butanesulfinamide (Scheme 5),[15] utilizing the methodology developed by Alcudia and co-workers for the synthesis of optically pure *tert*-butanesulfoxides[31] and applied by Garcia-Ruano for the synthesis of *N*-*tert*-butanesulfinyl imines (see section 3.1.1).[32] In this sequence, racemic (configurationally unstable) *tert*-butanesufinyl chloride (**7**) is reacted with diacetone-D-glucose (**12**) in the presence of amine base, and dynamic kinetic resolution occurs, providing an 86:14 mixture of sulfinate ester diastereomers **13**, which can be separated by chromatography. Treatment with LHMDS followed by $KF \cdot Al_2O_3$ provides enantiomerically pure *tert*-butanesulfinamide (**1**), which can be chromatographically separated from the chiral auxiliary.

Building upon pioneering work by Wudl and Lee,[33] Snyder and Benson,[34] and Kagan and co-workers,[35] Senanayake and co-workers at Sepracor developed a chiral auxiliary-based method for the synthesis of diverse chiral sulfoxides and sulfinamides, including *tert*-butanesulfinamide (Scheme 6).[36] In this method, a chiral auxiliary **15** derived from *cis*-1-amino-2-indanol (**14**) is treated with thionyl chloride under basic conditions to provide diastereomerically enriched 1,2,3-oxathiazolidine-2-oxide **16** (use of 3,5-lutidine provides **16** while 2,4,6-collidine allows access to the other diastereomer). Crystallization at this stage enables isolation of diastereomerically pure **16**. To synthesize *tert*-butanesulfinamide, this intermediate is then treated with *tert*-butyl magnesium bromide, providing **17** with inversion of stereochemistry at the sulfur. The selectivity in this displacement step results from the electron-withdrawing arenesulfonyl substituent on

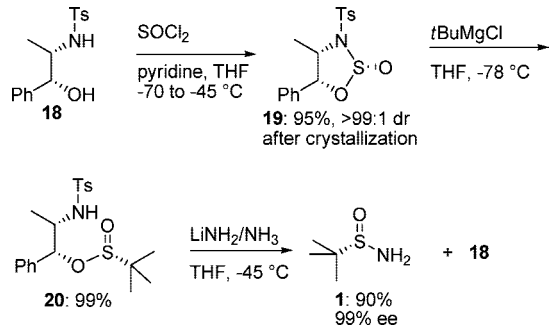
Scheme 5. Synthesis of *tert*-Butanesulfinamide Utilizing DAG Methodology



Scheme 6. Amino Indanol-Based Chiral Auxiliary



Scheme 7. Norephedrine-Based Chiral Auxiliary

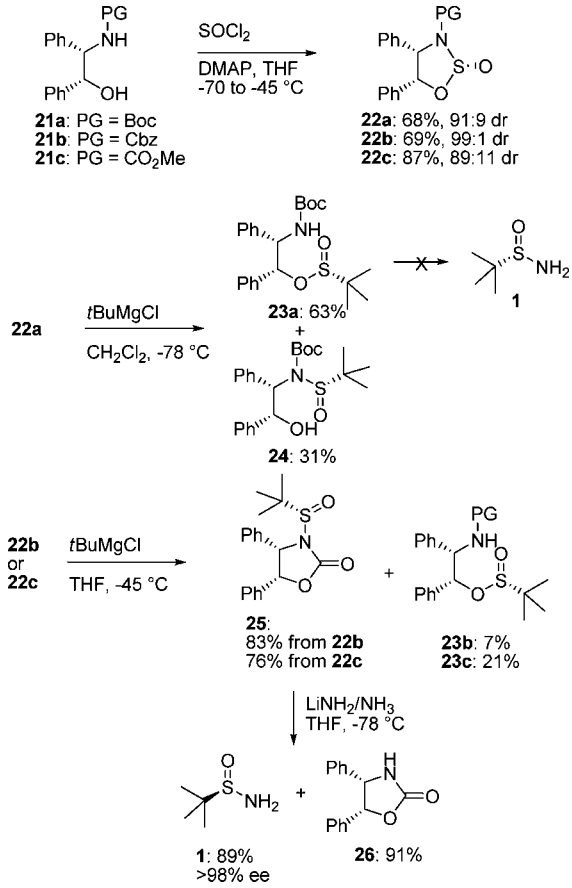


the nitrogen of the chiral auxiliary. Finally, treatment of **17** with lithium amide in ammonia and THF provides sulfinamide **1** (again with inversion of configuration at sulfur) and regenerates chiral auxiliary **15**, which may be separated from the sulfinamide chromatographically.

Further optimization of this methodology by the same group led to the development of norephedrine-based chiral auxiliary **18** (Scheme 7).[37] In this case, an 85% overall yield of enantiomerically pure *tert*-butanesulfinamide is obtained in three steps from *N*-tosyl norephedrine (**18**), which has proven to be a very versatile intermediate for the synthesis of diverse sulfoxides and sulfinamides. While the original route utilized chromatographic separation of the chiral auxiliary from the sulfinamide (Scheme 7), a chromatography-free procedure is provided for performing this three-step reaction sequence on a large scale (171 mmol) without isolation of intermediate **20** and utilizing a solvent replacement/crystallization procedure to allow separation of the sulfinamide from the chiral auxiliary. This streamlined method provides sulfinamide **1** in 76% yield and 99% ee from cyclic intermediate **19**, with 97% recovery of the chiral auxiliary **18** from intermediate **19**.

Another synthesis of *tert*-butanesulfinamide (**1**) was reported by Qin, Jiang, and co-workers.[38] In the first step of this sequence, treatment of chiral *N*-acyl amino alcohols **21** with thionyl chloride and DMAP provided 1,2,3-oxathiazolidine-2-oxides (**22**) in moderate yields and with high diastereoselectivity (Scheme 8). The intended reaction sequence, sequential displacement of the auxiliary analogous to the route developed by Senanayake, failed to proceed as expected. Low regioselectivity was observed in the ring-opening step. For example, *N*-Boc sulfinate ester **23a** could be isolated in moderate yield (63%) from the mixture of products (31% yield of regioisomer **24**). Moreover, treatment with either LHMDS or $LiNH_2/NH_3$ failed to provide the

Scheme 8. Synthesis of *tert*-Butanesulfinamide via Rearrangement to *N*-Sulfinyl Oxazolidinone



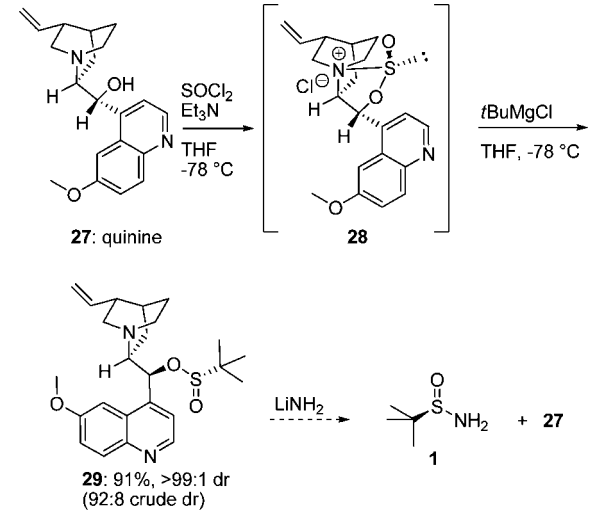
desired sulfinamide product. When the carboxybenzyl (Cbz) or carboxymethyl protecting groups were used, treatment with *tert*-butyl magnesium chloride resulted in an unexpected competitive rearrangement to provide *N*-sulfinyl oxazolidinone **25**. Consistent with Evans and co-workers' reported use of *N*-sulfinyl oxazolidinones as sulfinyl transfer reagents,[39] the authors found that addition of lithium amide in ammonia to *N*-sulfinyl oxazolidinone **25** proceeded smoothly, providing *tert*-butanesulfinamide (**1**) in 89% yield and with >98% ee.

Senanayake and co-workers also reported the use of cinchona alkaloid quinine (**27**) as a chiral auxiliary (Scheme 9).[40] Synthesis of *tert*-butanesulfinate ester **29** was carried out in one pot, with **28** as the suggested intermediate. High diastereoselectivity (92:8) was obtained, and chromatographic separation of the diastereomers provided pure **29** in 91% yield. The conversion of sulfinate ester to a variety of enantiomerically pure *tert*-butyl sulfoxides was demonstrated, but while conversion to *tert*-butanesulfinamide (**1**) was suggested, no experimental details were provided.

2.2.4. Catalytic Enantioselective Sulfinyl Transfer

Catalytic sulfinyl transfer to an achiral alcohol, utilizing dynamic kinetic resolution of *tert*-butanesulfinyl chloride (**7**) by a chiral catalytic amine, has been developed for the synthesis of enantiomerically enriched sulfinate esters **34** (Table 2). These are potential intermediates for the synthesis of enantiomerically pure sulfinamides. For example, Miller, Ellman, and co-workers developed peptide catalyst **30** (entries 1 and 2, Table 2) for this purpose,[41] based upon a successful acyl-transfer peptide catalyst.[42] Subsequently,

Scheme 9. Quinine as a Chiral Auxiliary



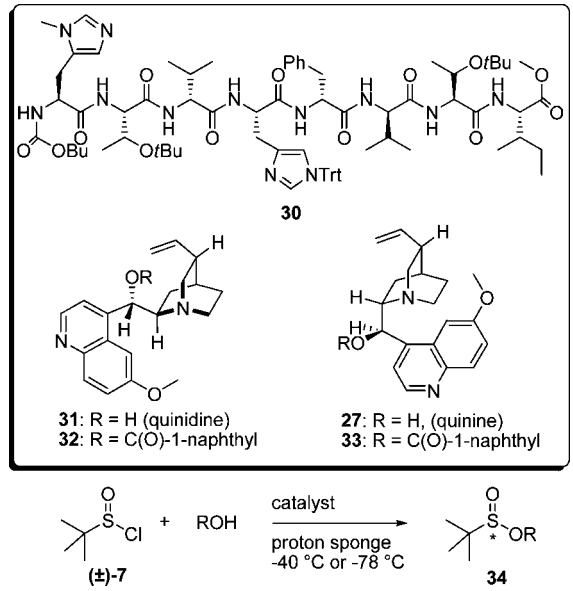
Ellman and co-workers reported the use of cinchona alkaloids such as quinidine (**31**) and quinine (**27**) for the catalytic enantioselective sulfinylation of alcohols (entries 3−5).[43] A key feature for the success of these transformations is the use of proton sponge as an HCl scavenger because it is nonnucleophilic and therefore does not catalyze nonselective sulfinate ester formation, which proved to be problematic for common hindered amine bases such as Et_3N, *i*-Pr_2EtN, and even 1,2,2,5,5-pentamethylpiperidine. Shibata, Toru, and co-workers reported the use of cinchona alkaloid derivatives **32** and **33** in a similar transformation (entries 6 and 7).[44] In each of these cases, optimization of the alcohol sulfinyl acceptors was undertaken both to enhance the enantioselectivity of the process and, in some cases, to enable crystallization of the sulfinate esters to enantiomeric purity (entries 2, 4, and 6).

2.3. Recycling *tert*-Butanesulfinamide

Wakayama and Ellman recently reported a very practical method for recycling the *tert*-butanesulfinyl group from *N-tert*-butanesulfinyl amines to provide racemic *tert*-butanesulfinamide with virtually complete recovery.[45] The key feature of this study was the HCl-mediated cleavage of the sulfinyl group from *N-tert*-butanesulfinyl amines in the absence of a nucleophilic solvent to provide *tert*-butanesulfinyl chloride as the byproduct, which can be readily recycled to *tert*-butanesulfinamide. As exemplified for *N-tert*-butanesulfinyl amine **35** (Scheme 10), treatment with HCl in cyclopentyl methyl ether results in complete conversion to *tert*-butanesulfinyl chloride (**7**) and the corresponding amine hydrochloride salt **36**, which was separated from the sulfinyl chloride solution in analytically pure form by simple filtration in 98% yield. Addition of aqueous ammonia to the sulfinyl chloride solution then provides analytically pure *tert*-butanesulfinamide in 97% overall yield based upon the starting amine **35**. The process showed no scale dependence from 1 to 80 mmol scale and should be applicable to considerably larger reaction scales.

This method was also extended to the conversion of the configurationally unstable **7** to enantiomerically pure **1** as a potentially cost-effective method for recycling enantiomerically pure **1** (Scheme 11). With this goal in mind, simple, inexpensive achiral alcohols were investigated as the sulfinyl group acceptor in a catalytic dynamic kinetic resolution

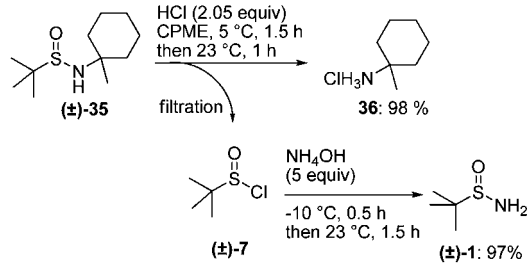
Table 2. Enantioselective Sulfinyl Transfer Catalysis



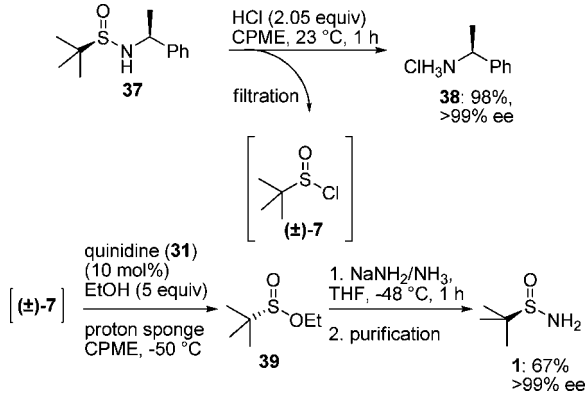
entry	catalyst	R	solvent	conv (%)	ee (%)
1	**30** (0.5 mol %)	Bn	THF	99	80 (*S*)
2	**30** (0.5 mol %)	2-naphthylmethyl	THF	99 (61)[a]	79 (>99)[a] (*S*)
3	**31** (10 mol %)	Bn	toluene	>99	87 (*S*)
4	**31** (10 mol %)	2,4,6-trichloroBn	THF	>99 (72)[a]	90 (>99)[a] (*S*)
5	**27** (10 mol %)	2,4,6-trichloroBn	THF	82	82 (*R*)
6	**32** (10 mol %)	9-fluorenyl	toluene	90[b]	94 (>99)[a] (*S*)
7	**33** (10 mol %)	9-fluorenyl	toluene	87[b]	80 (*R*)

[a] Isolated yield and ee after recrystallization. [b] Isolated yield.

Scheme 10. Recovery and Reycling of (±)-*tert*-Butanesulfinamide

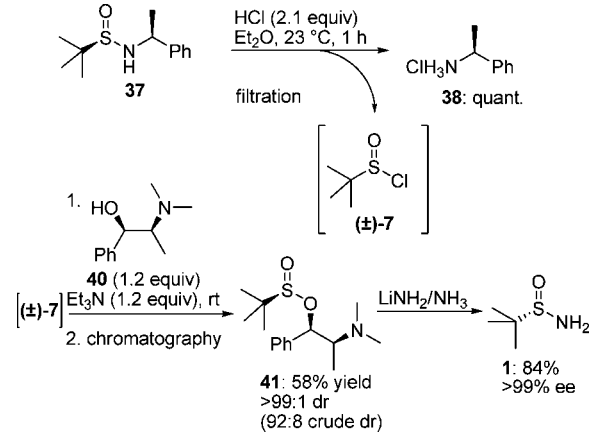


Scheme 11. Recovery and Recycling of Enantiomerically Pure *tert*-Butanesulfinamide



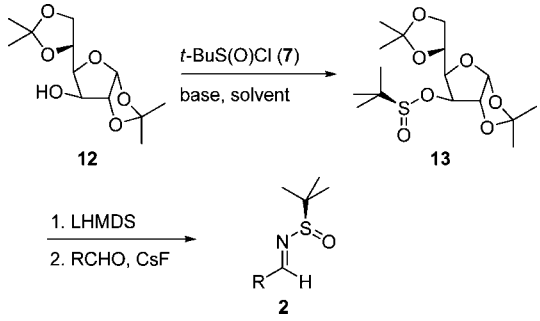
process (see section 2.2.4). Ethanol was found to perform suitably as a sulfinyl acceptor, with catalytic quinidine (**31**) and excess proton sponge. The sulfinyl transfer reaction provides sulfinate ester **39** with 87% ee under the optimized conditions. The quinidine/proton sponge mixture can be recovered by a simple extractive workup, and reuse of this mixture was demonstrated with no loss in performance. Straightforward conversion of the enantioenriched sufinate ester to *tert*-butanesulfinamide was carried out by treatment with $NaNH_2/NH_3$ with no loss of optical purity. A simple workup, including filtration to remove the inorganic salts followed by solvent replacement and trituration with octane, provided enantiomerically pure *tert*-butanesulfinamide **1** in 67% overall yield based upon the starting *N-tert*-butanesulfinyl amine **37**.

Scheme 12. Recovery and Recycling of the *tert*-Butanesulfinyl Group



Aggarwal and co-workers have also recently developed an alternative method for sulfinyl group recycling (Scheme 12).[46] In their procedure, *N-tert*-butanesulfinyl amine **37** was treated with HCl in ether to provide amine HCl salt **38**, which was removed by filtration, and a solution of *tert*-butanesulfi-

Scheme 13. Synthesis of *tert*-Butanesulfinyl Aldimines Utilizing the DAG Methodology



nyl chloride **7**. The sulfinyl chloride solution was added dropwise to a mixture of triethylamine and chiral alcohol **40**, previously developed by Drabowicz, Mikolajczyk, and co-workers as a resolving agent,[47] to provide **41** with 92:8 dr. Chromatographic separation of the diastereomers provided sulfinate ester **41** in 58% yield, from which an 84% yield of enantiomerically pure *tert*-butanesulfinamide **1** was obtained after treatment with $LiNH_2/NH_3$.

3. Synthesis and Functionalization of N-tert-Butanesulfinyl Imines

The synthesis of *N*-*tert*-butanesulfinyl imines **2** or **3** is usually carried out via a straightforward condensation reaction between *tert*-butanesulfinamide **1** and a precursor aldehyde or ketone. A wide variety of imines have been prepared to date, ranging from very simple to densely functionalized. Other *N*-*tert*-butanesulfinyl C=N containing derivatives, such as amidines and imidate esters, have also been prepared. The synthesis of more complex imines from simpler ones has also been demonstrated, both via metalloenamine intermediates and via conjugate addition to α,β-unsaturated imines.

The combination of the ease of synthesis (including functional group compatibility), hydrolytic stability (most *N*-*tert*-butanesulfinyl imines are stable enough to be purified by silica gel chromatography and handled on the benchtop with exposure to air), electrophilicity (the *N*-*tert*-butanesulfinyl group activates the imine toward nucleophilic attack), and stereocontrol (the *N*-*tert*-butanesulfinyl group is a powerful chiral directing group for diastereoselective reactions) makes *N*-*tert*-butanesulfinyl imines attractive intermediates for the synthesis of amine-containing compounds.

3.1. Synthesis of N-tert-Butanesulfinyl Imines via Condensation with tert-Butanesulfinamide

3.1.1. Synthesis of Aldimines

The first synthesis of *tert*-butanesulfinyl aldimines **2** in enantiomerically pure form was reported by Garcia Ruano and co-workers in 1996, in the context of their work on the preparation of chiral aziridines.[32] They utilized diacetone-D-glucose (DAG, **12**) as a chiral auxiliary to obtain diastereomerically pure *tert*-butanesulfinate ester **13** (Scheme 13) by a method previously developed for the synthesis of optically pure sulfoxides.[31] By changing the base and solvent, either epimer of **13** could be obtained. Following the one-pot procedure developed by Davis and co-workers for the synthesis of the analogous *p*-toluenesulfinyl imines,[48] treatment of this sulfinate ester intermediate with LHMDS formed *N*,*N*-bis(trimethylsilyl)-*tert*-butanesulfinamide *in situ*, which was then reacted with an aldehyde (benzaldehyde or cinnamaldehyde) in the presence of cesium fluoride to produce the desired aldimine **2**, which was chromatographically separated from the DAG chiral auxiliary.

The synthesis of *tert*-butanesulfinyl aldimines via the direct condensation of *tert*-butanesulfinamide **1** with carbonyl compounds was first reported by Ellman and co-workers in 1997.[16] The condensation of enantiomerically pure **1** with 2−3 equiv of aldehyde was carried out in the presence of the acidic catalyst pyridinium *p*-toluenesulfonate (PPTS) and an excess amount of $MgSO_4$ in CH_2Cl_2 to provide high yields of both aromatic and aliphatic aldimines **2**, as shown in Table 3. No racemization of the sulfinyl stereocenter was observed. Further studies revealed that the more Lewis acidic $CuSO_4$ was a more effective agent for this transformation, allowing the use of a smaller excess (1.1 equiv) of aldehyde.[49,50] A few substrates were found to be unreactive under the $CuSO_4$ conditions; in these cases, it was found that $Ti(OEt)_4$ was an effective water scavenger and Lewis acid catalyst. Select examples of the product imines derived from each of these methods were analyzed by chiral HPLC using racemic standards, demonstrating that no racemization of the sulfinyl stereocenter occurred during the condensation reaction.

All of the aldimines **2** reported in this study were found to be reasonably hydrolytically stable, allowing isolation by silica gel chromatography.[50] The imines can be handled in air at room temperature, although prolonged storage at room temperature in air and with exposure to light resulted in minor decomposition over a period of weeks or months. Decomposition could be prevented by storing the aldimines in closed containers at −5 °C.

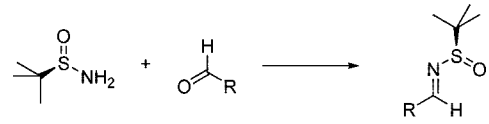
In 2004, Nakata and co-workers reported on the use of Cs_2CO_3 as an activating and dehydrating reagent with gentle heating for the synthesis of *N*-*tert*-butanesulfinyl aldimines.[51] This procedure was performed using equimolar amounts of sulfinamide, aldehyde, and base, in contrast to previously published methods that utilized excess amounts of the activating reagents. Chiral HPLC analysis of one of the product imines again demonstrated that no racemization occurred.

Qin and co-workers developed a protocol for the condensation of aldehydes with *tert*-butanesulfinamide mediated by $KHSO_4$ with gentle heating.[52] As shown in Table 3, these conditions were found to be effective for a broad range of substrates, including electron rich and electron poor aromatic aldehydes, α,β-unsaturated aldehydes, and both sterically hindered and unhindered aliphatic aldehydes. While 2 equiv of aldehyde were used in most cases, the use of 1.1 equiv of benzaldehyde gave only a slightly lower yield of the corresponding imine (86% vs 91%). The authors note that 5 equiv of aldehyde were required to obtain satisfactory yields of imines **2** derived from volatile aliphatic aldehydes.

The synthesis of sulfinyl imines promoted by catalytic amounts of the Lewis acid $Yb(OTf)_3$ has also been reported.[53] While this protocol was developed for the synthesis of *N*-*p*-toluenesulfinyl imines, it was also shown to be effective toward the synthesis of *N*-*tert*-butanesulfinyl imines **2**. In this case, a large excess of aldehyde was used to drive the reaction toward completion in the absence of a stoichiometric acid or drying agent.

Another method for the synthesis of *N*-*tert*-butanesulfinyl imines **2** utilizes NaOH or *t*BuOK as a base.[54] While these conditions were not found to be suitable for the synthesis of imines derived from enolizable aliphatic aldehydes, high

Table 3. Synthesis of Sulfinyl Aldimines



1 **2**

	yield (%)							
R	$MgSO_4$[a]	$CuSO_4$[b]	$Ti(OEt)_4$[c]	Cs_2CO_3[d]	$KHSO_4$[e]	$Yb(OTf)_3$[f]	NaOH[g]	BnZnBr[h]
primary alkyl	96	96	quantitative	73	80			92
secondary alkyl	90	90		76	80	87		78−91
tertiary alkyl		trace	82	59	81			56
Bn	86	79	84		60			
alkenyl			75−95[k]		91−93	87	72[i]	91
Ph	90	91		85[j]	91	84	91	92
4-MeOPh		81		55[j]	80		92	89
4-NO_2Ph				99[j]	92			
2-furyl		40	82		84		87	83
2-Pyr		95			95			57
3-Pyr		trace	quantitative		88			60
4-Pyr				99[j]	93			

[a] RCHO (2−3 equiv), $MgSO_4$ (5 equiv), PPTS (0.05 equiv), CH_2Cl_2, rt.[50] [b] RCHO (1.1 equiv), $CuSO_4$ (2 equiv), CH_2Cl_2, rt.[50] [c] RCHO (1.1 equiv), $Ti(OEt)_4$ (2 equiv), THF, rt.[50] [d] RCHO (1.0 equiv), Cs_2CO_3 (1 equiv), CH_2Cl_2, 40−45 °C.[51] [e] RCHO (2−5 equiv), $KHSO_4$ (2 equiv), toluene, 45 °C.[52] [f] RCHO (3.5−4 equiv), $Yb(OTf)_3$ (0.1 equiv), THF, rt.[53] [g] RCHO (1.5 equiv), NaOH (1 equiv), MeOH, rt.[54] [h] RCHO (1.5 equiv), Zn dust (3 equiv), BnBr (2 equiv), THF, rt, (±)-**1** was used.[55] [i] *t*BuOK was used as the base in THF. [j] Conversion based on crude ^{1}H NMR. [k] RCHO (1.0 equiv), $Ti(OEt)_4$ (3 equiv), THF, rt.[56]

yields were obtained for aromatic and α,β-unsaturated derivatives. In addition to chiral HPLC analysis of the product imines and comparison of optical rotation to literature values, the Kawecki group also developed a procedure for the determination of the enantiopurity of sulfinyl aldimines utilizing (*S*)-BINOL as a chiral solvating agent for ^{1}H NMR analysis.[57] Racemization of the sulfinyl stereocenter was found to be negligible in all cases.

Recently, Fan and co-workers reported a procedure for the synthesis of aldimines under Barbier-type conditions.[55] These conditions were demonstrated for the synthesis of both *N*-sulfonyl and *N*-sulfinyl imines and utilized racemic *tert*-butanesulfinamide. In this procedure, benzyl bromide and zinc dust are reacted to form BnZnBr *in situ* and then the sulfinamide and aldehyde are added. It is proposed that the BnZnBr acts as a base to deprotonate the sulfinamide, and then the coordinated zinc acts as a Lewis acid to activate the carbonyl to attack via a 4-membered transition state. This protocol was shown to be effective for a wide range of substrates, including aliphatic, α,β-unsaturated, aromatic, and heteroaromatic aldehydes.

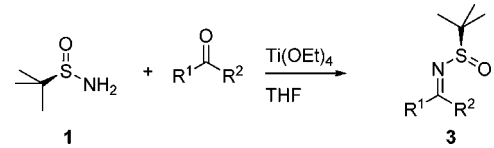
3.1.2. Synthesis of Ketimines

The synthesis of *N*-*tert*-butanesulfinyl ketimines **3** is more challenging than that of aldimines **2**. Most of the conditions reported for the synthesis of aldimines fail to provide condensation products when ketones are used as the reactant. The synthesis of *N*-*tert*-butanesulfinyl ketimines **3** was first reported by the Ellman group in 1999.[49,50] Several titanium(IV) reagents were investigated, and it was determined that the use of 1.1 equiv of ketone and 2 equiv of $Ti(OEt)_4$ in THF at elevated temperatures provided high yields of the desired imines **3** (Table 4). It was noted that some of the ketimine products are susceptible to thermal decomposition; therefore, careful TLC monitoring of the reactions is advised to prevent decomposition. The standard protocol is to initially heat the reaction mixture to 60 °C, increasing to reflux temperatures if the reaction is sluggish. Many of the imines are observed as exclusively the *E* isomer, while those imines bearing R groups that are very similar in steric bulk (for example, Bu or *i*-Bu with Me, entries 6 and 7) are observed as rapidly equilibrating mixtures of *E*/*Z* isomers that can be observed on the ^{1}H NMR time scale.

The *tert*-butanesulfinyl ketimines **3** investigated in this study could all be handled in the air, although they were found to be less hydrolytically stable than the corresponding aldimines. The relative stabilities of the imines to silica gel chromatography were found to correspond to the rates of hydrolysis in air. Chromatographic purification was successful, though precautions to limit the silica exposure time of the more hydrolytically unstable derivatives were necessary. The α-aryl derivatives were observed to be less prone to hydrolysis than the aliphatic derivatives, some of which hydrolyze fully over the course of two days in air. All of the derivatives investigated, including the aliphatic ones, could be stored in closed containers at −5 °C for months with no signs of decomposition.

The synthesis of a variety of cyclic ketimines via $Ti(OEt)_4$-mediated condensation of ketones with *tert*-butanesulfinamide has also been reported (Figure 1). The synthesis of cyclohexanone derivative **42** was initially reported under the same reaction conditions as those shown in Table 4,

Table 4. Condensation of Ketones with *tert*-Butanesulfinamide Mediated by $Ti(OEt)_4$[50]



1 **3**

entry	R^1	R^2	temp (°C)	time (h)	yield (%)	*E*/*Z* ratio
1	Ph	Me	75	15	89	one isomer
2	*i*-Pr	Me	60	7	84	one isomer
3	*i*-Pr	Bu	75	24	77	one isomer
4	Ph	Bu	75	5	77	one isomer
5	2-naphthyl	Me	75	15	73	one isomer
6	*i*-Bu	Me	60	10	88	6:1
7	Bu	Me	60	10	77	5:1
8	*t*-Bu	Me	75	24	82	one isomer

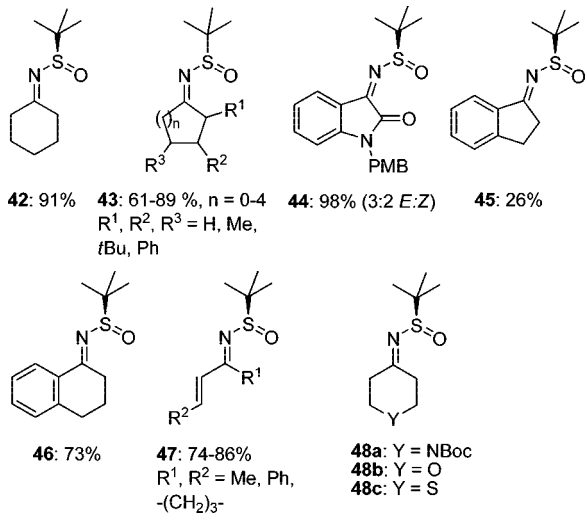


Figure 1. Additional *N-tert*-butanesulfinyl ketimines.

providing the imine in 91% yield after bulb-to-bulb distillation.[50] Imines with a variety of ring sizes and substitution patterns (**43**) have also been synthesized under similar conditions and were isolated in good yields after rapid silica gel chromatography.[9,13,58] Additionally, the syntheses of isatin derivative **44**[59] and both indanone derivative **45** (in low yield) and tetralone derivative **46** (in high yield)[60] have all been reported under similar condensation conditions. The synthesis of α,β-unsaturated ketimines **47** has also been accomplished.[61] In this case, a larger excess of $Ti(OEt)_4$ (4.0 equiv instead of 2.0 equiv) was found to help promote complete conversion to the imine product. The synthesis of ketimine **48a**, derived from *N*-Boc-piperidin-4-one, was explored by Caldwell and Collins.[6] While attempts to isolate this ketimine directly were unsuccessful due to hydrate formation, both trapping with TMSCN in a reversible Strecker reaction or direct use of the ketimine *in situ* after its formation were successful (see section 5.1). Other heterocyclic derivatives such as **48b** and **48c** have also been reported.[7]

3.1.3. Synthesis of α-Heteroatom Substituted Imines

In addition to the synthesis of aliphatic, α,β-unsaturated, aromatic, and heteroaromatic imine derivatives, the condensation of *tert*-butanesulfinamide with aldehydes and ketones bearing other functional groups has also been accomplished. For example, aliphatic imines bearing α-heteroatom functionality, including α-alkoxy aldimines **49**[62−64] and ketimines **50**,[63] α-amino aldimines **51**,[65] and ketimine **53**,[66] and α-chloro aldimines[67] and ketimines[68] **54** (Figure 2) have been reported. In cases where enantiomerically pure α-chiral aldehyde or ketone precursors were used, no epimerization at the α-stereocenter was detected.

N-tert-Butanesulfinyl imino esters **55** (eq 1) have been synthesized in two different ways. $CuSO_4$ was found to be effective, mediating the condensation of *tert*-butanesulfinamide **1** with methyl glyoxalate to provide **55a** in 65% yield.[50] Alternatively, Davis and co-workers reported the use of 4 Å molecular sieves to give 94% yield of the desired imine **55b** from an equimolar mixture of sulfinamide **1** and ethyl glyoxalate.[69] The *tert*-butyl ester **55c**[70] and benzyl ester **55d**[71] have also been prepared under these conditions. In contrast to *N*-sulfonyl[72] and *N*-Boc imino esters,[73] these *N-tert*-butanesulfinyl imino esters **55** are stable enough to be purified by rapid silica gel chromatography and can be stored dry in

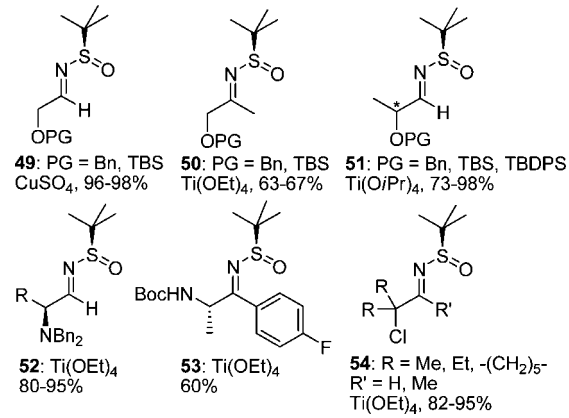
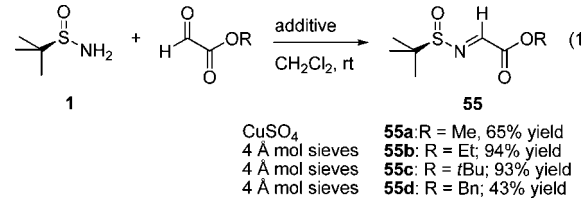


Figure 2. α-Heteroatom imines.

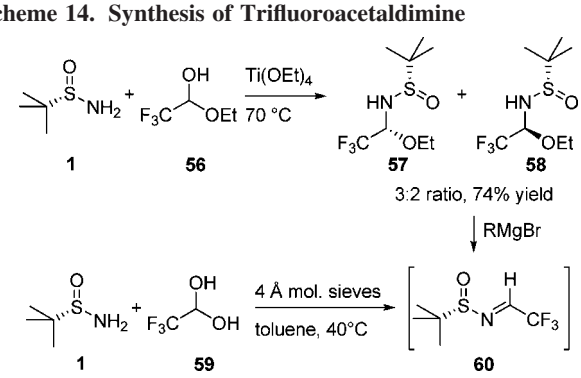
closed containers for prolonged time periods at low temperature (−20 °C).



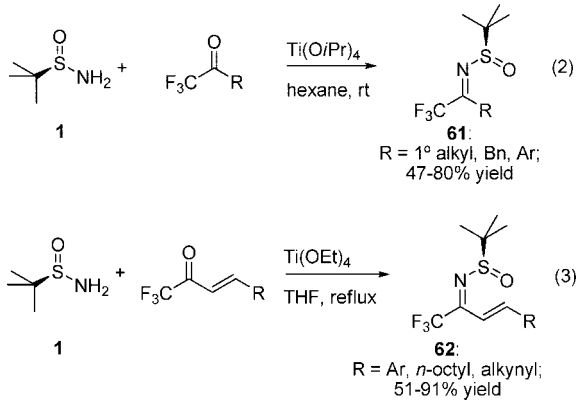
N-tert-Butanesulfinyl trifluoroacetaldimine (**60**) is a synthetically useful imine that was not reported in the early studies on substrate scope (Scheme 14). The strong electron-withdrawing character of the trifluoromethyl group prevents isolation of the imine; however, Kuduk and co-workers at Merck were able to demonstrate the synthesis and isolation of the imine−ethanol adduct as a separable mixture of diastereomers **57** and **58**.[74] This adduct is then used to form the imine *in situ* in the presence of Grignard reagents. Alternatively, Truong and co-workers reported the synthesis of imine **60** via the condensation of *tert*-butanesulfinamide with trifluoroacetaldehyde hydrate **59** in toluene in the presence of molecular sieves.[75] Although the imine was converted to an aminal upon aqueous quenching, and distillation provided a poor yield (22%) due to decomposition, the crude imine solution could be used directly in subsequent reactions.

N-tert-Butanesulfinyl ketimines bearing the trifluoromethyl substituent have also been reported (eqs 2 and 3). Lu and co-workers reported the synthesis of a variety of alkyl and aryl trifluoromethyl ketimines in the presence of $Ti(OiPr)_4$ in hexanes.[76] In contrast to the corresponding aldimine **60**, ketimines **61** are stable enough to be quickly isolated by silica gel chromatography, although they cannot be stored for

Scheme 14. Synthesis of Trifluoroacetaldimine



extended periods of time. Still more stable are the trifluoromethyl α,β-unsaturated *N-tert*-butanesulfinyl ketimines **62**, which Liu and Liu reported can be synthesized via $Ti(OEt)_4$-mediated condensation and can be chromatographed and stored at room temperature for several months with no signs of decomposition.[77]



3.1.4. Synthesis of Imidate Esters and Amidines

The syntheses of *N-tert*-butanesulfinyl imidate esters and amidines such as **63** and **64**, respectively, have been reported (Scheme 15).[78,79] Acid-catalyzed condensation of *tert*-butanesulfinamide with an orthoformate provides imidate esters **63**. Treatment of these intermediates with an amine such as morpholine yields the corresponding amidines **64**. The use of amidines as chiral ligands for catalysis has been explored (see section 20.1.1).[80−82] Additionally, both imidate esters and amidines have been used as substrates for α-alkylation reactions (see section 3.2.5). Following α-alkylation of amidines **64**, treatment with a reductant or an organometallic reagent provides *N-tert*-butanesulfinyl aldimine or ketimine products, respectively, that can then be used in further transformations (see Scheme 28 and section 3.2.5).[79] Alternatively, deprotection after α-alkylation of *N-tert*-butanesulfinyl imidate esters **63** can lead to primary amides and esters (see Scheme 31 and section 3.2.5).[78]

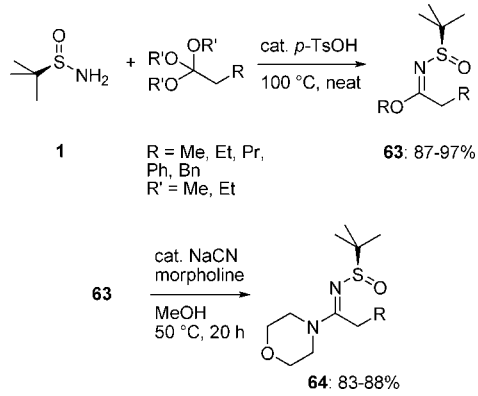
3.2. Functionalization of *N-tert*-Butanesulfinyl Imines via Metalloenamine Intermediates

3.2.1. 1,2-Addition of Metalloenamines to Aldehydes and Ketones

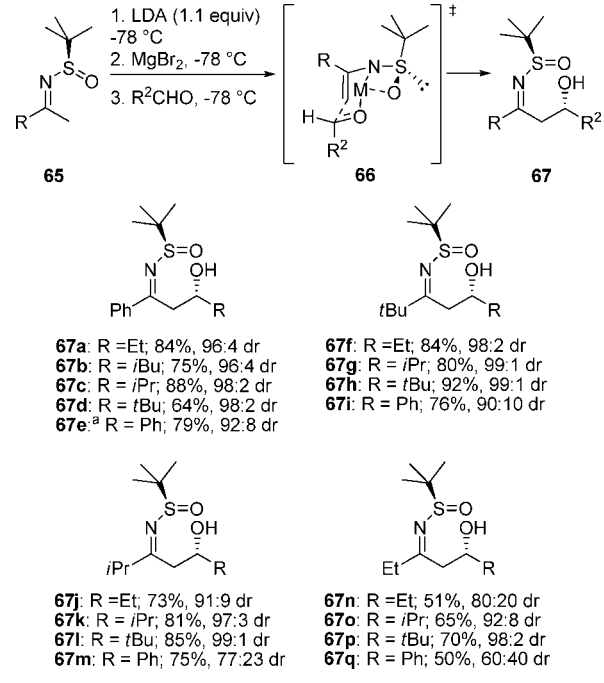
The chemistry of enamines derived from *N-tert*-butanesulfinyl ketimines was first described by Ellman and coworkers in a 2002 Communication[83] and was further developed in a full account.[84] In their initial report, the *N-tert*-butanesulfinyl metalloenamine derived from imine **65** (R = Ph) was added to aldehydes to provide β-hydroxy *N-tert*-butanesulfinyl imines **67** (Scheme 16). In initial studies, deprotonation of ketimine **65** (R = Ph) with LDA in THF at low temperature (−78 °C) followed by reaction with propionaldehyde gave **67a** in 80% yield and 86:14 diastereomeric ratio. Evaluation of metal additives revealed that a higher diastereoselectivity and yield were achieved in the presence of $MgBr_2$ (84%, 96:4 dr, Scheme 16). Addition of the same metalloenamine to aryl and β- and α-branched aldehydes in the presence of $MgBr_2$ or $ZnBr_2$ gave **67b−e** in 64−88% yield and with diastereomeric ratios ranging from 92:8 to 98:2. The scope of the starting ketimine **65** was expanded in the full paper to include several structurally diverse aliphatic substituents, including *tert*-butyl, isopropyl, and ethyl. When *N-tert*-butanesulfinyl ketimines **65** with two different α protons were utilized, only the products derived from deprotonation at the less hindered methyl position followed by addition to the aldehyde were observed (**67j−q**). For these ketimine precursors (R = *i*Pr or Et), the yields and diastereoselectivities were generally very good for additions to aliphatic aldehydes, while lower diastereomeric ratios were observed when benzaldehyde was used as the electrophile (**67m** and **67q**). The absolute configuration of β-hydroxy *N-tert*-butanesulfinyl imine **67e** was determined by X-ray structural analysis, and the configuration of **67c** was determined by chemical correlation. The stereochemical outcome was rationalized by the cyclic transition state **66**, with the approach of the aldehyde occurring from the side opposite the *tert*-butyl group.

The highly stereoselective reduction of the β-hydroxy *N-tert*-butanesulfinyl imines **67** to provide either the *syn*- or *anti*-1,3-amino alcohols **68** or **69** (Scheme 17) was disclosed (the details of which are discussed in section 13.1), providing a very efficient method for the stereoselective synthesis of each of the four possible stereoisomers of a broad range of

Scheme 15. Synthesis of *N-tert*-Butanesulfinyl Amidines

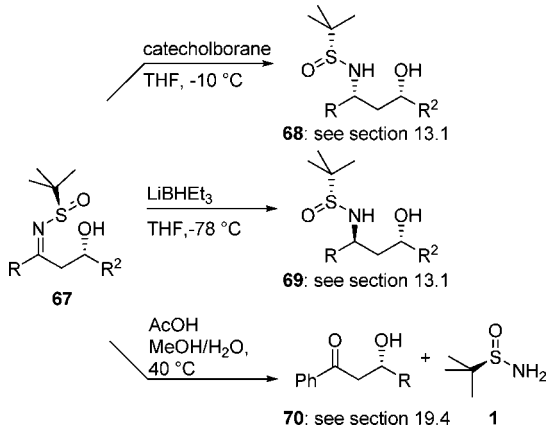


Scheme 16. Addition of Metalated *N-tert*-Butanesulfinyl Ketimines to Aldehydes

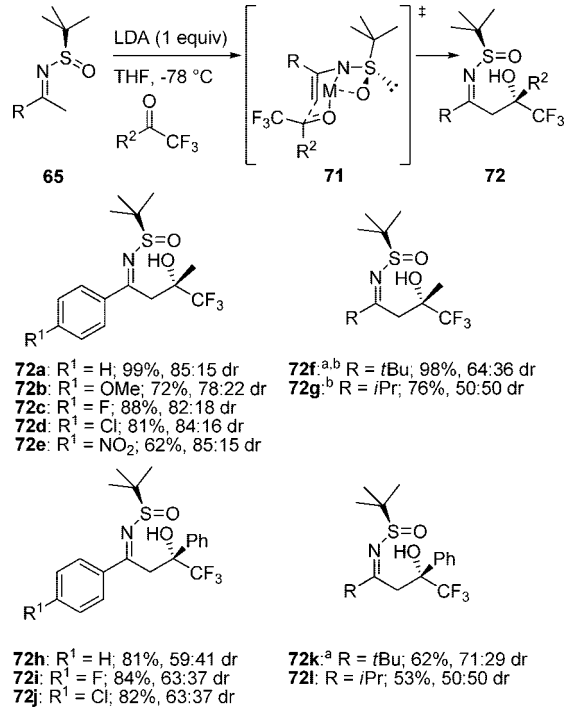


[a] $ZnBr_2$ was used as an additive instead of $MgBr_2$.

Scheme 17. Synthetic Transformations of β-Hydroxy *N-tert*-Butanesulfinyl Imines 67



Scheme 18. Addition of *N-tert*-Butanesulfinyl Metalloenamines to Trifluoromethyl Ketones

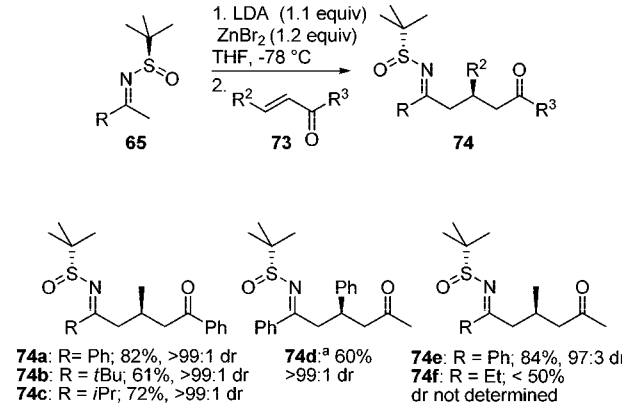


[a] The diastereomers could not be separated by column chromatography. [b] $MgBr_2$ was used as an additive.

1,3-amino alcohols. The hydrolysis of the β-hydroxy *N-tert*-butanesulfinyl imines **67c** and **67e** to give the corresponding β-hydroxy ketones **70** was also performed (see section 19.4).

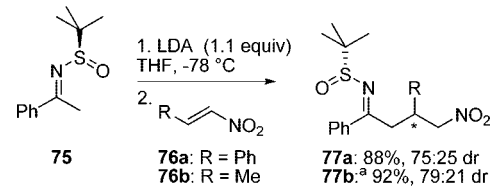
The synthesis of β-hydroxy-β-trifluoromethyl imines was achieved by Liu and co-workers via the addition of the metalloenamine derived from ketimines **65** to a number of trifluoromethylated ketones (Scheme 18).[85] Several parameters were examined, and the best results were achieved by using LDA in THF at low temperature (−78 °C). A series of aryl *N-tert*-butanesulfinyl ketimines were reacted with trifluoroacetone to provide **72a**−**e** in good yields and with diastereomeric ratios ranging from 78:22 to 85:15. Two alkyl *N-tert*-butanesulfinyl ketimines were also evaluated, but adducts **72f** and **72g** were isolated with modest diastereoselectivities. The authors noted that increased yields of **72f** and **72g** were obtained upon addition of $MgBr_2$ (76−98% versus 50−63%), but modest diastereoselectivities were still observed. Additions of aryl and alkyl-*N-tert*-butanesulfinyl ketimines **65** to trifluoroacetophenone (R^2 = Ph) were also demonstrated. Although **72h**−**l** were synthesized in good yields, poor diastereoselectivities were observed (up to 71:29 dr). For most of the transformations, the major and minor diastereomers were separated by column chromatography. The absolute configuration of **72a** was established by X-ray structural analysis and the stereochemical outcome was rationalized by the chelated transition state **71**, which is analogous to the one previously invoked by Ellman and coworkers for metalloenamine additions to aldehydes (*vide supra*). Hydrolysis of **72a** was also demonstrated (see section 19.4).

Scheme 19. Additions of *N-tert*-butanesulfinyl Metalloenamines to α,β-Unsaturated Ketones



[a] Reaction mixture was warmed from −78 to −20 °C.

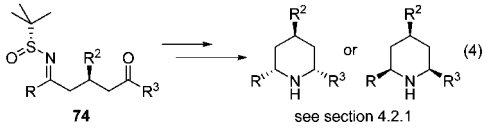
Scheme 20. Additions of *N-tert*-butanesulfinyl Metalloenamines to Nitroalkenes



[a] $MgBr_2$ (1.2 equiv) was used as an additive.

3.2.2. 1,4-Addition of Metalloenamines to α,β-Unsaturated Ketones

The scope of *N-tert*-butanesulfinyl metalloenamine chemistry was expanded by Ellman and Peltier to include α,β-unsaturated ketones as competent electrophiles (Scheme 19).[86] Deprotonation of the *N-tert*-butanesulfinyl ketimine **65** (R = Ph) with LDA in the presence of $ZnBr_2$ followed by 1,4-addition to a number of α,β-unsaturated ketones **73** provided **74a**, **d**, and **e** in good yields (60−84%) and with 96:4 to 99:1 dr. Alkyl ketimines **65** (R = *t*Bu) and (R = *i*Pr) gave Michael addition products **74b** and **74c** in good yields and with high diastereoselectivities, respectively, but ketimine **65** (R = Et) provided addition product **74f** in less than 50% yield, and the diastereoselectivity was not ascertained. Additions of *N-tert*-butanesulfinyl metalloenamines to nitroalkenes **76a** and **76b** were also explored, providing **77a** and **77b** in high yields, but with only moderate diastereoselectivities (Scheme 20). The Michael addition products **74** were further utilized in the asymmetric syntheses of 2,4,6-trialkyl-substituted piperidines (eq 4, see section 4.2.1 for the details of this transformation).

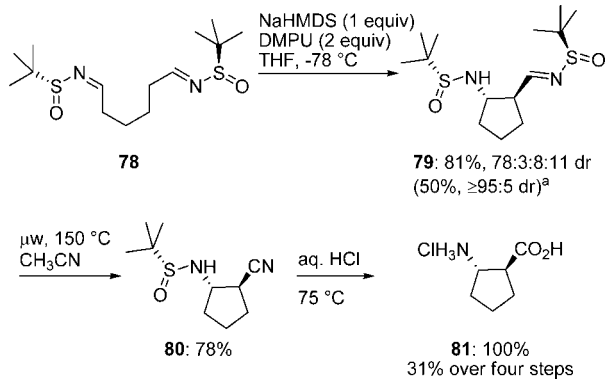


3.2.3. 1,2-Addition of Metalloenamines to Imines

The use of *N-tert*-butanesulfinyl metalloenamines derived from aldimines was explored in an effort to broaden the scope of the metalloenamine methodology. However, self-condensation of the enamine during the deprotonation step was the prevailing reaction observed. This pathway was exploited by Ellman and Schenkel in the synthesis of two biologically significant heterocycles: *trans*-2-aminocyclopentanecarboxylic acid (**81**) and SC-53116 (**87**) (Schemes 21 and 22).[87] An intramolecular self-condensation toward **81**, a β-amino acid that has been incorporated into homo- and heterogeneous foldamers, was first explored with bis-*N-tert*-butanesulfinyl aldimine **78**. A high level of diastereocontrol was observed with sodium hexamethyldisilazide (NaHMDS) as the optimal base, and addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was important for allowing the reaction to proceed in high yield (Scheme 21). Significantly, recrystallization of **79** provided diastereomerically pure material in 50% yield. Conversion of sulfinyl imine **79** to nitrile **80** was achieved in one step by heating to 150 °C under microwave conditions (see also section 19.3). Concomitant removal of the sulfinyl group and hydrolysis of the nitrile furnished **81** without detectable racemization to complete the synthesis in four steps and 31% overall yield.

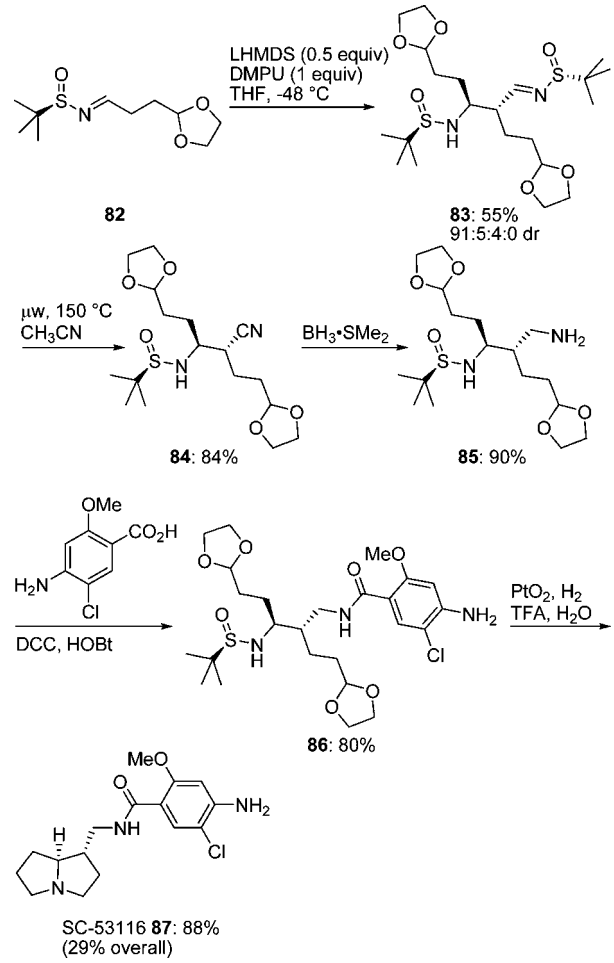
A diastereoselective intermolecular self-condensation reaction was used for the synthesis of the highly potent and selective serotonin 5-HT_4 agonist SC-53116 (**87**) (Scheme 22). For the self-condensation of **82**, lithium hexamethyldisilazide (LHMDS) was identified as the optimal base, and **83** was generated in 55% yield as a 91:5:4:0 mixture of diastereomers. Microwave irradiation of *N*-sulfinyl imine **83** produced nitrile **84**, which was separated from the minor diastereomers by column chromatography and was subsequently reduced to the primary amine **85**. Amide-bond formation yielded intermediate **86** in 80% yield. Concomitant removal of the sulfinyl and acetal protecting groups and cyclization to form the pyrrolizidine core was achieved under acidic reducing conditions. This highly efficient synthesis of **87** was completed in five steps and 29% overall yield from the *N-tert*-butanesulfinyl imine **82**. The authors also

Scheme 21. Synthesis of *trans*-2-Aminocyclopentanecarboxylic Acid 81

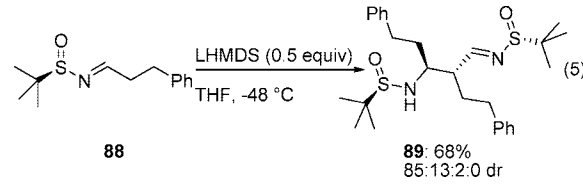


[a] Isolated yield and dr after crystallization.

Scheme 22. Synthesis of SC-53116

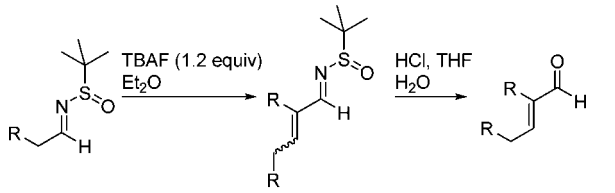


demonstrated that the high selectivity in this type of intermolecular self-condensation transformation could also be achieved with *N-tert*-butanesulfinyl imines lacking a coordinating group, such as **88** (eq 5).



The synthesis of α,β-unsaturated *N-tert*-butanesulfinyl imines **91** via intermolecular self-condensation of racemic *N-tert*-butanesulfinyl aldimines **90** followed by elimination was reported by Qin and co-workers (Table 5).[88] A variety of bases and solvents were tested, and tetrabutylammonium fluoride and Et_2O provided the best combination for achieving high yields and *E/Z* ratios of the double bond. A number of *N-tert*-butanesulfinyl aldimines were evaluated as substrates, providing moderate to good yields of the *E*-α,β-unsaturated imine products **91a**−**e** (entries 1−5). Imines **91a** and **91c** were further transformed to the corresponding enals **92** as single isomers in excellent yields by treatment with HCl in THF−H_2O. The direct preparation of several enals (**92f**−**h**, entries 6−8) was also demonstrated. Notably, when imine precursors **90** with phenyl or *tert*-butyl substitution at the α-position were explored, none of the desired α,β-unsaturated *N-tert*-butanesulfinyl imines were obtained (entries 9−10). A cross-condensation of the *N-tert*-butanesulfi-

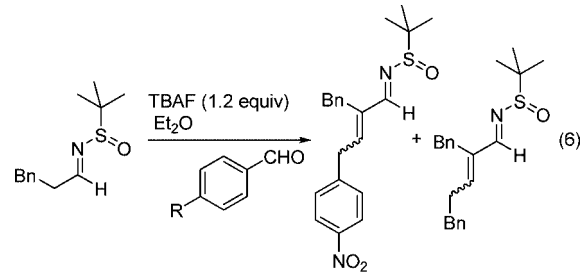
Table 5. Synthesis of α,β-Unsaturated *N-tert*-Butanesulfinyl Imines 91 and Enals 92



(±)-90 (±)-91 92

entry	R	91	yield (%)	*E/Z*	92	yield (%)	*E/Z*
1	hexyl	**91a**	82	43:1	**92a**	89	99:1
2	Et	**91b**	68	11:1			
3	Bn	**91c**	50	99:1	**92c**	90	99:1
4	$AcO(CH_2)_2$	**91d**	80	11:1			
5	$BnO(CH_2)_2$	**91e**	82	16:1			
6	$Me(CH_2)_{13}$				**92f**	66	99:1
7	$BnO(CH_2)_3$				**92g**	54	99:1
8	$BnO(CH_2)_4$				**92h**	55	99:1
9	Ph	**91i**	0				
10	*t*Bu	**91j**	0				

nyl aldimine **93** with *p*-nitrobenzaldehyde was demonstrated and provided a mixture of products **94** and **91c** (eq 6). However, when electron-rich aromatic aldehydes were employed, the self-condensation product **91c** was observed exclusively.



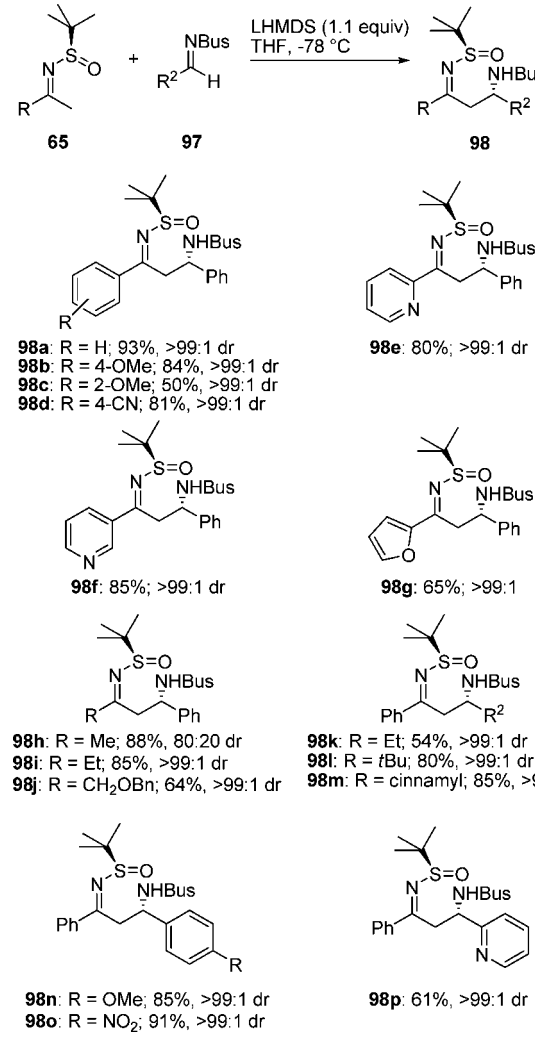
93

R = NO_2 **94**: 58% **91c**: 29%
R = Me **95**: 0% **91c**: 47%
R = OMe **96**: 0% **91c**: 49%

The development of an aza-Mannich reaction between *N-tert*-butanesulfinyl metalloenamines and highly electrophilic (*E*)-*N-tert*-butanesulfonyl (Bus) aldimines **97** was conducted by Lanter and co-workers (Scheme 23).[89] As previously observed for the intermolecular self-condensation of *N-tert*-butanesulfinyl metalloenamines (*vide supra*),[87] lithium hexamethyldisilazide (LHMDS) was the best base. A number of electron-rich and electron-deficient substituted aryl and heteroaryl *N-tert*-butanesulfinyl ketimines **65** were reacted with the *N*-Bus imine of benzaldehyde, providing **98a**−**g** in varying yields (50−93%) with exquisite diastereoselectivity. Reactions utilizing alkyl *N-tert*-butanesulfinyl ketimines **65** also proceeded efficiently and with high diastereoselectivity (**98i**−**j**, >99:1 dr), with the ketimine **65** derived from acetone being the notable exception (**98h**, 80:20 dr). Alkyl, alkenyl, and aryl substituents on the Bus-imine electrophile were also effective substrates, providing **98k**−**p** as single diastereomers in moderate to good yields (54−91%). The utility of this method was illustrated by the elegant synthesis of manzacidin C (**102**, Scheme 24; see section 14.1 for details).

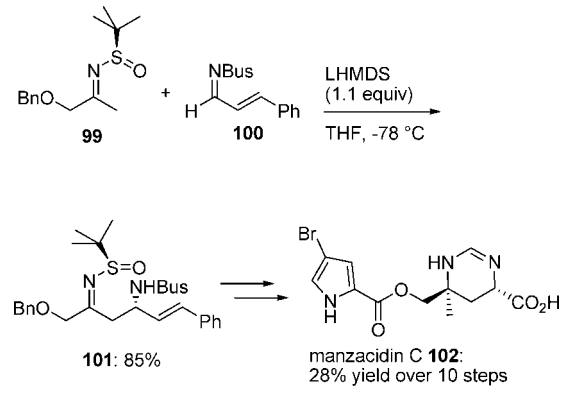
The aza-Mannich reaction between acetophenone-derived *N-tert*-butanesulfinyl metalloenamines was also explored with *N-p*-toluenesulfonyl aldimines as the electrophilic coupling partners by Wang, Chen, and co-workers (Scheme 25).[90] A screen of bases and solvents was conducted, with LDA in

Scheme 23. Additions of *N-tert*-Butanesulfinyl Metalloenamines to *N-tert*-Butanesulfonyl Aldimines

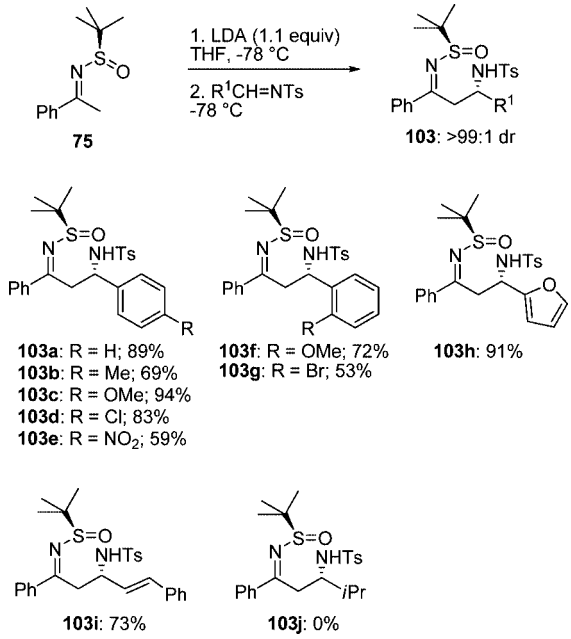


THF providing the best results. A number of electronically diverse aryl and alkenyl *N-p*-toluenesulfonyl aldimines were evaluated, affording **103a**−**i** in high yields and with excellent diastereoselectivities. Notably, the aliphatic *N-p*-toluenesulfonyl aldimine (R^1 = *i*Pr) was not a suitable substrate in this transformation (**103j**: 0% yield). The absolute configuration of adduct **103c** was established by X-ray structural analysis and was consistent with the chelated transition state proposed by Ellman and co-workers for the analogous reaction of *N-tert*-butanesulfinyl metalloenamines with aldehydes (see Scheme 16). Several subsequent synthetic

Scheme 24. Synthesis of Manzacidin C



Scheme 25. Additions of *N-tert*-Butanesulfinyl Metalloenamines to *N-p*-Toluenesulfonyl Aldimines

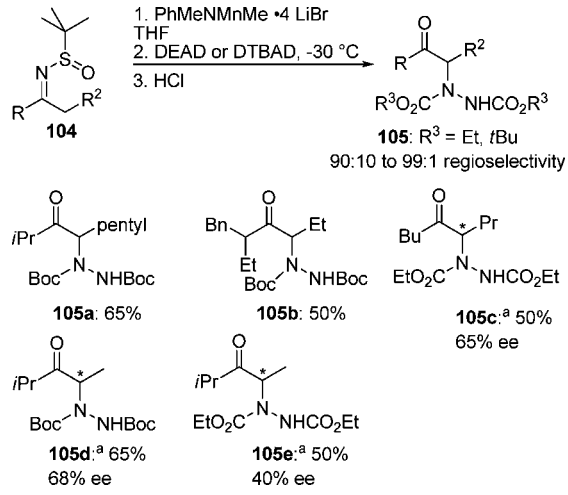


transformations were demonstrated on the *N*-protected β-amino *N-tert*-butanesulfinyl ketimines, including hydrolysis (see section 19.4), enolate additions (see section 10.1.1), Grignard additions (see section 14.1), and diastereoselective reductions (see section 14.1) to provide a diverse range of products.

3.2.4. Addition of Metalloenamines to Azodicarboxylates

The α-amination of *N-tert*-butanesulfinyl ketimines was explored by Ricci and co-workers, and a number of α-hydrazino ketones were prepared after acidic hydrolysis (Scheme 26).[91] For this transformation, the *N-tert*-butanesulfinyl metalloenamines were generated from the organomanganese amide, PhMeNMnMe·4LiBr, prepared by treatment of the $MnBr_4Li_2$ "ate" complex with MeLi and *N*-methylaniline. Subsequent reaction with either di-*tert*-butyl azodicarboxylate (DTBAD) or diethyl azodicarboxylate (DEAD) as the electrophilic aminating reagents followed by

Scheme 26. Addition of *N-tert*-Butanesulfinyl Metalloenamines to Azodicarboxylates



[a] An imine synthesized with (*R*)-*tert*-butanesulfinamide was employed.

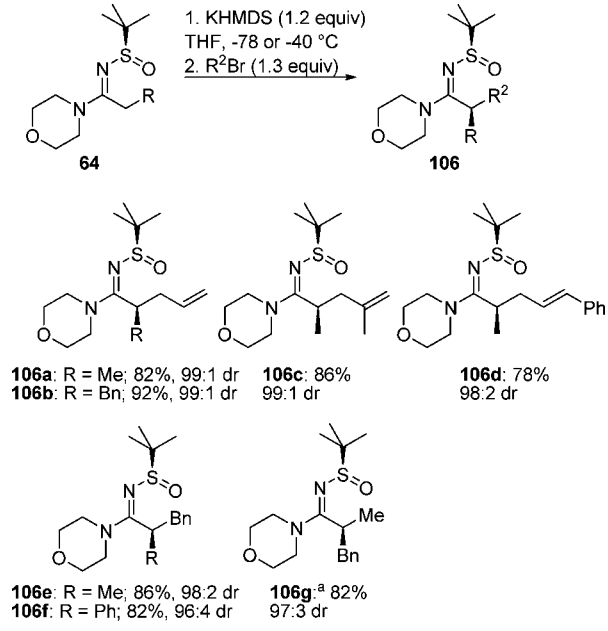
hydrolysis provided α-hydrazino ketones **105**. Two racemic *N-tert*-butanesulfinyl ketimines **104** were examined, providing **105a** and **105b** in moderate yields, primarily as the kinetic regioisomers with amination at the least hindered site (Scheme 26). When enantiomerically pure *N-tert*-butanesulfinyl imines **104** were evaluated, the kinetically favored α-amino ketones **105c**−**e** were generated with moderate yields (50−65%) and enantioselectivities (40−68%). Unfortunately, the absolute configurations of these products were not identified.

3.2.5. α-Alkylation N-tert-Butanesulfinyl Amidines and Imidate Esters

After Ellman and co-workers demonstrated the addition of *N-tert*-butanesulfinyl metalloenamines to aldehydes for the efficient synthesis of either *syn*- or *anti*-1,3-amino alcohols (see sections 3.2.1 and 13.1), they explored the expansion of this methodology to include other electrophiles. However, the authors noted that the analogous alkylations of *N-tert*-butanesulfinyl metalloenamines by alkyl halides failed, presumably due to the highly electron-withdrawing nature of the *tert*-butanesulfinyl group. In order to circumvent this limitation, the more basic metalloenamines derived from *N-tert*-butanesulfinyl amidines (the syntheses of which are described in section 3.1.4) were employed (Scheme 27).[79] Deprotonation of **64** (R = Me) with KHMDS in THF at low temperature (−78 °C) provided **106a** in 82% yield and with 99:1 diastereomeric ratio. Similarly impressive yields and diastereoselectivities were achieved when other alkyl bromides were employed (**106c**−**e**). When the more hindered amidines **64** (R = Ph or Bn) were utilized, it was necessary to increase the temperature to −40 °C, but even at this elevated temperature, high levels of diastereoselectivity were obtained for **106b**, **f**, and **g** (≥96:4).

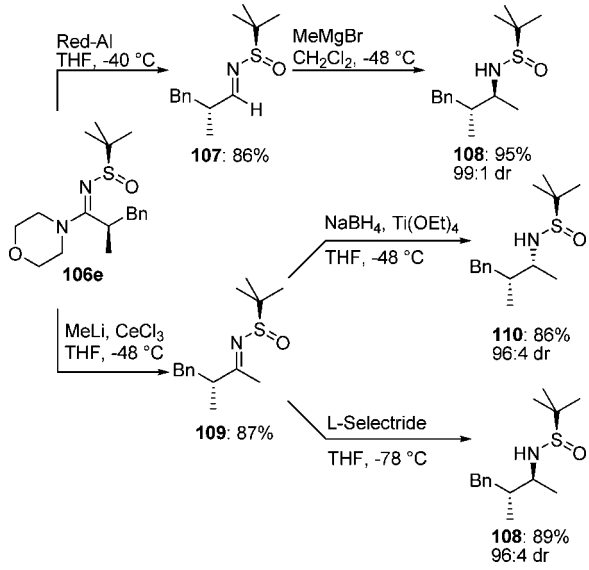
The resulting α-alkylated product **106e** was further transformed into the *N-tert*-butanesulfinyl aldimine **107** or ketimine **109** by treatment with Red-Al or MeLi and $CeCl_3$, respectively (Scheme 28). The utility of these intermediates

Scheme 27. Diastereoselective Alkylation of *N-tert*-Butanesulfinyl Amidines

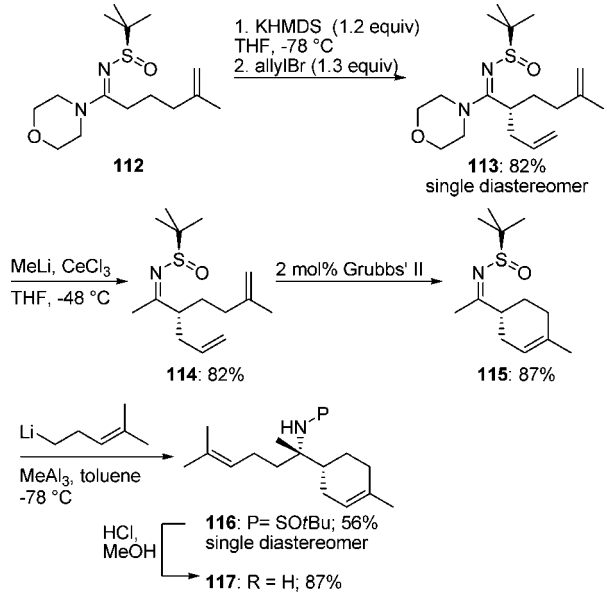


[a] Reaction performed with 3 equiv of MeI.

Scheme 28. Further Synthetic Transformations with 106e



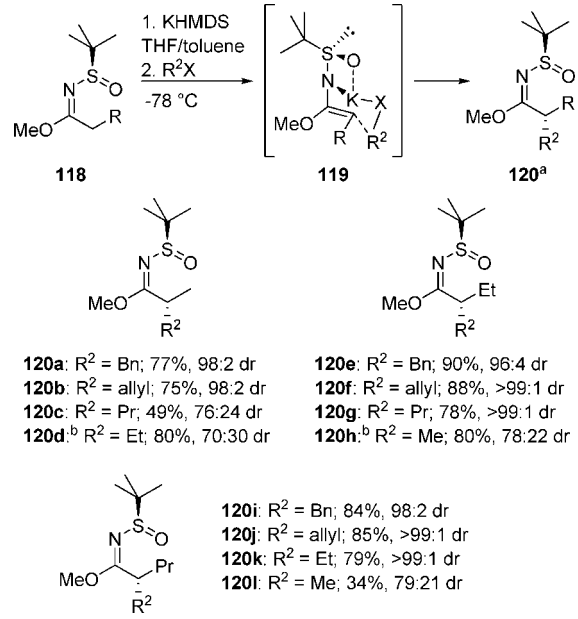
Scheme 29. Asymmetric Total Synthesis of (6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene (117)



was demonstrated by their conversion to *N-tert*-butanesulfinyl protected chiral amine products via nucleophilic addition reactions. Addition of MeMgBr to aldimine **107** provided amine **108**. Reduction of the ketimine **109** to provide either *N-tert*-butanesulfinyl amine isomer **110** or **108** was also demonstrated (for a stereochemical rationale for these reductions, see section 4.2.1). In this way, chiral amines with both α- and *β*-stereocenters may be synthesized.

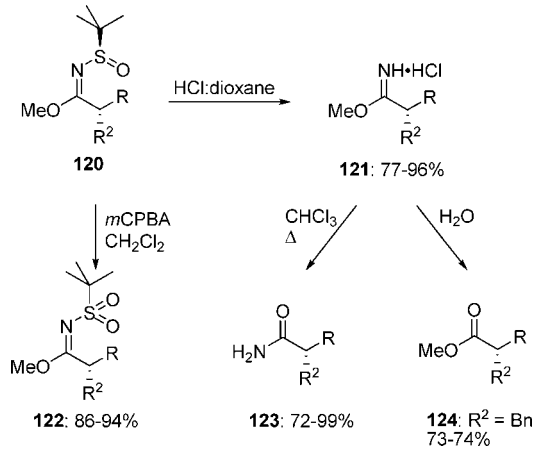
The utility of this methodology was demonstrated by the first asymmetric total synthesis of the marine natural product (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene (Scheme 29).[79] Amidine **112**, synthesized in four steps from commercially available material, was subjected to the optimized α-alkylation conditions, generating **113** in 82% yield as a single diastereomer. Formation of the ketimine **114** with MeLi and $CeCl_3$ followed by ring-closing olefin metathesis using Grubbs' second generation catalyst provided **115** in high yield. Organolithium addition to ketimine **115** provided **116** in 56% yield as a single diastereomer. Removal of the sulfinyl group completed the synthesis of **117**.

Scheme 30. Asymmetric Alkylation of *N-tert*-Butanesulfinyl Imidates 118 with Alkyl Halides



[a] Yields given for the isolated major diastereomer. [b] Diastereomers could not be separated by column chromatography, and the yield is reported for the diastereomer mixture.

Scheme 31. Further Manipulations of Imidates 120



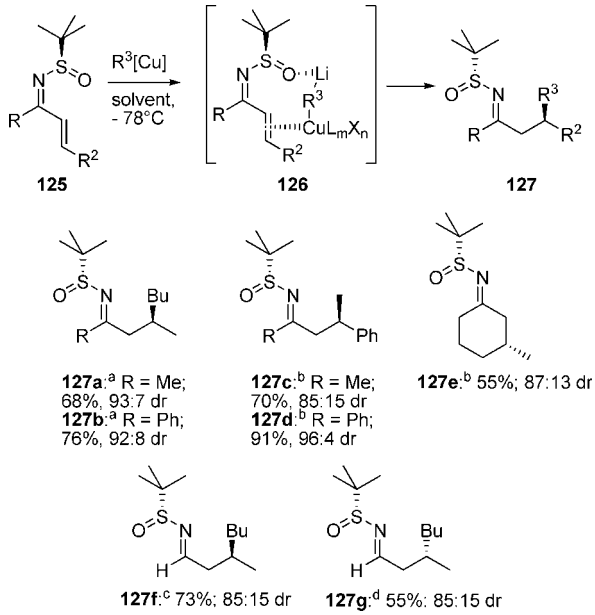
Recently, De Kimpe and co-workers disclosed the alkylation of metalloenamines derived from *N-tert*-butanesulfinyl imidates **118** by alkyl halides (Scheme 30).[78] Optimization of the reaction conditions revealed that enhanced yields and diastereoselectivities were obtained when KHMDS was used as the base. Several *N-tert*-butanesulfinyl imidates were used to prepare the corresponding α-alkylated imidates. Addition of allyl or benzyl bromide to all imidates surveyed provided the desired products **120a**−**b**, **e**−**f**, and **i**−**j** in 75−90% yield and with excellent diastereoselectivity (≥96:4). However, addition of alkyl iodides (R^2 = Pr, Et, or Me) proceeded with more variable diastereoselectivity, and separation of the diastereomeric mixtures was only sometimes possible. Cleavage of the sulfinyl group under acidic conditions yielded the imidate hydrochlorides **121** in good yields (Scheme 31), which could be further manipulated to provide chiral α-alkylated amides **123** or esters **124**. Oxidation of the *N-tert*-butanesulfinyl imidates **120** to the corresponding *N*-Bus imidates **122** was also demonstrated (Scheme 31). The stereochemical outcome of the alkylation of imidates **118** was determined by chemical correlation of the imidate

hydrochloride **121** prepared from **120b**. The stereoselectivity of the alkylation reaction was rationalized by cyclic transition state **119** (Scheme 30).

3.3. Conjugate Addition to α,β-Unsaturated *N-tert*-Butanesulfinyl Imines

Ellman and McMahon developed a method to access *N-tert*-butanesulfinyl imines with β-stereocenters via conjugate addition of copper reagents to α,β-unsaturated *N-tert*-butanesulfinyl ketimines and aldimines (Scheme 32).[61] The reaction was optimized for the addition of a butyl cuprate, and the highest yields and diastereoselectivities were obtained with *n*BuLi, CuCN, and $BF_3 \cdot OEt_2$ in THF, providing **127a** and **127b** in good yields (68−76%) and with high diastereoselectivities (≥92:8). Notably, the diastereomeric ratio of **127a** was higher than the 2:1 *E*/*Z* isomer ratio of the α,β-unsaturated ketimine precursor, suggesting that cuprate addition occurs preferentially to one imine isomer with concomitant rapid imine isomerization. The scope of the reaction was also investigated; however, application of these reaction conditions to the addition of the less reactive methyl cuprate (Me_2CuLi) to α,β-unsaturated *N-tert*-butanesulfinyl imines was not effective. Changing the solvent from THF to Et_2O provided superior results, generating **127c**, **127d**, and the cyclic ketimine **127e** in good to excellent yields and diastereoselectivities. Conjugate addition of a butyl cuprate to an *N-tert*-butanesulfinyl aldimine was also explored, but application of the conditions optimized for the analogous conjugate additions to *N-tert*-butanesulfinyl ketimines provided **127f** with moderate diastereoselectivity (80:20). However, addition of PBu_3 gave improved diastereoselectivity for **127f** (85:15), while changing the copper source from CuCN to CuOAc resulted in a reversal of diastereoselectivity (**127g**). The absolute configurations at the β-stereocenter of the ketimine products were determined by chemical correlation. The facial selectivity was rationalized by transition state **126**, where coordination of the cuprate to the sulfinyl oxygen and delivery of the nucleophile occurs on the face opposite to the *tert*-butyl group.

Scheme 32. Conjugate Addition of Copper Reagents to α,β-Unsaturated *N-tert*-Butanesulfinyl Imines



[a] Method A: $Bu_2CuCN \cdot BF_3 \cdot OEt_2$ in THF. [b] Method B: Me_2CuLi in Et_2O. [c] Method C: $Bu_2CuCN \cdot PBu_3$ in THF. [d] Method D: $Bu_2CuOAc \cdot PBu_3$ in THF.

4. Synthesis of α-Branched Amines

The synthesis of unfunctionalized α-branched amines from imines may be accomplished by addition of organometallic reagents to *N-tert*-butanesulfinyl aldimines. For addition to aldimines, a variety of nucleophiles have proven effective, including Grignard reagents, organolithium reagents, and other carbanion reagents. Additionally, transition-metal catalyzed reactions have been developed. The stereochemical outcome of the addition reaction is dependent on the type of nucleophile employed. In particular, Grignard additions and organolithium additions typically provide products with the opposite relative stereochemistry from each other.

Alternatively, the same class of product may be accessed via reduction of the appropriate *N-tert*-butanesulfinyl ketimines. Several different types of reductants have been used, most notably sodium borohydride and L-Selectride, which provide products with complementary stereoselectivity. One-pot reductive aminations have been developed, eliminating the need for isolation of the imine intermediate. Catalytic reductions have also been described.

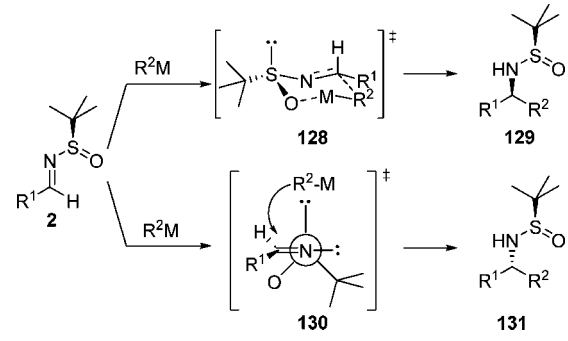
4.1. 1,2-Addition to Aldimines

Several early studies[92−94] examined the effects of solvent, metal, and additives on the selectivity in additions of organometallic reagents to unfunctionalized *N-tert*-butanesulfinyl aldimines **2**. On the basis of these studies, transition state models have been proposed to explain the stereochemical outcome of these reactions. Depending on the choice of reaction conditions, either diastereomer of the addition product, **129** or **131**, can be obtained (Scheme 33). Chelated transition state **128**, which gives rise to product **129**, is typically favored by the use of Grignard reagents in noncoordinating reaction solvents such as CH_2Cl_2 or toluene. In contrast, open transition state **130**, which provides product **131**, is favored by the use of organolithium reagents in coordinating solvents such as THF.

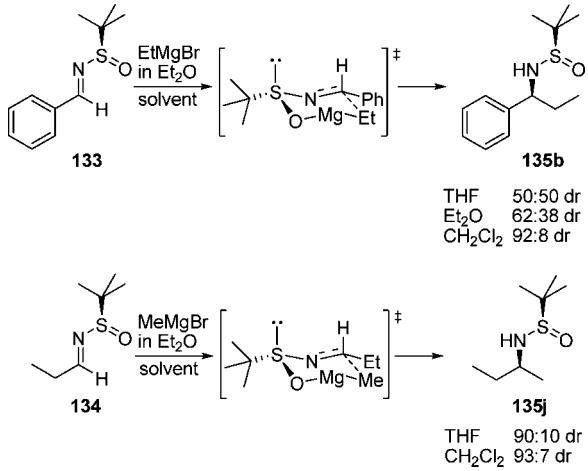
4.1.1. 1,2-Addition of Grignard Reagents to Aldimines

The addition of Grignard reagents to *N-tert*-butanesulfinyl aldimines **2** was first reported by Ellman and co-workers in 1997.[16] Exclusive attack at the imine carbon was observed, which contrasts with Grignard addition to *N*-toluenesulfinyl imines, where undesired attack at the sulfinyl group typically predominates.[2,69] In a subsequent full paper, Ellman and co-

Scheme 33. Transition State Models for Stereoselectivity in 1,2-Additions to *N-tert*-Butanesulfinyl Aldimines



Scheme 34. Solvent Effects in Grignard Additions

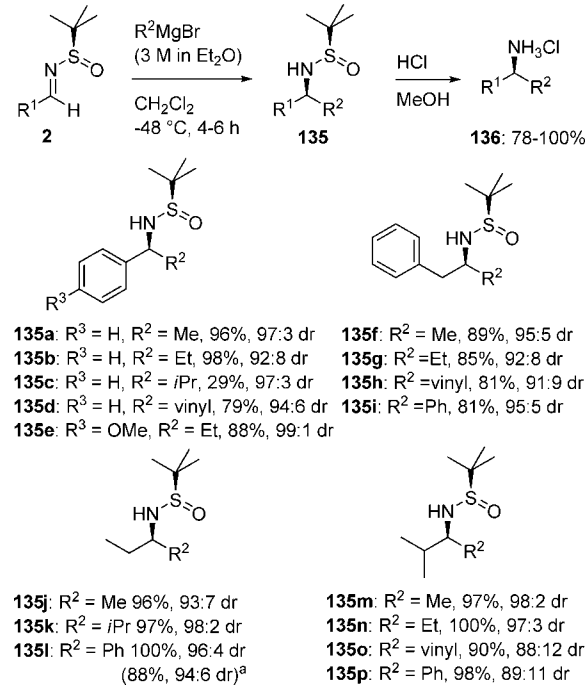


workers provided details of a dramatic solvent effect on the stereoselectivity of this reaction (Scheme 34).[92] For example, the addition of EtMgBr to aldimine **133** proceeded with low stereoselectivity in Et_2O and THF, while much higher diastereoselectivity was obtained in CH_2Cl_2. The addition of MeMgBr to aldimine **134**, while proceeding with reasonable stereoselectivity (90:10 dr) in THF, similarly benefited from use of CH_2Cl_2 as the solvent (93:7 dr). In this study, a 3.0 M solution of the Grignard reagent in Et_2O was added dropwise to a cold (−48 °C) solution of imine. It is important to note that the use of Grignard reagents in THF instead of in Et_2O resulted in much lower diastereoselectivity. This observed solvent effect is consistent with the proposed chelated transition state, because competitive coordination of ethereal solvents such as THF would interfere with the formation of the six-membered-ring transition state, resulting in diminished stereocontrol.

The addition of Grignard reagents to alkyl, benzyl, and aryl aldimines in CH_2Cl_2 was found to be quite general, as illustrated in Scheme 35. An array of different Grignard reagents were used, including, aryl, vinyl, and alkyl derivatives. In most cases, high yields and diastereoselectivities were obtained. However, the addition of *i*PrMgBr to an aryl aldimine was less successful, providing only 29% yield of addition product **135c** (see section 4.1.2 for addition of *i*PrLi in high yield). In this case, the major product of the reaction was *N*-benzyl *tert*-butanesulfinamide, formed via competitive reduction of the imine. It is worthwhile to note that additions to the highly enolizible phenylacetaldimine provided the desired addition products **135f**−**i** in high yields (81−89%).[95] While organolithium reagents provide low stereoselectivity under these reaction conditions, transmetalation by addition of $MgBr_2$ to PhLi provided satisfactory results (**135l**). The resulting chiral *N*-*tert*-butanesulfinyl amine products **135** could be easily deprotected by treatment with HCl in MeOH, providing high yields of the corresponding amine hydrochloride salts **136**.

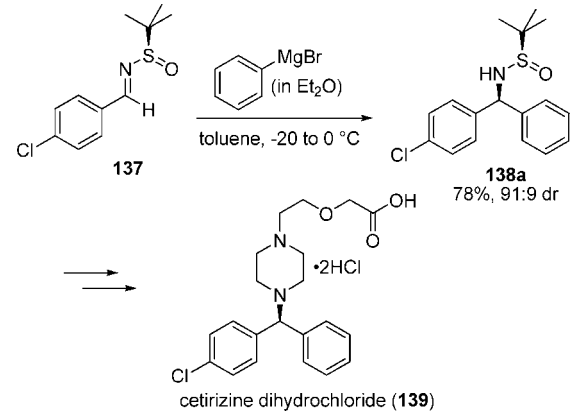
The first example of the addition of an aryl Grignard reagent to an *N*-*tert*-butanesulfinyl aromatic aldimine was reported by Senanayake and co-workers for the asymmetric synthesis of (*S*)-cetirizine dihydrochloride (**139**, Scheme 36).[93] Racemic cetirizine HCl, a histidine H_1-receptor antagonist used for the treatment of allergies, is marketed in the U.S. as Zyrtec. The more pharmacologically active (*R*) enantiomer, levocetirizine dihydrochloride, was approved by the FDA in 2007 and is marketed in the U.S. under the brand name Xyzal.[96]

Scheme 35. Grignard Additions to *N*-*tert*-Butanesulfinyl Aldimines



[a] $PhLi/MgBr_2$ used instead of PhMgBr.

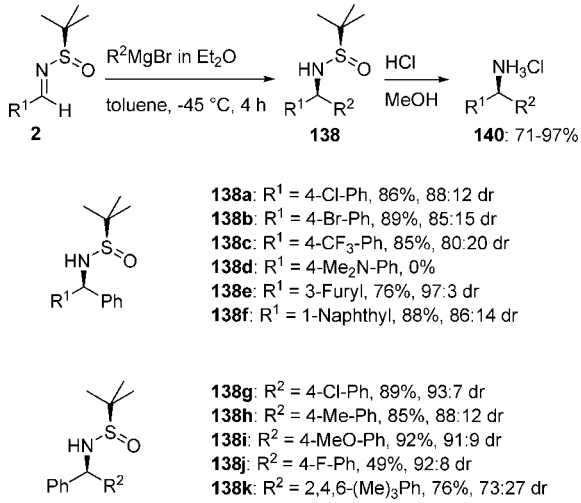
Scheme 36. Synthesis of (*S*)-Cetirizine Dihydrochloride



While CH_2Cl_2 as a reaction solvent provided high diastereoselectivity for Grignard addition to **137**, low reactivity was observed. Upon examination of a variety of solvents, toluene was chosen for further studies. A number of Lewis acid additives were screened, including $AlMe_3$, $BF_3 \cdot OEt_2$, $Cu(OTf)_2$, $ZnCl_2$, $Mg(OTf)_2$, and $Ti(O\mathit{i}Pr)_4$, and in all cases diminished stereoselectivity was observed (60:40 to 81:19 dr) compared to the reaction in the absence of additives (91:9 dr). Single-crystal X-ray analysis of *N*-*tert*-butanesulfinyl amine product **138a** confirmed the expected stereochemistry, which is consistent with the proposed chelated transition state **128** (Scheme 33). Use of PhLi instead of PhMgBr was also investigated, providing the opposite diastereomer as the major addition product via an open transition state such as **130** (Scheme 33, see section 4.1.2 for details). Further optimization of this transformation revealed that the use of the *N*-triisopropylphenylsulfinyl imine instead of the *N*-*tert*-butanesulfinyl imine as a substrate allowed this reaction to take place in 97:3 dr.[97]

Shortly after the initial report by Senanayake and co-workers,[93] Plobeck and Powell disclosed a full study on the

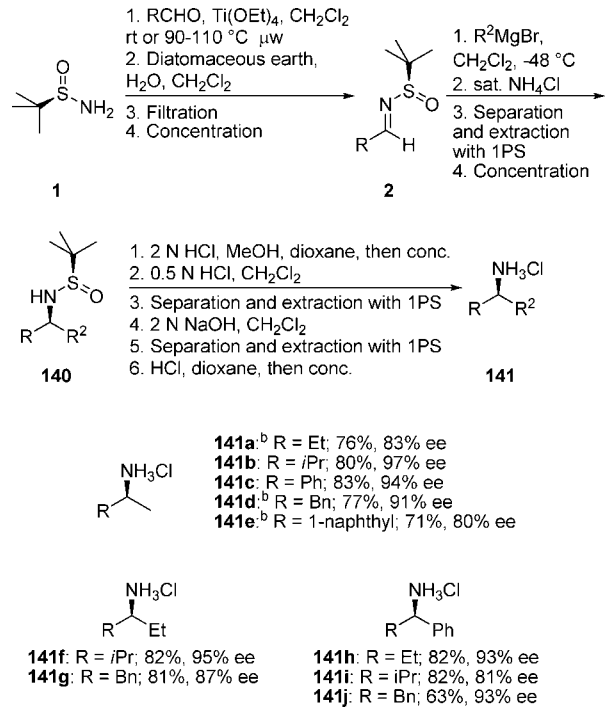
Scheme 37. Addition of Aryl Grignard Reagents to Aryl *N*-*tert*-Butanesulfinyl Aldimines



addition of aryl Grignard reagents (Scheme 37) and aryl lithium reagents (see section 4.1.2) to *N*-*tert*-butanesulfinyl aromatic aldimines **2**, and with this study they demonstrated that a broadly general reversal in selectivity could be achieved for the two classes of reagents.[94] Addition of a solution of PhMgBr in Et_2O to imine **137** was again found to take place smoothly in toluene at low temperatures (−45 °C), in this case providing product **138a** in 86% isolated yield with an 88:12 ratio of diastereomers, with the major diastereomer again corresponding to a chelated transition state. Application of these reaction conditions to other aryl imine substrates as well as other aryl Grignard reagents was successful, providing access to a variety of chiral diarylmethylamine hydrochlorides **140** in good yield and stereoselectivity after acidic methanolysis of the *N*-*tert*-butanesulfinyl amine products **138**. Only the addition of 4-Me_2N-PhMgBr failed to provide desired product **138d** under these conditions.

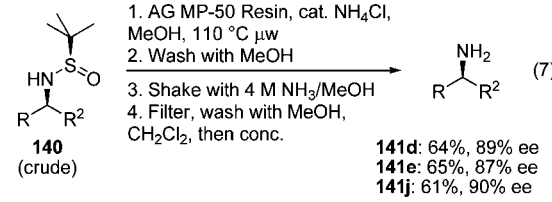
A general method for a parallel solution-phase asymmetric synthesis of α-branched amines from Grignard reagents and enantiomerically pure *N*-*tert*-butanesulfinyl imines was developed by Ellman and co-workers (Scheme 38).[98] The condensation of (*R*)-*tert*-butanesulfinamide with a number of aldehydes was conducted with $Ti(OEt)_4$ as a Lewis acid and water scavenger. The *N*-*tert*-butanesulfinyl imines **2** were synthesized either at room temperature over several hours or at 90−110 °C for 10 min in the microwave. Attempts to effect direct Grignard addition to the resulting imines in the presence of the titanium reagent and its byproducts were unsuccessful. However, removal of the titanium-derived material could be accomplished by mixing the reaction mixture with water-saturated diatomaceous earth and filtration. The crude imines were then dissolved in CH_2Cl_2 and treated with an excess of the Grignard reagent in Et_2O, providing the *N*-*tert*-butanesulfinyl amines **140** after quenching the reaction with aqueous NH_4Cl and phase separation with a commercially available 1PS filter. Cleavage of the sulfinyl group was achieved under acidic conditions, and the desired amine hydrochloride was isolated after acid/base extraction and reacidification. The practicality of this procedure was demonstrated by the syntheses of **141a**−**j**, which were obtained in high overall yields and with good enantioselectivities from *tert*-butanesulfinamide **1**. An alternate protocol to cleave the sulfinyl group was also developed by microwave irradiation of a mixture of **140** with a macroporous

Scheme 38. Parallel Solution-Phase Asymmetric Synthesis of α-Branched Amines[a]



[a] Unless otherwise noted, the imine condensation step was performed at room temperature. [b] The *N*-*tert*-butanesulfinyl imine precursor **2** was also synthesized under the microwave reaction conditions and provided the corresponding product in comparable yields and enantioselectivities.

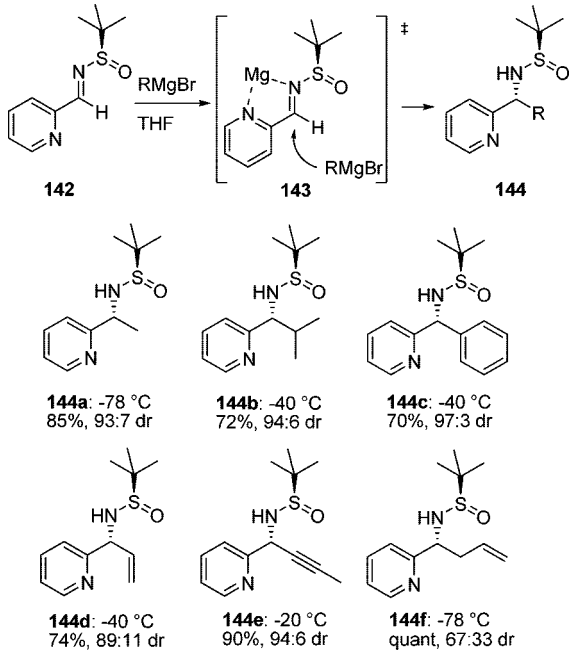
sulfonic acid resin in the presence of a catalytic amount of ammonium chloride (eq 7). Purification of the product by washing it with methanol followed by elution with methanolic ammonia provided **141d**, **141e**, and **141j** with comparable enantioselectivities but lower yields than those for the HCl cleavage protocol.



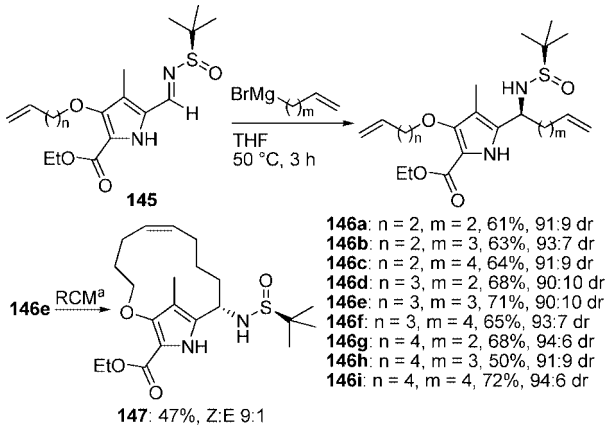
Kuduk and co-workers reported the addition of organometallic reagents to *N*-*tert*-butanesulfinyl 2-pyridyl aldimine **142** (Scheme 39).[99] Optimization of reaction conditions revealed that addition of Grignard reagents in THF at low temperature gave adducts **144a**−**f** in moderate to high yield. Alkyl, aryl, vinyl, and alkynyl additions proceeded with high diastereoselectivities (89:11 to 97:3 dr), while allyl addition provided adduct **144f** with low stereoselectivity. The stereochemical outcome of this reaction, established via chemical correlation experiments, reveals the opposite stereochemistry at the newly formed stereocenter from that observed in additions to other aldimines (*vide supra*). The authors propose open transition state **143** to account for these results. The low selectivity observed for allyl addition is likely due to competition between the open and chelated transition states.

Konig and co-workers reported the addition of terminal alkene-containing Grignard reagents of varying chain lengths

Scheme 39. Opposite Stereochemistry in 1,2-Addition to *N-tert*-Butanesulfinyl 2-Pyridyl Aldimine 142



Scheme 40. Grignard Additions to *N-tert*-Butanesulfinyl 2-Pyrrole Aldimines

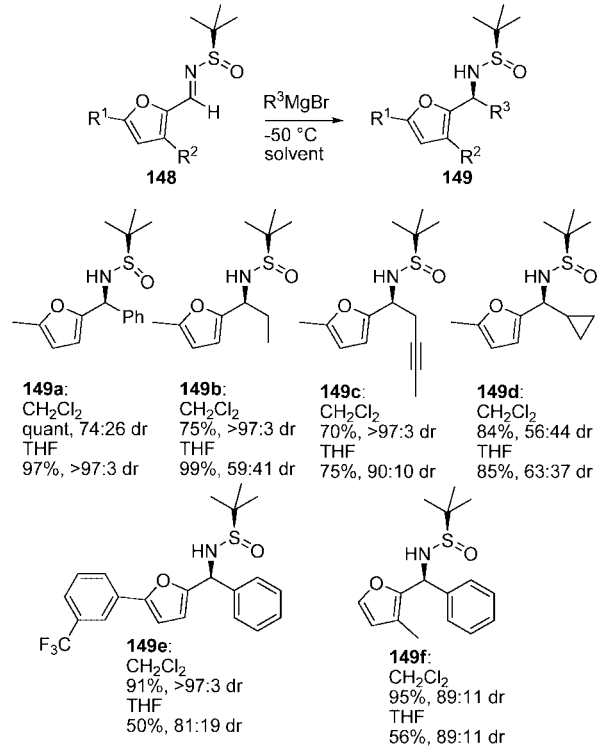


[a] RCM conditions: Grubbs' I catalyst (2 × 15 mol %), 0.0005 M in CH_2Cl_2.

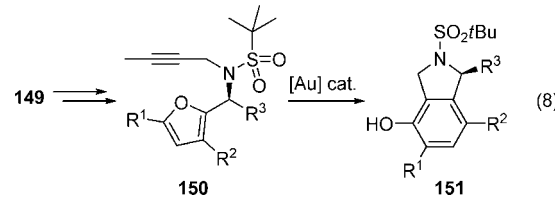
($m = 2-4$) to pyrrole imines **145** containing a tethered alkene with various tether lengths ($n = 2-4$).[100] All permutations were carried out, providing *N*-sulfinyl amine products **146a−i** in 50−72% yield with 90:10 or better diastereoselectivity (Scheme 40). Unfortunately, the relative stereochemistries of products **146** were not rigorously determined but were tentatively assigned based on a chelated transition state model. Subsequently, attempted ring closing metathesis was unsuccessful for most tether length combinations, but in the case of **146e** under dilute conditions, cyclized product **147** was obtained in 47% yield as a 9:1 mixture of *Z*/*E* isomers, in the presence of a mixture of dimeric products.

Hashmi and co-workers reported the addition of Grignard reagents to *N-tert*-butanesulfinyl furanyl aldimines **148** (Scheme 41).[101] While the moderate to excellent yields of the addition reactions appeared to be relatively independent of solvent effects, conflicting results were observed with respect to the optimal solvent for stereoselectivity. Products

Scheme 41. Grignard Additions to *N-tert*-Butanesulfinyl Furanyl Aldimines



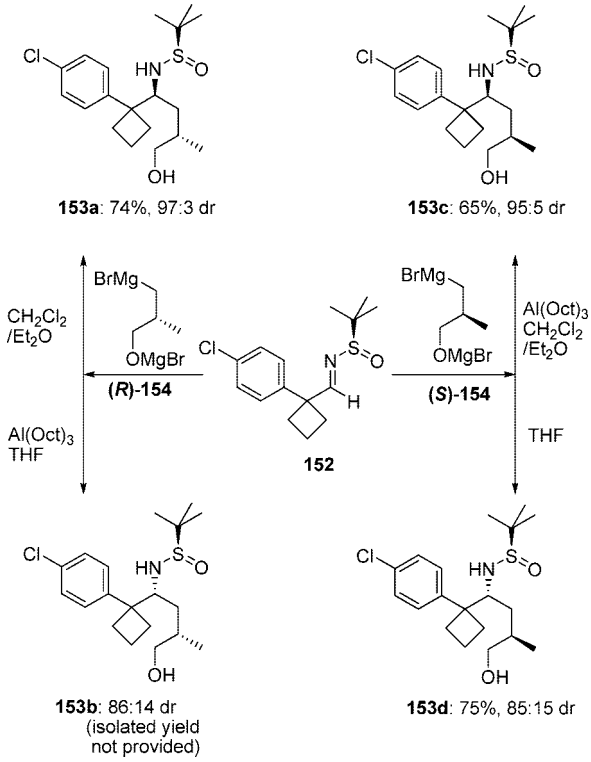
149b, **c**, and **e** were obtained with higher diastereoselectivity when the reactions were conducted in CH_2Cl_2, while products **149a** and **d** were formed more selectively in reactions carried out in THF, and **149f** was formed with the same stereoselectivity in both solvents. In all cases, the configuration of the major diastereomer was determined by X-ray crystallography to be the one that would arise from a chelated transition state. Further elaboration of the reaction products led to sulfonamides **150**, which could be treated with Au(I) or Au(III) catalysts to effect a cyclization reaction, providing dihydroisoindol-4-ols **151** (eq 8).



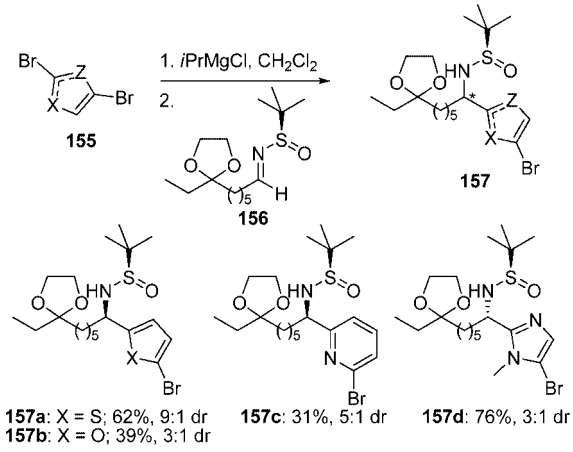
Lu, Senanayake, and co-workers found a dramatic solvent effect, involving reversal of observed stereochemistry, in the addition of functionalized chiral Grignard reagents **(*R*)-154** and **(*S*)-154** to imine **152** (Scheme 42).[102] This was exploited to allow isolation of all four diastereomers of hydroxyl sibutramine derivatives **153a−d**, from a single imine precursor **152**. The stereochemical outcomes of the reactions carried out in CH_2Cl_2 (with the Grignard reagent in Et_2O) are consistent with a chelated transition state mechanism, while the stereochemical outcomes of the reactions carried out in THF are consistent with an open transition state. In some cases, addition of trialkylaluminum Lewis acids enabled enhanced diastereoselectivity.

Kinzel and co-workers developed the addition of heteroaromatic nucleophiles to *N-tert*-butanesulfinyl imine **156** for the synthesis of histone deacetylase (HDAC) inhibitors.[103]

Scheme 42. Divergent Synthesis of Hydroxyl-Sibutramine Derivatives



Scheme 43. Addition of Heteroaromatic Grignard Reagents to Imine 156

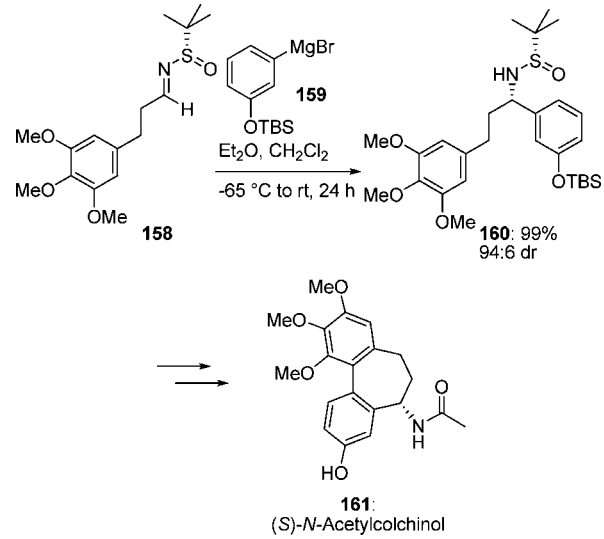


Both lithium−bromine exchange (see section 4.1.2) and magnesium−bromine exchange (Scheme 43) were investigated. The diastereoselectivity was highly dependent on the structure of the heterocycle, and the absolute configurations of each product were assigned by ^{1}H NMR after conversion to the corresponding Mosher amides.

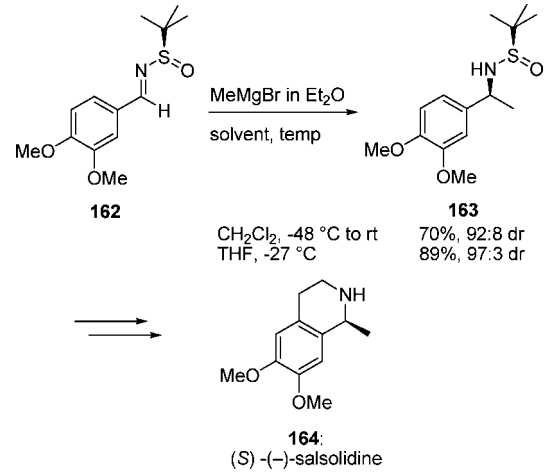
Kocienski and co-workers described the asymmetric synthesis of tubulin polymerization inhibitor (*S*)-*N*-acetylcolchinol (**161**) in nine steps and 31% overall yield (Scheme 44).[104] Diastereoselective addition of aryl Grignard reagent **159** to *N*-*tert*-butanesulfinyl aldimine **158** was one of the key steps in the synthesis, and proceeded in excellent yield and with high diastereoselectivity.

Kosciolowicz and Rozwadowska reported the stereoselective addition of MeMgBr to aldimine **162** in THF to provide *N*-*tert*-butanesulfinyl amine **163** in 89% yield with 97:3 dr, which upon crystallization was increased to 99:1 dr

Scheme 44. Synthesis of *N*-Acetyl Colchinol



Scheme 45. Synthesis of (*S*)-Salsolidine

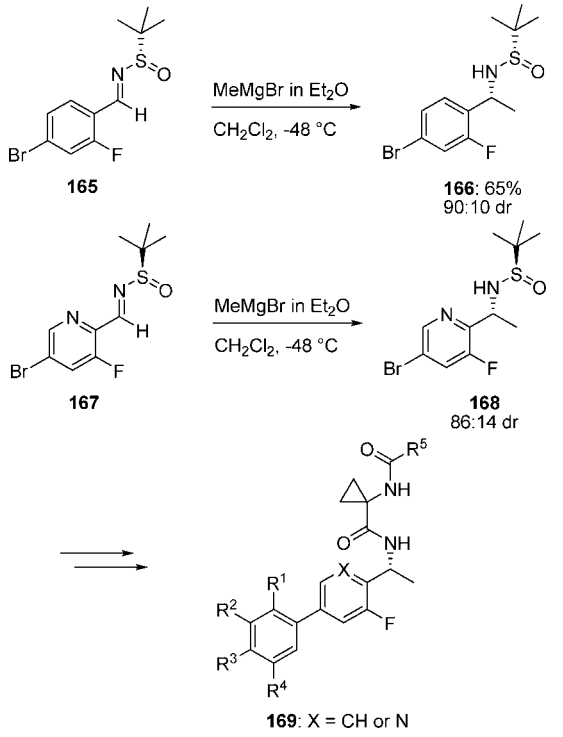


(Scheme 45).[105] Other reaction conditions were investigated, including the use of MeLi and the use of alternative solvents; however, inferior results were obtained. Subsequent transformations provided the isoquinoline alkaloid (*S*)-salsolidine (**164**) with 98% ee in 24% overall yield from the precursor aldehyde (over five steps). Alternatively, the synthesis of (*R*)-salsolidine via reduction of the appropriate *N*-*tert*-butanesulfinyl ketimine was also disclosed (see section 4.2.1).[106]

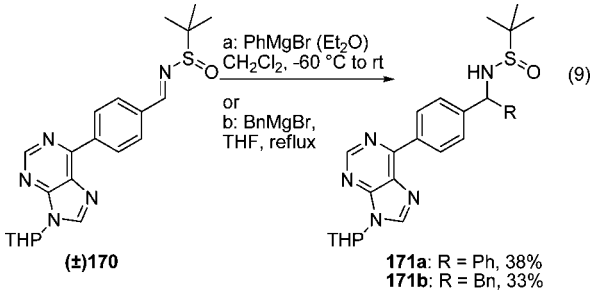
Kuduk and co-workers at Merck utilized the addition of MeMgBr to *N*-*tert*-butanesulfinyl imine **165** for the stereoselective synthesis of versatile intermediate **166** (Scheme 46).[107] Heterocyclic (2-pyridyl) analogues were also synthesized by the addition of MeMgBr to *N*-*tert*-butanesulfinyl 2-pyridyl imine **167** to provide intermediate **168**. Opposite stereocontrol is observed due to the pyridyl subtituent (*vide supra*). A variety of compounds **169** for SAR studies were synthesized by subsequent cross-coupling and amide bond formation reactions. Compounds **169** were tested as bradykinin B_1 receptor agonists for potential use in treatment of pain and inflammation.

Collins and co-workers reported the addition of PhMgBr and BnMgBr to *N*-*tert*-butanesulfinyl aryl aldimine **170** for the rapid synthesis of potential 6-phenyl purine inhibitors of protein kinase B (eq 9).[108] In this study, the diastereose

Scheme 46. Synthesis of Bradykinin B1 Receptor Agonists

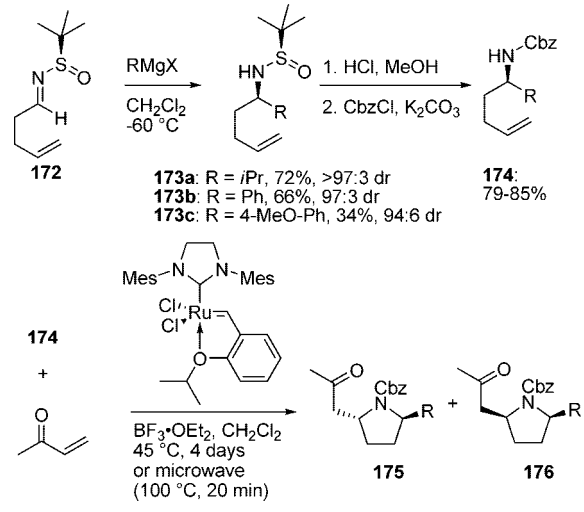


lectivity of the addition reaction was not relevant because racemic sulfinamide was used.

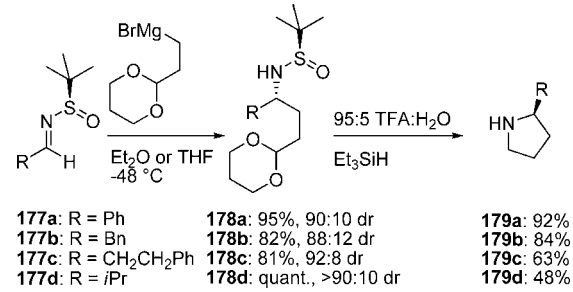


The addition of a variety of Grignard reagents to aldimine **172** was reported by Fustero and co-workers, providing **173a**−**c** with high diastereoselectivity (Scheme 47).[109] After protecting group manipulation, the chiral amine products **174** were utilized as substrates for a tandem cross-metathesis−aza-

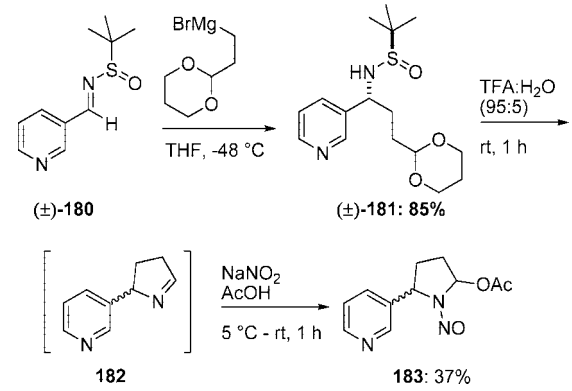
Scheme 47. Synthesis of 2,5-Substituted Pyrrolidines



Scheme 48. Synthesis of 2-Substituted Pyrrolidines



Scheme 49. Synthesis of (±)-*N*′-Nitrosonornicotine 5′-Acetate



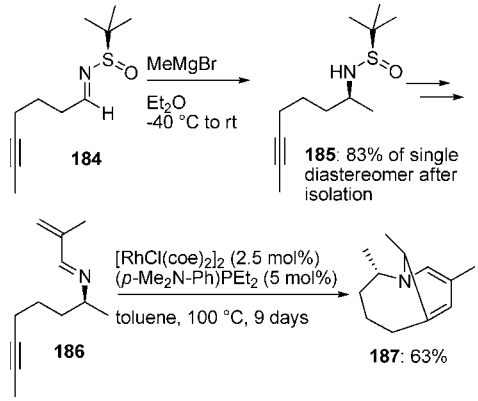
Michael reaction protocol, providing diastereomeric chiral pyrrolidine products **175** and **176**. Use of conventional heating favored formation of **175**, while a microwave heating protocol was employed to favor formation of diastereomer **176**.

Brinner and Ellman reported the addition of an acetal-functionalized Grignard reagent to several *N*-*tert*-butanesulfinyl aldimines, providing adducts **178a**−**d** in high yield and stereoselectivity (Scheme 48).[110] Upon deprotection, adducts **178** cyclize to form pyrrolines, which are reduced *in situ* with Et_3SiH to provide 2-substituted pyrrolidines **179** in high yield. The stereochemical outcome of Grignard addition is consistent with an open transition state rather than a chelated one, presumably due to disruption of chelation control by the coordinating ability of the pendant acetal. This method of pyrroline synthesis was utilized by Marriner and Kerwin in a concise synthesis of racemic *N*′-nitrosonornicotine 5′-acetate (**183**) (Scheme 49).[111] Instead of *in situ* reduction of pyrroline **182** to the corresponding pyrrolidine, nitrosoacylation provided the desired adduct **183** in 37% yield over two steps. Very recently, Reddy and Prashad reported an alternative approach to the asymmetric synthesis of 2-substituted pyrrolidines by addition of Grignard reagents to a γ-chloro-*N*-*tert*-butanesulfinyl aldimine followed by cyclization.[112]

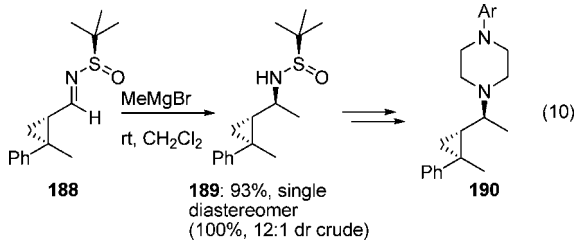
Diastereoselective addition of MeMgBr to *N*-*tert*-butanesulfinyl aldimine **184** was employed by Yotphan, Bergman, and Ellman for the formation of chiral amine product **185**, which was isolated as a single diastereomer in high yield (Scheme 50).[113] This chiral amine was manipulated to provide unsaturated imine **186**, which was utilized as a substrate in a novel tandem C−H bond activation/alkynylation/electrocyclization protocol, furnishing bicyclic bridgehead enamine **187** as a single diastereomer in good yield.

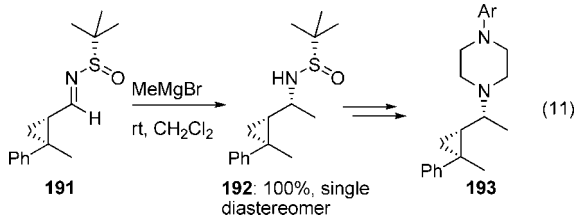
The addition of MeMgBr to diastereomeric imines **188** and **191** was similarly successful, yielding products **189** and

Scheme 50. Synthesis of a Bicyclic Bridgehead Enamine



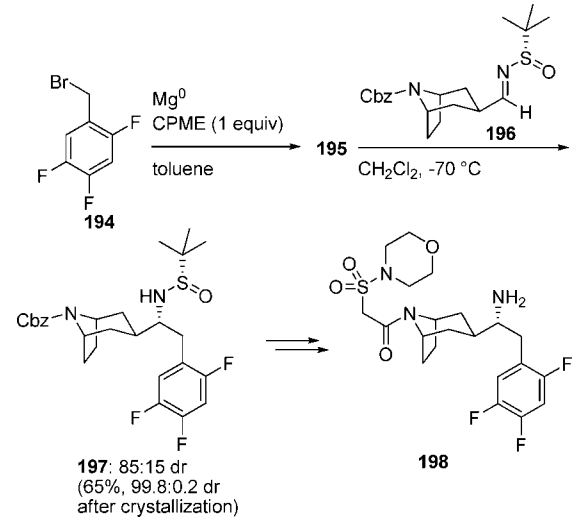
192 in which the configuration of the newly formed stereocenter depended on the sulfinyl group configuration (eqs 10 and 11).[114] The addition products were further elaborated into **190** and **193**, conformationally restricted analogues of the antipsychotic drug haloperidol, as part of a series of molecules tested as potential antidopaminergic agents.





Shieh, Prasad, and co-workers at Novartis recently disclosed an optimized, scalable synthesis of chiral amine **198**, a novel and potent inhibitor of dipeptidyl peptidase 4 (DPP-4) in clinical trials for the treatment of type 2 diabetes.[115] The key step is addition of a benzylic Grignard reagent **195** to *N*-*tert*-butanesulfinyl aldimine **196** to yield chiral amine **197** (Scheme 51). Initial optimization of reaction conditions revealed that addition of a solution of the Grignard reagent in diethyl ether to a cold (−78 °C) solution of the imine provided the desired product with 70:30 diastereoselectivity. However, the use of diethyl ether in a manufacturing plant is unsafe due to its volatility and flammability; therefore, alternative solvents were investigated. Synthesis of the Grignard reagent was therefore carried out in toluene, in the presence of 1 equiv of cyclopentyl methyl ether (CPME) as a stabilizer. The Grignard reagent was diluted with CH_2Cl_2 and cooled, and then a CH_2Cl_2 solution of the imine was added. In addition to improved safety, this revised protocol also provided **197** with higher stereoselectivity (85:15 dr), which was sufficiently high to enable isolation of diastereomerically pure material by crystallization of the crude product from methanol. A variety of Lewis acid additives were screened, but consistent with prior studies (*vide supra*), no beneficial effect was observed. The absolute stereochemistry of the product, as well as the observed additive and solvent

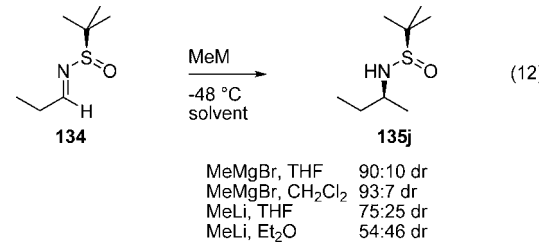
Scheme 51. Scalable Synthesis of a DPP-4 Inhibitor for Clinical Trials



effects, are consistent with chelated transition state **128** (Scheme 33) for this addition reaction.

4.1.2. 1,2-Addition of Organolithium Reagents to Aldimines

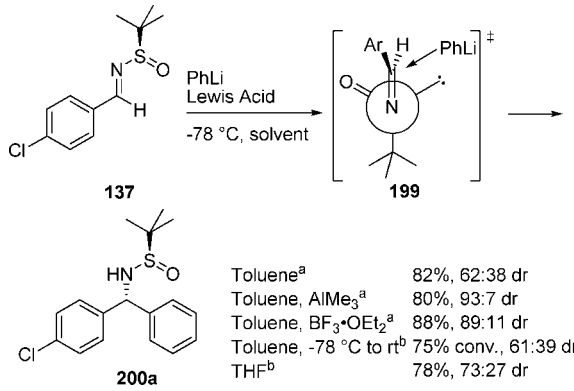
Early work on the additions of organometallic reagents to aldimines revealed that addition of MeLi to imine **134** was less stereoselective than addition of MeMgBr (eq 12).[92]



In their work on the synthesis of (*S*)-cetirizine,[93] Senanayake and co-workers found that the addition of PhLi to aryl aldimine **137** proceeded with opposite diastereoselectivity from the addition of PhMgBr (see Scheme 36, section 4.1.1) to the same aldimine. Furthermore, while a variety of Lewis acid additives had a detrimental effect on the stereoselective addition of the Grignard reagent, several Lewis acids enhanced the diastereoselectivity of the PhLi addition, consistent with Ellman and co-workers' prior report on organolithium additions to *N*-*tert*-butanesulfinyl ketimines.[49] Particularly, reactions containing $AlMe_3$ or $BF_3 \cdot OEt_2$ provided the product **200a** with 93:7 dr and 89:11 dr, respectively, compared to a modest 62:38 dr in the absence of Lewis acid additives (Scheme 52). Other Lewis acid additives were tested but provided inferior results.

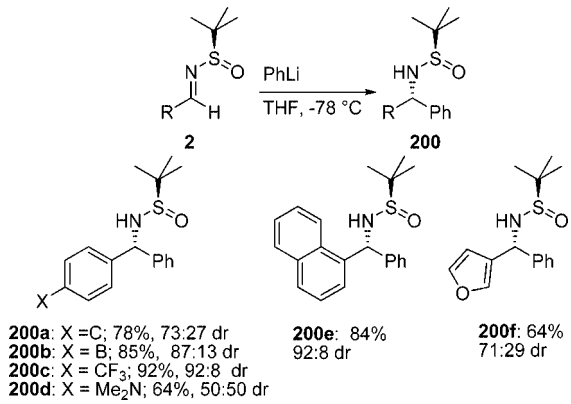
In their related study, Plobeck and Powell also investigated the use of aryl lithium reagents for addition to aryl *N*-*tert*-butanesulfinyl aldimines.[94] Rather than testing Lewis acid additives, they examined the effect of solvent on the diastereoselectivity of this reaction. Switching the solvent from toluene to THF enhanced the stereoselectivity from 61:39 to 73:27 (Scheme 52). To explain the observed diastereoselectivity for the addition of organolithium reagents to aldimines, open transition state **199** was proposed.[94] This is consistent with the observed solvent and additive effects.

Scheme 52. Solvent and Additive Effects in PhLi Additions to an *N-tert*-Butanesulfinyl Aldimine



[a] Pflum et al.[93] [b] Plobek and Powell.[94]

Scheme 53. PhLi Additions to Aryl *N-tert*-Butanesulfinyl Aldimines

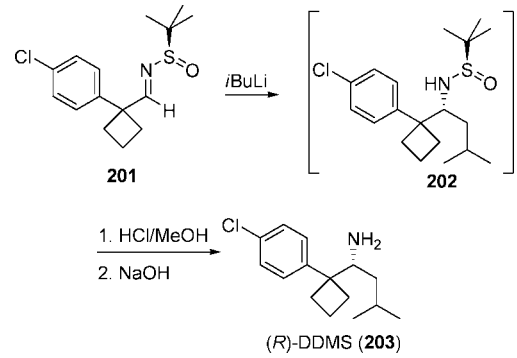


While noncoordinating solvents such as toluene and dichloromethane would favor a chelated transition state, both Lewis acid additives and coordinating solvents such as THF interfere with chelation control, favoring instead an open transition state.

The scope of this addition was investigated with a variety of *N-tert*-butanesulfinyl aryl aldimines **2**, in most cases providing moderate to high diastereoselectivity (Scheme 53).[94] However, addition product **200d**, bearing 4-NMe_2-Ph substitution, was formed as a 50:50 mixture of diastereomers in 64% yield (this imine was unreactive under Grignard addition conditions; see Scheme 37 and section 4.1.1).

Krishnamurthy, Senanayake, and co-workers optimized the addition of *i*BuLi to *N-tert*-butanesulfinyl aldimine **201** followed by sulfinyl cleavage in one pot to provide (*R*)-didesmethylsibutramine (DDMS; **203**), a pharmacologically active metabolite of the drug sibutramine for the potential treatment of CNS disorders.[116] Several Lewis acid/solvent combinations were examined (Table 6). In toluene as a reaction solvent, the use of $BF_3 \cdot OEt_2$ or TMEDA favored the desired (*R*) configuration at the newly formed stereocenter, which can be explained by an open transition state. In contrast, the use of Al-based Lewis acids in toluene provided the product in low yield with a moderate excess of the (*S*) configuration. However, in THF, all four Lewis acid additives were effective, allowing access to the desired (*R*) enantiomer of the product in high yield (84−90%) and with very high stereoselectivity (≥98% ee). In this study, alternative sulfinyl groups were also investigated. While the use of aromatic sulfinyl groups proved unsatisfactory in terms of

Table 6. Solvent and Additive Effects in the Synthesis of (*R*)-DDMS (203)



entry	solvent	Lewis acid	temp (°C)	conv (%)	ee (%)
1	toluene	$BF_3 \cdot OEt_2$	−78	78	98
2	toluene	$AlMe_3$	−45	36	−38[a]
3	toluene	$AlOct_3$	−20	37	−76[a]
4	toluene	TMEDA	−78	85	95
5	THF	$BF_3 \cdot OEt_2$	−78	90	99
6	THF	$AlMe_3$	−78	90	99
7	THF	$AlOct_3$	−78	85	98
8	THF	TMEDA	−78	84	99

[a] (*S*)-**203** obtained as major enantiomer.

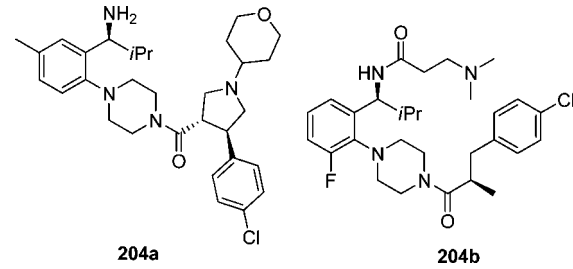


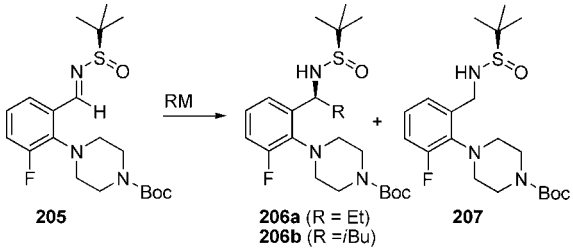
Figure 3. Melanocortin 4 receptor ligands.

yield and stereoselectivity, the 2-ethylpentanesulfinyl group was found to perform similarly to the *tert*-butanesulfinyl group for this transformation.

Tucci and co-workers at Neurocrine Biosciences developed methodology for organolithium additions to *N-tert*-butanesulfinyl aldimines to synthesize enantiomerically pure α-branched 2-piperazinylbenzylamines.[117] These amines were used as intermediates for the preparation of a large number of compounds for SAR studies targeted at finding both agonists (such as **204a**)[118] and antagonists (such as **204b**)[119] of the human melanocortin 4 receptor, a G-protein-coupled receptor that has been found to play an important role in the regulation of feeding behavior (Figure 3).[118−122] *N-tert*-Butanesulfinyl imines were selected as ideal intermediates for this project due to their accessibility from readily available starting materials, the potential for high stereoselectivity and predictability of the stereochemical outcome of the addition reactions, and scalability of the procedure to enable the synthesis of kilogram quantities of intermediates during preclinical studies. Additionally, the ability to achieve selective deprotection of either the *N*-Boc group (using TFA) or the *N*-sulfinyl group (using HCl/MeOH) from building blocks **208** allowed flexibility in the synthetic route.

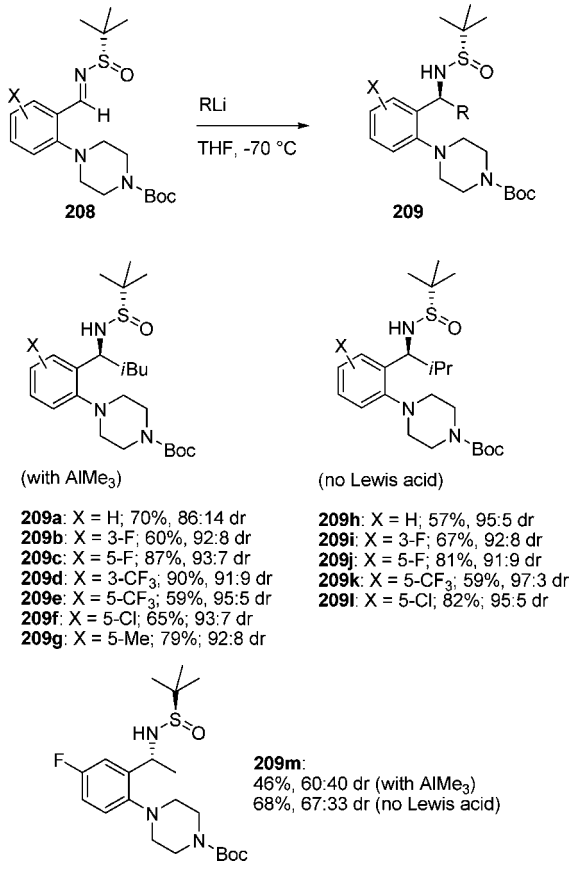
Addition of EtMgBr to imine **205** provided 94% yield of the desired adduct **206a** with 91:9 diastereoselectivity via a chelated transition state, along with a small amount of reduction side product **207** (Scheme 54). Unfortunately, in the analogous addition of *i*BuMgBr to imine **205**, solvent optimization was unsuccessful in suppressing competitive

Scheme 54. Competitive Reduction in Addition of Grignard Reagents to Imine 205



EtMgBr, CH_2Cl_2 , -40 °C	11:1 **206a** (91:9 dr):**207**
*i*BuMgBr, CH_2Cl_2, -40 °C	1:10 **206b**:**207**
*i*BuMgBr, THF, -40 °C	6:5 **206b**:**207**
*i*BuMgBr, toluene, -40 °C	1:5 **206b**:**207**
*i*BuMgBr, Et_2O, -40 °C	1:3 **206b**:**207**

Scheme 55. Scope of α-Branched 2-Piperazinylbenzylamine Synthesis



209a: X = H; 70%, 86:14 dr
209b: X = 3-F; 60%, 92:8 dr
209c: X = 5-F; 87%, 93:7 dr
209d: X = 3-CF_3; 90%, 91:9 dr
209e: X = 5-CF_3; 59%, 95:5 dr
209f: X = 5-Cl; 65%; 93:7 dr
209g: X = 5-Me; 79%; 92:8 dr

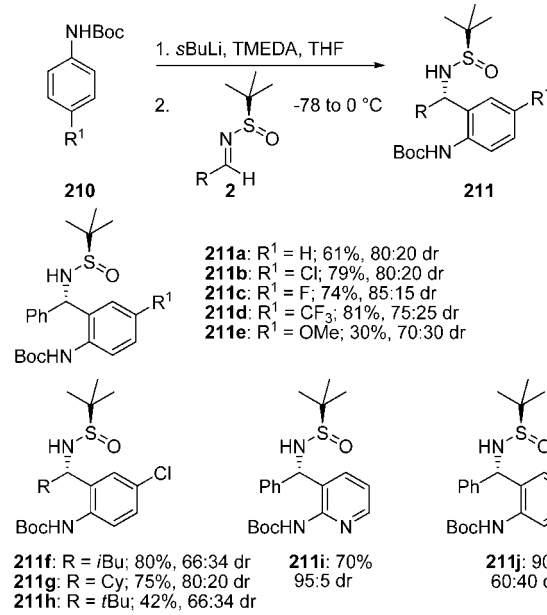
209h: X = H; 57%, 95:5 dr
209i: X = 3-F; 67%, 92:8 dr
209j: X = 5-F; 81%, 91:9 dr
209k: X = 5-CF_3; 59%, 97:3 dr
209l: X = 5-Cl; 82%; 95:5 dr

209m:
46%, 60:40 dr (with $AlMe_3$)
68%, 67:33 dr (no Lewis acid)

imine reduction. This is consistent with previous work by Ellman and co-workers,[92] in which addition of *i*PrMgBr to *N*-*tert*-butanesulfinyl benzaldimine proceeded in poor yield due to competitive imine reduction (see **135c**, Scheme 35). In contrast to the Grignard additions, when *i*BuLi was added to imine **208** (X = 3-F) in THF, none of reduction product **207** was observed, and the desired adduct **209b** was obtained in 58% yield with 88:12 dr via an open transition state (Scheme 55).

Addition of $AlMe_3$ provided a modest improvement in the diastereoselectivity of the addition of *i*BuLi to a variety of imines **208**, and products **209a**−**g** were isolated in diastereomerically pure form by either chromatography or recrystallization (Scheme 55). Addition of *i*PrLi to the same set of imines was explored, and in this case, slightly higher diastereoselectivity was observed in the absence of any Lewis acid additives, providing adducts **209h**−**l** in moderate to high

Scheme 56. Addition of *ortho*-Lithiated Anilines to *N*-*tert*-Butanesulfinyl Aldimines

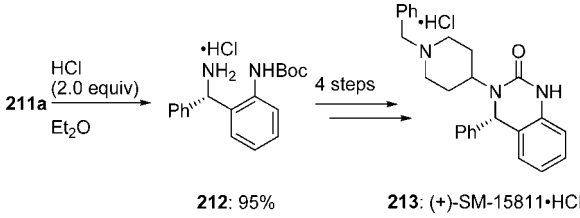


yield. Addition of MeLi to imine (*R*)-**208** (X = 5-F) for the formation of **209m** provided an acceptable yield but poor stereoselectivity in both the presence and absence of $AlMe_3$.

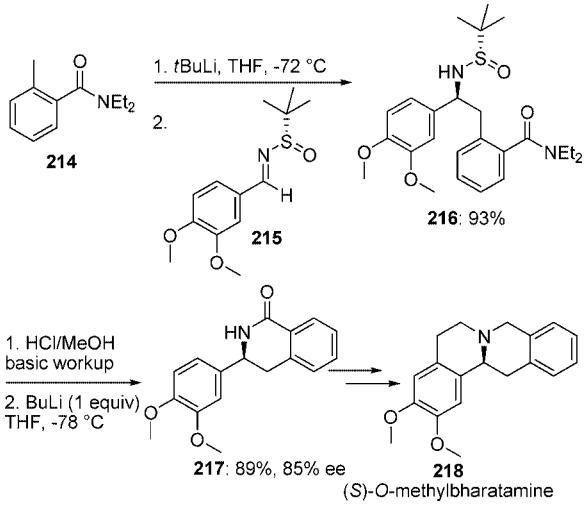
Rajapakse and co-workers at Merck reported the *ortho*-lithiation of *N*-Boc anilines **210** followed by addition to *N*-*tert*-butanesulfinyl imines **2** with moderate diastereoselectivity (Scheme 56).[123] The observed stereoselectivity of this addition reaction, as determined by X-ray crystallography, is consistent with an open transition state. The addition of TMEDA to the reaction mixture was found to be essential to reactivity, as the authors note that no product was formed in the absence of this additive. The authors postulate that the TMEDA helps to diminish aggregation of the aryl lithium species, resulting in enhanced nucleophilicity. High isolated yields of the desired adducts were obtained in the presence of electron-withdrawing groups on the aniline species (**211b**−**d**), while only a 30% yield of electron-rich derivative **211e** was obtained. Mixed results were obtained for additions to aliphatic imines, with additions to form the isobutyl (**211f**) and *tert*-butyl (**211h**) derivatives proceeding with lower stereoselectivity (66:34 dr) than the addition to form cyclohexyl derivative **211g** (80:20 dr). Additions to *N*-*tert*-butanesulfinyl ketimines were also investigated, but low yields were obtained (see section 5.1). The utility of the products **211** for the asymmetric synthesis of dihydroquinazolinones was demonstrated by the selective removal of the *tert*-butanesulfinyl group in the presence of the acid-labile Boc protecting group to form **212** in high yield, followed by further elaboration to (+)-SM-15811 (**213**), an effective Ca^{2+}/Na^{+} ion exchanger inhibitor with potential utility for the management of ischemic heart disease (Scheme 57).

Grajewska and Rozwadowska utilized the addition of laterally lithiated *o*-toluamide **214** to *N*-*tert*-butanesulfinyl aryl imine **215** in the synthesis of isoquinoline alkaloid (*S*)-(−)-*O*-methylbharatamine (**218**) (Scheme 58).[124] This work is in analogy to the work by Davis and co-workers on the addition of similar nucleophiles to *N*-*p*-toluenesulfinyl imines.[125] While the dr of **216** was not directly reported, subsequent sulfinyl cleavage followed by cyclization provided intermediate **217** with 85% ee, suggesting a dr of 93:7 for adduct **216**.

Scheme 57. Asymmetric Synthesis of a Dihydroquinazolinone



Scheme 58. Synthesis of (*S*)-(−)-*O*-Methylbharatamine

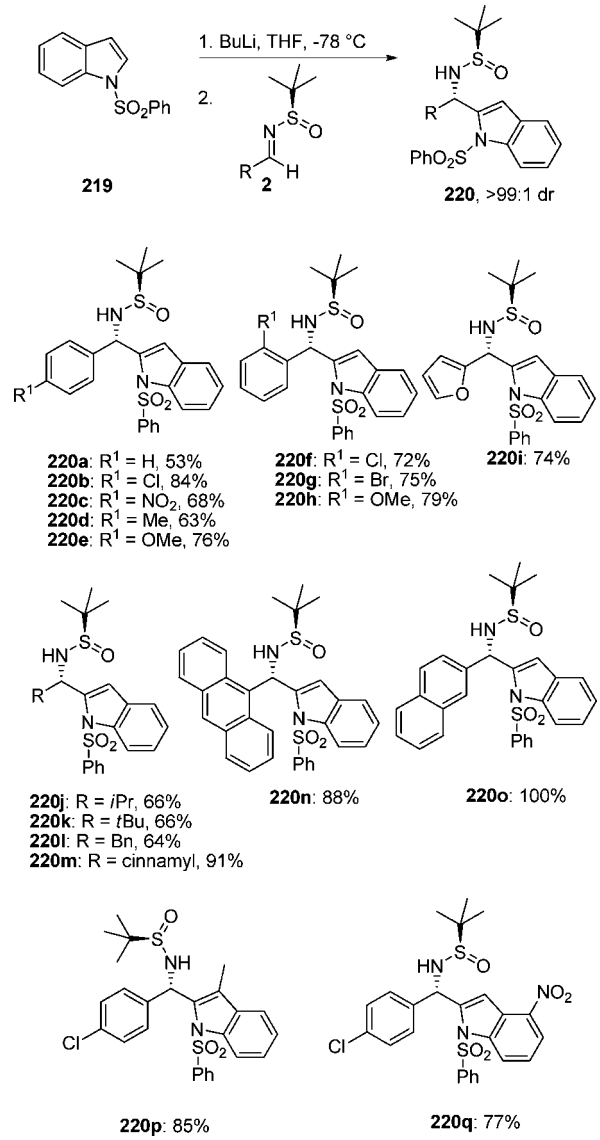


Liu, Chen, and co-workers disclosed the highly diastereoselective addition of 2-lithiated *N*-sulfonyl indoles **219** to *N-tert*-butanesulfinyl aldimines **2** (Scheme 59).[126] A variety of imines were used, providing products with aromatic (**220a**−**h**,**n**,**o**), heteroaromatic (**220i**), α,β-unsaturated (**220m**), and alkyl (**220j**−**l**) substitution. Substitution on the indole was also tolerated (**220p**,**q**). In all cases, >99:1 dr was observed for this transformation, with isolated yields ranging from moderate (53%, **220a**) to quantitative (**220o**). The stereochemistry of the addition product, determined by X-ray crystallographic analysis of adduct **220g**, is consistent with addition to the less hindered face of the imine in an open transition state.

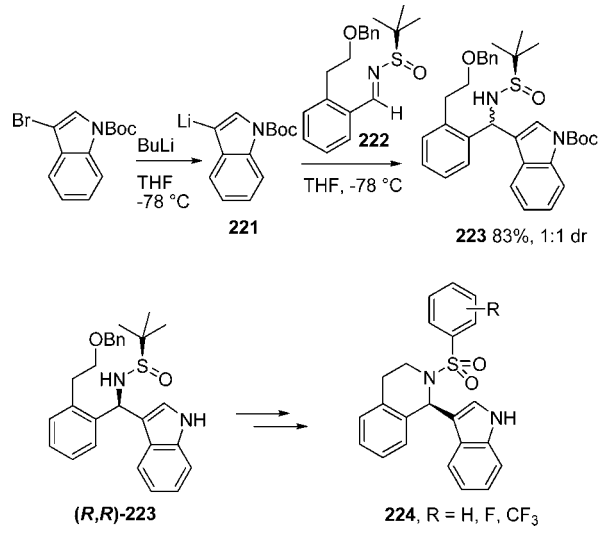
In contrast to the excellent stereoselectivity observed for the above transformation, Qiu, Lee, and co-workers reported that the addition of 3-lithiated *N*-Boc indole **221** to imine **222** provided product **223** as a 1:1 mixture of diastereomers (Scheme 60).[127] The authors postulate that the ether linkage on the aldimine side chain may coordinate to the incoming nucleophile, disrupting the expected transition state. While no stereoselectivity was observed for this transformation, the diastereomers were easily separated from each other chromatographically, allowing access to both enantiomers of **224** for testing as inhibitors of Rad51 for cancer treatment.

Kinzel and co-workers developed the addition of heteroaromatic nucleophiles to *N-tert*-butanesulfinyl imine **156** for the synthesis of histone deacetylase (HDAC) inhibitors.[103] Both magnesium−bromine exchange (see section 4.1.1) and lithium−bromine exchange (Scheme 61) were investigated. The diastereoselectivity was highly dependent on the structure of the heterocycle, and the absolute configurations of each product were established by ^{1}H NMR after conversion to the corresponding Mosher amides.

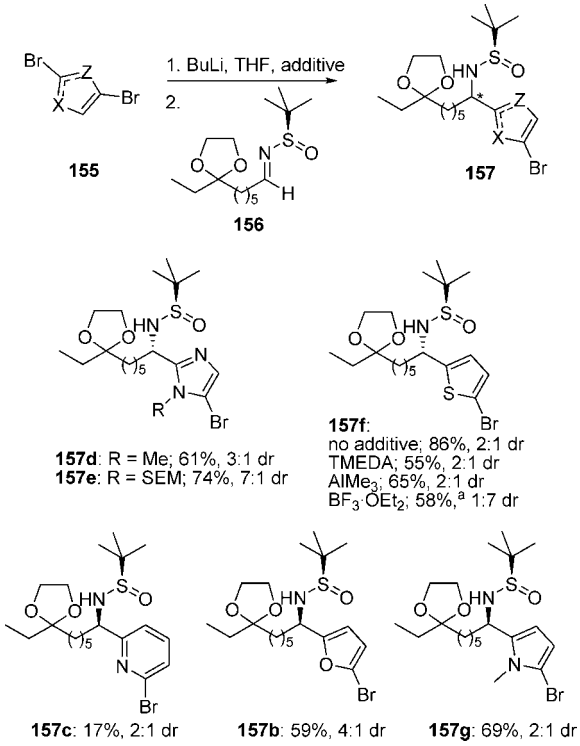
Scheme 59. Addition of 2-Lithiated *N*-Sulfonyl Indoles to *N-tert*-Butanesulfinyl Aldimines



Scheme 60. Synthesis of Chiral Rad51 Inhibitors



Scheme 61. Addition of Heteroaromatic Lithium Reagents to Imine 156

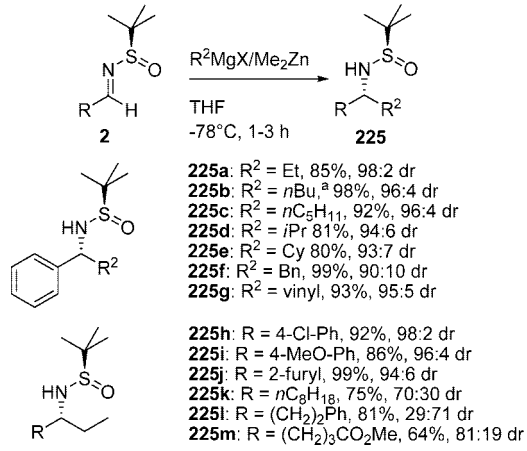


[a] Isolated yield after concomitant acetal deprotection.

4.1.3. 1,2-Addition of Other Carbanion Reagents to Aldimines

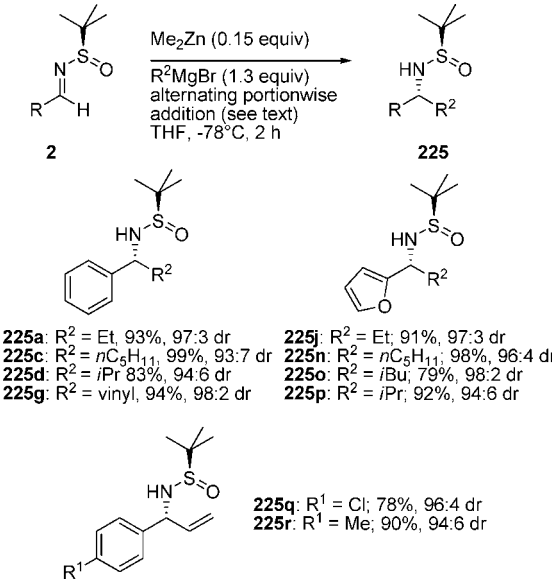
Guijarro, Yus, and co-workers reported the use of triorganozincates, prepared by premixing Grignard reagents with dialkylzinc reagents, as nucleophiles for diastereoselective additions to *N-tert*-butanesulfinyl imines (Scheme 62).[128,129] The very slow rate of methyl group transfer relative to other alkyl groups from the triorganozincates made it possible to use mixed reagents, with nontransferable methyl groups. Comparable results were obtained when the triorganozincate was created either using a Grignard reagent bearing the desired substituent with dimethyl zinc or using methyl magnesium bromide with the desired dialkyl zinc reagent. The additions were carried out at low temperature in THF,

Scheme 62. Addition of Triorganozincates to *N-tert*-Butanesulfinyl Aldimines



[a] BuLi was used instead of BuMgBr.

Scheme 63. Catalytic Me_2Zn for Triorganozincate Additions to *N-tert*-Butanesulfinyl Imines



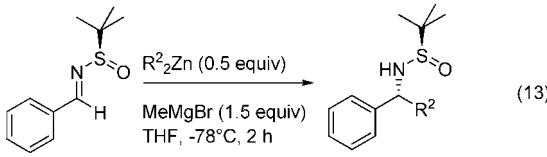
and in most cases a drastically lower dr was observed for slow additions of imines to Grignard reagents in the absence of dimethyl zinc compared to the slow additions of imines to the premixed triorganozincate reagent, suggesting that the active nucleophile was not simply the Grignard reagent. The observed stereochemistry of the reaction is consistent with an open transition state, similar to that observed for addition of organolithium reagents to these imines.

The scope of the reaction was explored. Additions of primary and secondary alkyl, benzyl, and vinyl groups were all successful, providing products **225a−g** in high yield and with excellent stereoselectivity (Scheme 62). Addition of an aromatic group, however, was unsuccessful. The reaction did not proceed at low temperature, and upon warming, the addition proceeded with identical stereoselectivity in both the presence and absence of Me_2Zn, suggesting that the triorganozincate bearing an aromatic group did not form. The scope with respect to the imine was also explored. Aromatic and heteroaromatic imines were excellent substrates, while aliphatic imines provided disappointing diastereoselectivity. In fact, product **225l** was formed with opposite stereochemistry relative to the other products. The aliphatic imine bearing a pendant ester coupled in slightly lower yield (64%) than the other substrates, providing product **225m** with a moderate 81:19 ratio of diastereomers. Two *N-tert*-butanesulfinyl ketimines derived from ketoesters were also tested as substrates, providing α,α-disubstituted-α-amino acid derivatives (see section 9.1).

To take full advantage of the opportunities created by the inability of the methyl group to transfer from the triorganozincate, this work has recently been extended either to allow the use of catalytic amounts (0.15 equiv) of dimethylzinc (Scheme 63) or to allow the use of excess MeMgBr in the presence of 0.5 equiv of a dialkylzinc reagent with transfer of both alkyl groups (eq 13).[130] In the first proceedure, the dimethylzinc is cooled to low temperature and a portion of the Grignard reagent is added, forming the triorganozincate in situ. A portion of the imine solution is then slowly added, consuming the triorganozincate, providing the desired product, and regenerating the dimethylzinc. Several more alternating slow additions of portions of

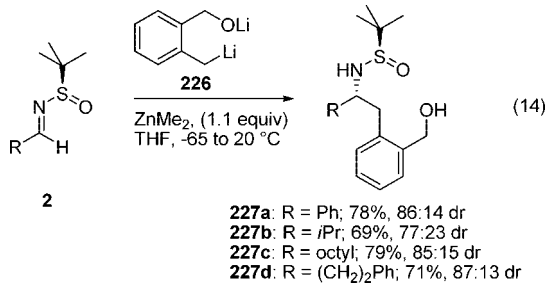
Grignard reagent, followed by portions of imine solution, are carried out. In this way, high yields (83−99%) and diastereoselectivities (93:7−98:2) of the products **225a**, **c**, **d**, and **g** are obtained using only 0.15 equiv of dimethylzinc (Scheme 63). Additions of Grignard reagents to a furyl imine were disclosed in a later study,[131] providing products **225j** and **n**−**p** in high yields and with good diastereoselectivities. Oxidative cleavage of the furan to provide α-amino acids was also demonstrated. Several examples (**225g**, **q**, and **r**) were also provided of vinyl additions to aryl *N-tert*-butanesulfinyl imines as well as their subsequent transformation to α-amino acids under oxidative conditions.

Alternatively, by slowly adding a solution of imine to a mixture of excess MeMgBr with 0.5 equiv of a dialkylzinc, it is possible to obtain the products of alkyl group transfer with high diastereoselectivity in 84−90% yield based on imine (eq 13). The higher than 50% yield requires that both alkyl groups from the dialkyl zinc reagent are utilized in this transformation.[130]

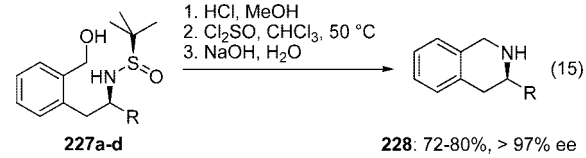


(13)

Recently, Yus and Foubelo reported the reaction between the dianionic intermediate **226** and *N-tert*-butanesulfinyl imines **2** for asymmetric synthesis of branched amines **227** (eq 14), which upon deprotection and cyclization provided tetrahydroisoquinolines **228** (eq 15).[132] Addition of the functionalized organolithium compound **226** to the *N-tert*-butanesulfinyl benzaldimine provided the desired product **227a**; however, optimization of the reaction conditions revealed that yields and diastereoselectivities were improved when the mixed organozincate, prepared upon addition of $ZnMe_2$, was used as the nucleophile. The addition of **226** to either aryl or alkyl *N-tert*-butanesulfinyl imines generated adducts **227a**−**d** with respectable diastereoselectivities (≥77:23 dr), and in each case the isolated major diastereomer was obtained in good yield (69−79%, eq 14). Comparable yields and diastereoselectivities were also obtained when (S_S)-*N-tert*-butanesulfinyl imines were used as substrates. The absolute configuration of **227a** was determined by X-ray structural analysis, and the stereochemical outcome of the reaction is consistent with an open transition state. The purified major diastereomers of **227a**−**d** were then converted to the chiral tetrahydroisoquinolines **228** in good yields without racemization after removal of the sulfinyl group under acidic conditions and successive treatment with thionyl chloride followed by aqueous sodium hydroxide to promote an intramolecular dehydration (eq 15).



(14)



(15)

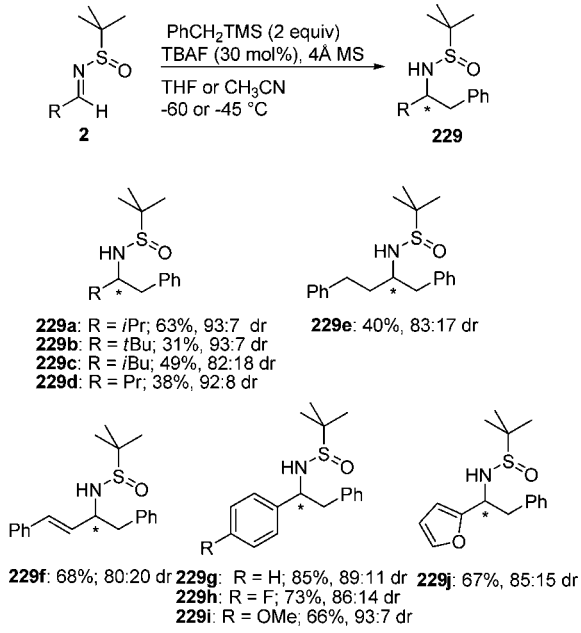
The fluoride promoted reaction of benzyltrimethylsilane with *N-tert*-butanesulfinyl imines **2** was published by Hou and coworkers (Scheme 64).[133] The optimal reaction conditions employed 30 mol % TBAF at low temperature. Additionally, 4 Å MS were included due to the beneficial effect observed in previous studies.[134] While the reaction conditions were optimized with a *N-p*-toluenesulfinyl imine, higher diastereoselectivities were observed when the analogous *N-tert*-butanesulfinyl imines **2** were employed. The scope of the reaction was examined with a number of structurally diverse aromatic and aliphatic *N-tert*-butanesulfinyl aldimines to provide products **229a**−**j** in varying yields and diastereoselectivities (Scheme 64). In general, higher yields were obtained for aromatic (66−85%, **229g**−**j**) than for aliphatic (31−68%, **229a**−**f**) *N-tert*-butanesulfinyl aldimines. The relative stereochemistry of the major isomer was unfortunately not determined.

4.1.4. Transition Metal Catalyzed 1,2-Additions to Aldimines

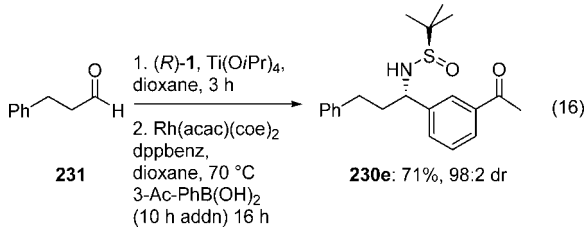
The aforementioned diastereoselective additions of organometallic reagents to *N-tert*-butanesulfinyl imines are extensively used; however, these methods are not always compatible with highly functionalized systems. In contrast, transition metal-catalyzed additions of organometallic reagents to carbonyl compounds have the ability to display increased functional group tolerance. Within this class of reactions, arylboronic acids are an especially attractive organometallic input because they are stable compounds, they are readily synthesized bearing a wide variety of functionality, and many are commercially available. Despite the poor nucleophilicity of arylboron reagents, rhodium(I)−phosphine complexes have been previously shown to effectively catalyze the addition of arylboronic acids to *N*-sulfonyl imines.[135]

The first example of this transformation with an *N-tert*-butanesulfinyl imine was reported by Ellman and co-workers in 2005, providing a new route toward the synthesis of chiral α-branched amines, a class of compounds found in many drugs and drug candidates.[136] After screening several rhodium precatalysts and phosphine ligands, $Rh(acac)(coe)_2$ with 1,2-bis(diphenylphosphino)benzene (dppbenz) was the most active catalyst system surveyed. The reaction was best performed in dioxane at 70 °C, and slow addition of the arylboronic acid was also shown to increase yields. Using these conditions, **230a** was synthesized in 96% yield and with a 97:3 diastereomeric ratio (Scheme 65). Notably, this method was also the first example of rhodium-catalyzed addition of arylboronic acids to an aliphatic aldimine.[137] Indeed, good yields (70−86%) and diastereoselectivities (96:4−98:2) were achieved for additions of both electron-rich and electron-poor arylboronic acids to the *N-tert*-butanesulfinyl imine derived from hydrocinnamaldehyde (**230b**−**e**). Additions of electronically diverse arylboronic acids to aryl aldimines also proved general, giving the desired chiral α-branched *N-tert*-butanesulfinyl amines **230f**−**h** in high yields (71−93%) and with excellent diastereoselectivities (≥98:2 dr). The efficiency of this procedure was also enhanced by the development of a one-pot protocol leading

Scheme 64. Addition of Benzyltrimethylsilane to *N-tert*-Butanesulfinyl Imines

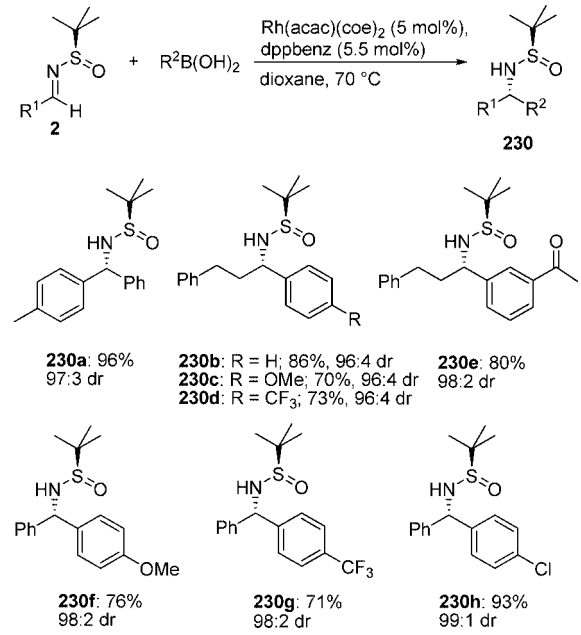


from the aldehyde precursor to the chiral amine (eq 16). Cleavage of the *tert*-butanesulfinyl group for select products under standard HCl-mediated conditions also occurred without racemization.

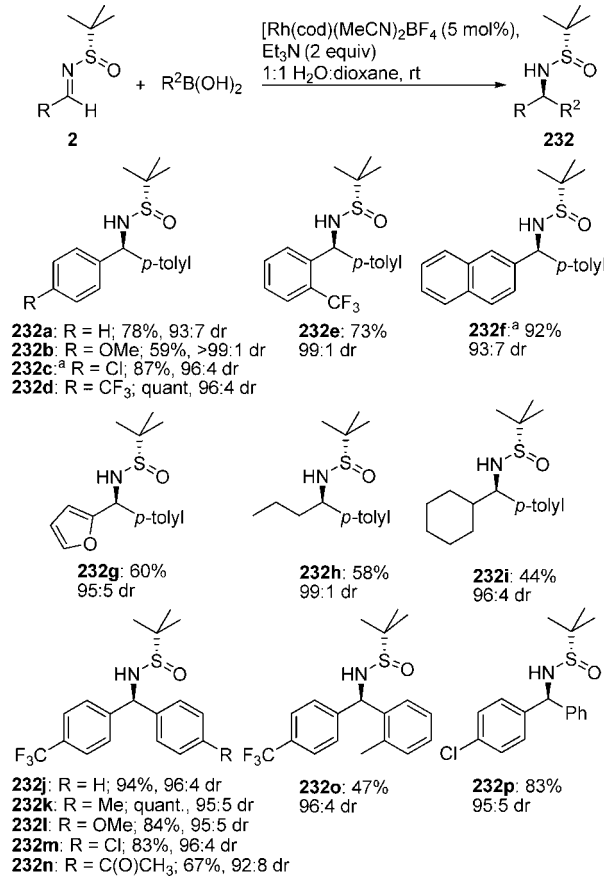


Batey and Bolshan published related conditions for the rhodium-catalyzed addition of arylboronic acids to aryl and alkyl *N-tert*-butanesulfinyl imines.[138] Their reactions were conducted at room temperature and utilized the cationic rhodium catalyst $[Rh(COD)(CH_3CN)_2]BF_4$ in the absence of added ligand in a 1:2 ratio of dioxane/H_2O, with Et_3N as an important additive. The authors hypothesized that Et_3N may act as a buffer to prevent protonation of the intermediate Ar−Rh(I) species and noted that water was a necessary cosolvent to maintain good yields. The scope of this method was probed by reacting *p*-tolylboronic acid with a range of aryl, heteroaryl, and alkyl *N-tert*-butanesulfinyl imines under the optimized conditions (**232a**−**i**, Scheme 66). In general, both yields and diastereoselectivities for the aryl imines were good (**232a**−**f**), with lower yields but high diastereomeric ratios for the heteroaryl and alkyl substrates (**232g**−**i**). While α-branched alkyl substrates provided only moderate yields (**232i**), it is noteworthy that this class of substrates did not couple using Ellman's conditions.[139] The scope of the arylboronic acid was also evaluated using the *N-tert*-butanesulfinyl *p*-trifluoromethylbenzaldimine, and the reaction was successful with both electron-rich and electron-poor arylboronic acids (**232j**−**n**). Substitution at the *ortho* position was tolerated, but diminished yields were observed (**232o**), and the yield and diastereoselectivity also suffered slightly when 4-acetylphenylboronic acid was employed (**232n**). Batey and Bolshan also reported that the sulfinyl group could

Scheme 65. Additions of Arylboronic Acids to *N-tert*-Butanesulfinyl Imines



Scheme 66. Cationic Rhodium-Catalyzed Additions of Arylboronic Acids to *N-tert*-Butanesulfinyl Imines

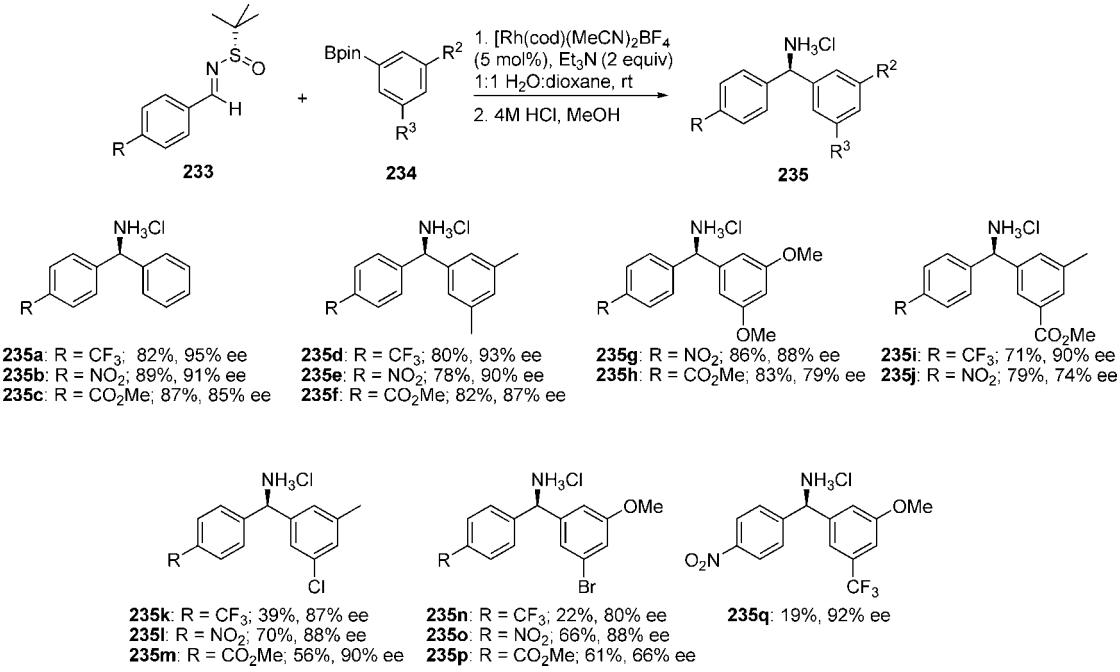


[a] Reaction performed at 0 °C to rt.

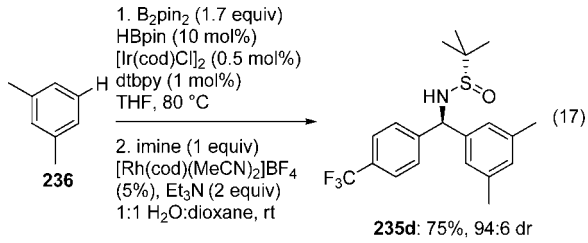
be cleaved under acidic conditions without erosion of the stereochemical purity for representative products **232f**, **h**, and **j**.

In their publication on the cationic rhodium-catalyzed additions of aryl boron reagents to *N-tert*-butanesulfinyl imines, Batey and Bolshan also reported that phenylpinacol

Scheme 67. Preparation of Chiral α,α-Diaryl Methaneamines from Boronate Esters



boronate ester was an effective coupling partner.[138] Following this observation, Hartwig and Boebel developed an iridium-catalyzed C−H functionalization of arenes to form 1,3-disubstituted boronate esters **234**, which were subsequently reacted with a variety of *N-tert*-butanesulfinyl aryl imines **233** bearing electron-withdrawing groups following Batey's protocol (Scheme 67).[140] Purification of the initial products of 1,2-addition by silica gel chromatography was problematic due to the coelution of the *N*-sulfinyl amine and a pinacol byproduct, and therefore cleavage of the sulfinyl group was first performed. The enantiomeric purity of the resulting amine hydrochloride salts **235** were evaluated by HPLC after acetylation of the amines. Yields for this procedure were higher for electron-rich aryl boronate esters than for electron-poor aryl boronate esters. In general, the enantiomeric excesses of the final amines were good, ranging from 66 to 95%. A one-pot protocol for the iridium-catalyzed C−H arene functionalization followed by the rhodium-catalyzed addition to a sulfinyl imine was also achieved (eq 17).



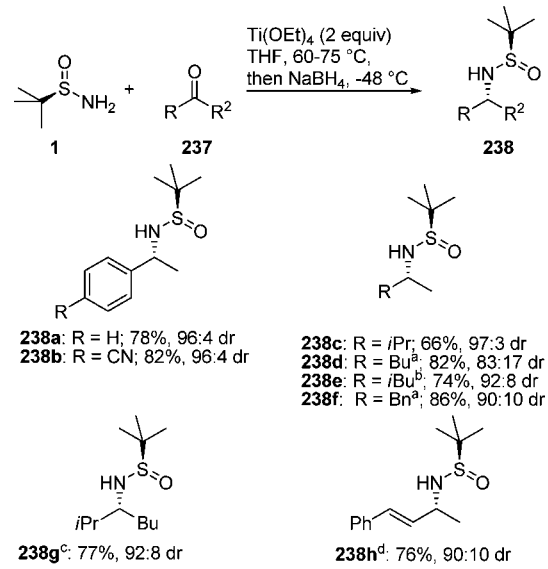
(17)

4.2. Reductions of Ketimines

4.2.1. Reduction of Ketimines using Borohydride Reagents

Ellman and co-workers reported the first example of a metal hydride reduction of an *N-tert*-butanesulfinyl ketimine,[141] providing a complementary approach to the 1,2-addition of organometallic reagents to *N-tert*-butanesulfinyl aldimines for the asymmetric synthesis of α-substituted amines. A number of reductants were surveyed at ambient temperature, and $NaBH_4$ provided the *N-tert*-butanesulfinyl

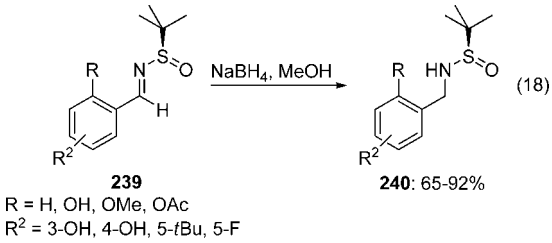
Scheme 68. Reductive Amination of Ketones 237 with *tert*-Butanesulfinamide



[a] 5:1 *E*/*Z* ratio for the isolated *N-tert*-butanesulfinyl ketimine. [b] 6:1 *E*/*Z* ratio for the isolated *N-tert*-butanesulfinyl ketimine. [c] Obtained with 3 equiv of $Ti(OEt)_4$ at −20 °C. [d] 3:1 *E*/*Z* ratio for the isolated *N-tert*-butanesulfinyl ketimine.

α-branched amine **238a** in the best yield and diastereoselectivity (83%, 91:9 dr). Further studies revealed that, by lowering the temperature (−48 °C) and adding $Ti(OEt)_4$, a higher yield and diastereoselectivity could be achieved (97%, 96:4 dr). Based on these observations, a one-pot protocol was developed for the *in situ* formation of the *N-tert*-butanesulfinyl ketimine followed by reduction to provide **238a** in 78% yield and with 96:4 dr (Scheme 68). Under these conditions, the $Ti(OEt)_4$ serves as both a water scavenger and catalyst for the formation of the ketimine as well as a Lewis acid in the reduction step, resulting in enhanced reduction rates and diastereoselectivities. A number of aryl−alkyl and dialkyl ketones were evaluated with this procedure, providing compounds **238b**−**h** in 66−86% yield

and with diastereomeric ratios ranging from 90:10 to 97:3, except for the most challenging compound **238d**, which was isolated with 83:17 dr. The authors also noted that the diastereomeric ratios of products **238d**, **f**, and **h** were higher than the *E*/*Z* ratios observed for the isolated *N*-*tert*-butanesulfinyl ketimine precursors. Importantly, the reductive amination to obtain **238h** proceeded with excellent chemoselectivity and only the 1,2-addition adduct was obtained. Additionally, no reduction of the nitrile in **238b** was observed. The diastereomeric ratios of the reduction products were ascertained by conversion to the MTPA-derivatives, and their absolute configurations were determined by chemical correlation to known amines. Later, a related method was employed by Sun and co-workers for the $NaBH_4$ reduction of *N*-*tert*-butanesulfinyl aldimines **239** (eq 18) in the context of synthesizing a number of *N*-*tert*-butanesulfinamide containing organocatalysts (for application, see section 20.2.2).[142]



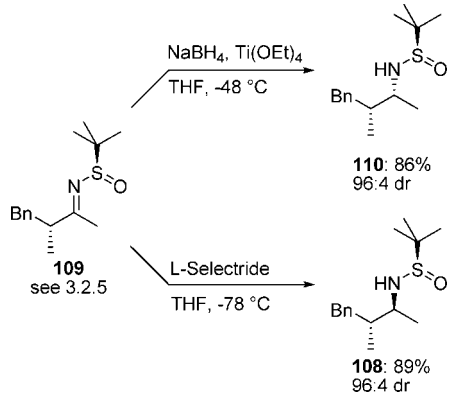
(18)

239
R = H, OH, OMe, OAc
R^2 = 3-OH, 4-OH, 5-*t*Bu, 5-F

240: 65-92%

Ellman and Kochi reported an isolated example of the stereoselective reduction of an *N*-*tert*-butanesulfinyl ketimine **109** bearing an α-stereocenter (prepared by the α-alkylation of an *N*-*tert*-butanesulfinyl amidine as discussed in section 3.2.5) to provide either amine diastereomer **110** or **108** (Scheme 69).[79] Reduction of **109** with $NaBH_4$ in the presence of $Ti(OEt)_4$ provided **110** in 89% yield with high diastereoselectivity (96:4). Conversely, the L-Selectride reduction provided **108** in equally high yield and diastereoselectivity, suggesting that the selectivity imparted by the *tert*-butanesulfinyl group dictates the stereochemical outcome of this reaction.

Scheme 69. Reduction of α-Chiral *N*-*tert*-Butanesulfinyl Ketimine 109



These conditions were later applied by Ellman and Peltier to the reduction of ketimines with a β-stereocenter (Scheme 70).[86] Again, the appropriate choice of a metal hydride reagent for the imine reduction of **74a** or **c** (prepared from addition of the *N*-*tert*-butanesulfinyl metalloenamine to an α,β-unsaturated ketone, see section 3.2.2) provided access to either diastereomer of the *N*-*tert*-butanesulfinyl amine (**241** or **243**). Sulfinyl cleavage and reductive cyclization of these intermedates provided piperidines **242a**, **242c**, and **244** in 46−72% yield without discernible racemization. Notably, this synthetic route installs an alkyl group in the 4-position of the piperidine, which is difficult to access by other methods.

Andersen and co-workers at Amgen were the first group to broadly demonstrate that, with the appropriate choice of metal hydride reagent, either diastereomer **247** or **249** could be obtained by the reduction of diverse *N*-*tert*-butanesulfinyl ketimines **246** (Table 7).[60] After a screen of many metal hydrides, $NaBH_4$ was found to be optimal for the synthesis of **247**, while L-Selectride was found to be best for the generation of the opposite diastereomer **249**. This reversal in diastereofacial selectivity between $NaBH_4$ and L-Selectride reductions was consistent with the observations by Ellman and Kochi[79] (*vide supra*). In line with Ellman's observations, the presence of $Ti(OEt)_4$ gave improved diastereoselectivities for $NaBH_4$ reductions (*vide supra*), but it did not benefit the L-Selectride reductions. Interestingly, the addition of 2% water to THF in the $NaBH_4$ reductions resulted in a moderate increase of the diastereoselectivity for the reduction of **246a** relative to anhydrous THF, negating the need for $Ti(OEt)_4$ as an additive, and subsequent $NaBH_4$ reductions utilized these conditions. A wide variety of *N*-*tert*-butanesulfinyl ketimines **246** were synthesized in 26−95% yield from ketone precursors **245a**−**n** to probe the generality of the reversal of the diastereoselectivity for the $NaBH_4$ and L-Selectride-mediated reductions. In general, moderate to excellent yields and diastereoselectivities were observed for both product stereoisomers. Overall, the L-Selectride reductions proceeded with enhanced diastereoselectivity relative to the corresponding $NaBH_4$ reductions, with the reduction of **246n** being a notable exception. After reduction, all products were converted to the corresponding amine salts **248** or **250** in moderate to excellent yields for the two-step procedure without erosion of the stereochemical purity. A scale-dependence was also observed with significant loss

Scheme 70. Synthesis of Piperidines by Stereoselective Reduction of *N*-*tert*-Butanesulfinyl Imines 74

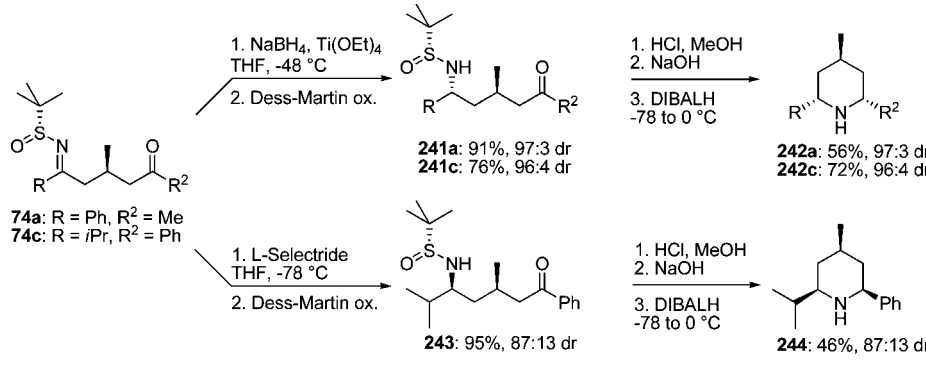
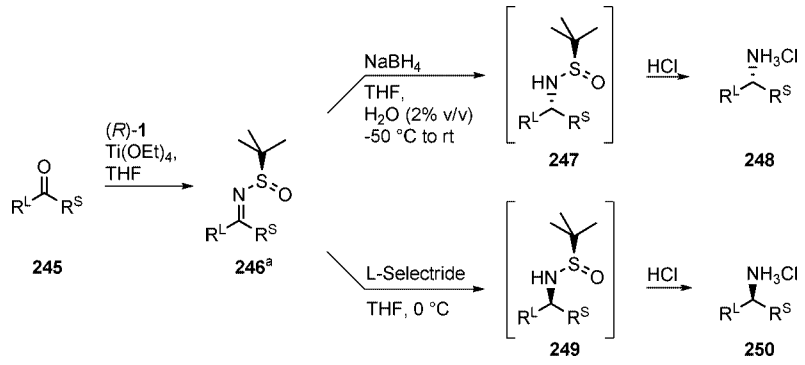
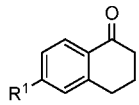
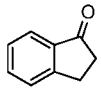
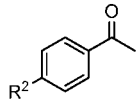
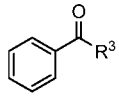


Table 7. Reductions of *tert*-Butanesulfinyl Ketimines[60]



Ketone **245**		yield (%) of **246**	NaBH$_4$ yield (%) of **248**	NaBH$_4$ dr **247**	L-Selectride yield (%) of **250**	L-Selectride dr **249**
	**245a**: R^1 = H	73	94	>98:2	98	>98:2
	245a: R^1 = H[b]		84	87:13	90	98:2
	245b: R^1 = OMe	73	77	97:3	96	99:1
	245c: R^1 = CN	74		77:23		81:19
	**245d**	26	87	98:2	93	>98:2
	**245e**: R^2 = H	71	95	91:9	98	92:8
	245e: R^2 = H[b]		80	87:13	82	92:8
	245f: R^2 = OMe	95	78	92:8	92	95:5
	245g: R^2 = CN	76	87	86:14	90	91:9
	245h: R^2 = Br	68	88	88:12	93	97:3
	245i: R^2 = CF_3	74	89	88:12	81	96:4
	**245j**: R^3 = Et	80	81	75:25	91	98:2
	245k: R^3 = Bu	79	84	74:26	86	98:2
	245l: R^3 = $(CH_2)_2$Ph	86	59	78:22	84	99:1
	**245m**: R^4 = *t*Bu	78	79	82:18	83	88:12
	245n: R^4 = $(CH_2)_2$Ph	58	55	76:24	84	51:49

[a] Reductions run on 0.2 mmol scale unless otherwise noted. [b] Reduction run on 20 mmol scale.

of diastereoselectivity for the NaBH$_4$ reduction of 20 mmol of ketimine **246a** or **246e** versus the analogous reduction of 0.2 mmol, while the L-Selectride reductions were not affected by scale.

The reversal in stereoselectivity upon changing reducing agents from NaBH$_4$ to L-Selectride was rationalized by a chelated versus an open transition state, respectively (Figure 4). For the NaBH$_4$ mediated reductions, the authors proposed the coordination of the sulfinyl oxygen to the metal with delivery of the hydride occurring from the *si*-face of the imine (**251**). Conversely, with the poorly coordinating metal hydride, L-Selectride, an open transition state **252** was proposed, with addition of the hydride occurring from the least hindered face.

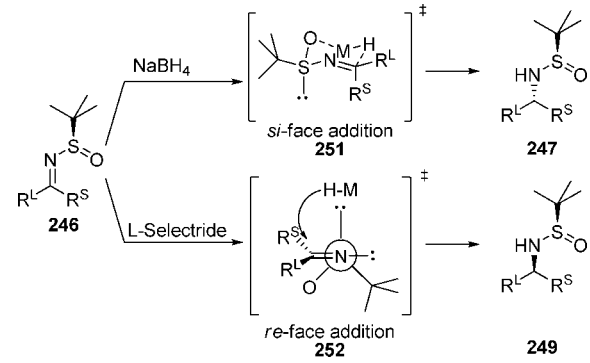
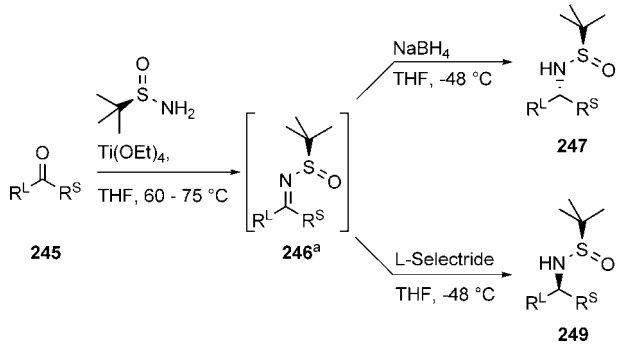


Figure 4. Stereochemical rationale for the reduction of *N-tert*-butanesulfinyl ketimines.

Soon after Andersen and co-workers' important study on the hydride reduction of unfunctionalized *N-tert*-butanesulfinyl ketimines, Ellman and co-workers reported one-pot protocols for imine formation and either NaBH$_4$ or L-Selectride mediated reduction (Table 8).[143] For these transformations, the conditions previously optimized for the one-pot NaBH$_4$ mediated reductive amination of ketones with *tert*-butanesulfinamide (see Scheme 68) were applied to additional ketone substrates, and the L-Selectride mediated reductive amination was applied to a large number of substrates. High yields and selectivities were observed for both sets of conditions for electron-poor, neutral, and electron-rich tetralones (**245a,b** and **o**), with the L-Selectride conditions consistently providing slightly higher diastereoselectivities. While very high selectivities were also observed for the one-pot reductive amination of indanone (**245d**), the yield was low due to competitive side reactions during imine formation. A low yield for the synthesis of this imine was

Table 8. One-Pot Reductive Amination of Ketones[143]



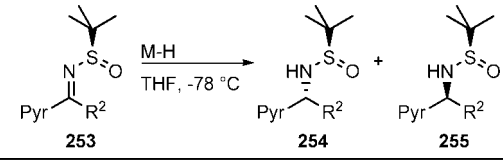
Ketone **245**	NaBH$_4$ yield (%) of **247**	NaBH$_4$ dr **247**	L-Selectride yield (%) of **249**	L-Selectride dr **249**
245a: R^1 = H[b]	80	84:16	83	99:1
245b: R^1 = OMe	89	91:9	80	97:3
245o: R^1 = NO$_2$	73	90:10	72	98:2
245d	28	99:1	27	>98:2
245p	100	58:42	49	88:12
245e: R^2 = Ph	78	96:4	89	97:3
245e: R^2 = Ph[b]	93	96:4		
245q: R^2 = Bu	82	83:17	72	86:14
245r: R^2 = *i*Pr	66	97:3	76	96:4
245s: R^2 = *i*Bu	74	92:8	70	96:4
245m: R^2 = *t*Bu	62	99:1	83	96:4

[a] Reductions run on 0.5−1.0 mmol scale unless otherwise noted. [b] Reduction run on 45 mmol scale.

also observed in Andersen's study (*vide supra*). When this method was extended to the seven-membered cyclic ketone **245p**, the $NaBH_4$ reduction proceeded in quantitative yield but with modest diastereoselectivity; in contrast, the L-Selectride reduction provided good diastereoselectivity but moderate yield. While the one-pot $NaBH_4$ reductive amination of acyclic ketones **245e** and **245q−s** had been previously described (see Scheme 68),[141] in this study the L-Selectride mediated reductive amination of these acyclic ketones was also evaluated and gave the desired amines **249** in 70−89% yields and with diastereomeric ratios ranging from 86:14 to 97:3. Interestingly, the $Ti(OEt)_4$ mediated reductive amination of hindered ketone **245m** with either reductant gave superior yields and diastereoselectivities compared to those reported previously for the reduction of the corresponding isolated *N*-*tert*-butanesulfinyl ketimine (see Table 7). Importantly, the reductive amination of **245e** with $NaBH_4$ did not display any scale dependence (from 1 to 45 mmol scale), which contrasts with the scale dependence of the diastereoselectivity observed for the $NaBH_4$ reductions of the corresponding isolated *N*-tert-butanesulfinyl imine **246e** when water was used as an additive (see Table 7). The stereochemical outcome of this reaction was consistent with the transition state models proposed by Andersen and co-workers (Figure 4).

The reduction of *N*-*tert*-butanesulfinyl ketimines **253** derived from pyridyl ketones was demonstrated by Chelucci

Table 9. Reduction of Pyridyl *N*-*tert*-Butanesulfinyl Ketimines[144]



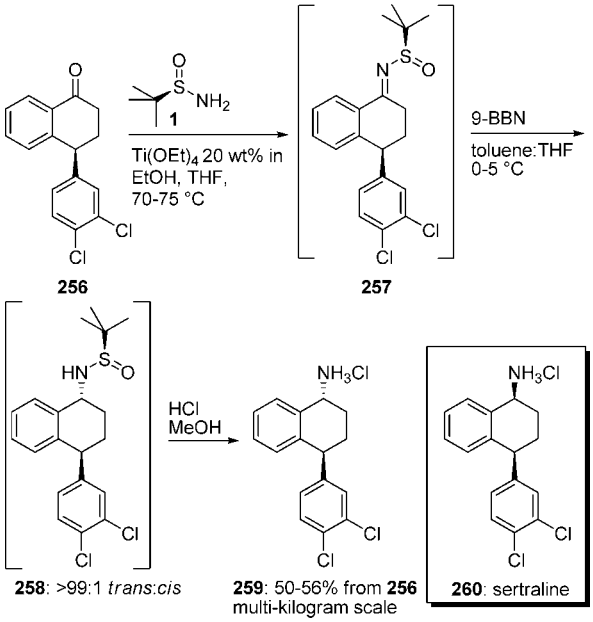
Imine	DIBALH yield (%)	DIBALH dr **254:255**	L-Selectride yield (%)	L-Selectride dr **254:255**
253a	90	99:1	82	1:99
253b	88	99:1	92	5:95
253c: R = Me[a]	72	88:12	31	1:99
253d: R = *i*Pr	87	42:58	69[b]	12:88
253e: R = *t*Bu	92	13:87	0	
253f: R = Ph	75	23:77	50	19:81

[a] Reductions of **253c** in the presence of 9-BBN at rt resulted in 99:1 dr and 50% yield. [b] Reaction conducted at −40 °C.

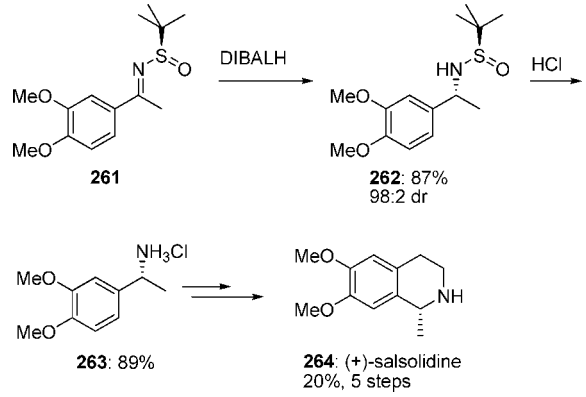
and co-workers (Table 9).[144] The ketimines **253a−c** were first examined with various hydride transfer reagents in THF at low temperature (−78 °C). The coordinating reagent, diisobutylaluminium hydride (DIBALH), provided the best combination of yield and diastereoselectivity, favoring the formation of **254**, which could arise via a chelated transition state. Conversely, the poorly coordinating bulky L-Selectride was optimal for the formation of **255**, indicative of an open transition state (see Figure 4). The scope of the reaction was further probed by reduction of a number of aryl and alkyl 2-pyridyl *N*-*tert*-butanesulfinyl ketimines (**253c−f**), revealing that the stereochemical outcome of the reaction was sensitive to both the reducing agent and the R substituent of the ketimine **253**. While the DIBALH and L-Selectride reductions of methyl derivative **253c** proceeded to provide either **254** or **255**, respectively, with excellent diastereoselectivities, increasing the steric bulk at the R position (**253d−f**) resulted in diminished diastereoselectivity. Indeed, while yields remained high, a switch in the observed facial selectivity was noted for the DIBALH reduction of bulkier subtrates. The L-Selectride reduction of **253d** required elevated temperatures in order to obtain the desired product, and no reaction was observed for **253e**, despite increasing the reaction temperature. Several reduction conditions were also surveyed with *N*-*tert*-butanesulfinyl 2-pyridyl ketimines bearing heteroaromatic functionality at the R position, but poor diastereoselectivity was observed in all cases. The diastereomeric ratios for all adducts were determined by ^1H NMR, and the configuration of the α-stereocenter for **255a−d** and **f** was assigned by chemical correlation experiments, while **255e** was assigned by analogy.

A large-scale synthesis of drug candidate **259** was developed at Sepracor, Inc. by Singh and co-workers. This compound was investigated as a therapeutic agent for central nervous system disorders and is a diastereomer of the

Scheme 71. Large-Scale Synthesis of 259



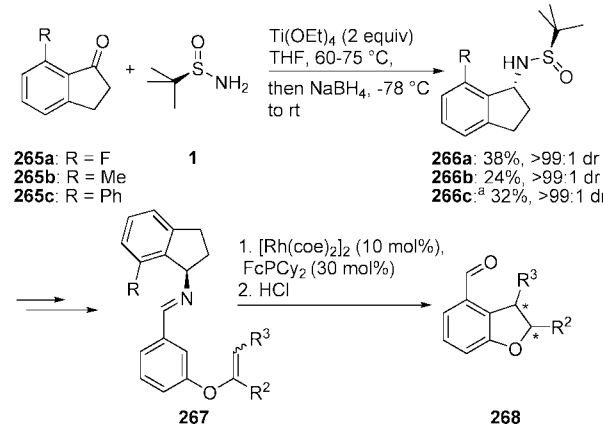
Scheme 72. Total Synthesis of (*R*)-(+)-Salsolidine 264



antidepressant sertraline (**260**) marketed by Pfizer in the United States as Zoloft (Scheme 71).[145] Condensation of (*R*)-**1** with ketone **256** provided *N*-*tert*-butanesulfinyl ketimine **257**, and the crude material was reduced with 9-BBN to generate **258** in high yield and with excellent diastereoselectivity. The stereochemistry of the hydride reduction was controlled by the sulfinyl group, overriding the substrate bias of the 4*S* stereocenter for the *cis*-diastereomer. Acidic methanolysis yielded **259** on a multikilogram scale in 50−56% overall yield from **256**.

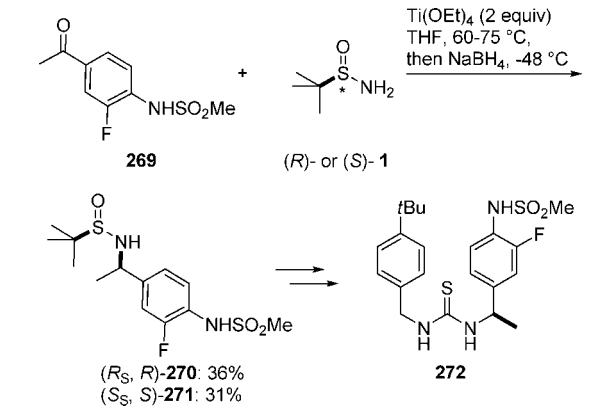
The synthesis of (*R*)-(+)-salsolidine (**264**) via the diastereoselective reduction of *N*-*tert*-butanesulfinyl ketimine **261** was accomplished by Rozwadowsak and Grajewska (Scheme 72).[106] This route complemented their previous approach to (*S*)-(−)-salsolidine (**164**), which was achieved via the nucleophilic addition of a Grignard reagent to the appropriate *N*-*tert*-butanesulfinyl aldimine (see section 4.1.1).[105] A number of reaction conditions for the reduction of **261** were examined, with DIBALH yielding **262** in 87% yield and with a 98:2 diastereomeric ratio. After subsequent synthetic transformations, the desired alkaloid **264** was obtained in 20% yield and with >95% enantiomeric purity for the five-step sequence. Correlation of the sign of the specific rotation of the synthetic natural product **264** to the literature value for (*R*)-(+)-salsolidine confirmed the absolute configuration.

Scheme 73. Reductive Amination of Substituted Indanones



[a] $Ti(OPh)_4$ (4 equiv) was used.

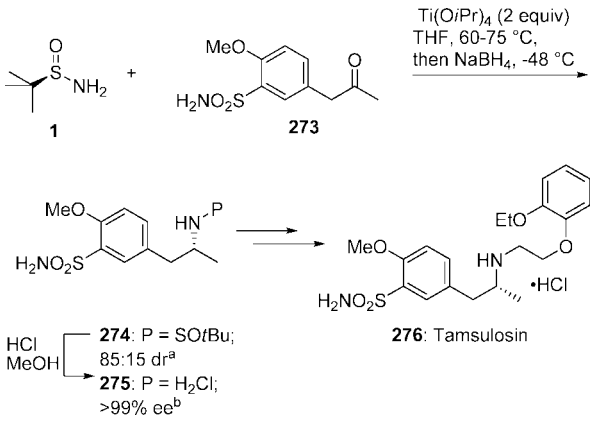
Scheme 74. Asymmetric Synthesis of TRPV1 Ligands



A one-pot reductive amination of substituted indanones was utilized by Ellman, Bergman, and co-workers for the synthesis of aminoindanes **266a**−**c**, which after sulfinyl deprotection and condensation with aldehydes served as chiral directing groups for rhodium-catalyzed intramolecular C−H activation and cyclization toward dihydrobenzofurans **268** (Scheme 73).[146] *In situ* formation of the *N*-*tert*-butanesulfinyl ketimines and reduction by $NaBH_4$ provided **266a** and **266b** in 38% and 24% yields as single diastereomers, respectively. The authors rationalized that the modest yields were due to competing enamine formation, and low yields for *N*-*tert*-butanesulfinyl ketimine formation from indanone had been noted previously (*vide supra*).[60,143] The attempted condensation of sterically hindered **265c** with (*R*)-**1** in the presence of a $Ti(OEt)_4$ reagent that contained 5−15% *i*PrOH resulted in Meerwien-Pondorf-Verley reduction to the corresponding indanol, but this problem was circumvented by employing $Ti(OPh)_4$ to yield **266c** in modest yield as a single diastereomer. Acidic removal of the sulfinyl group followed by formation of imines **267** provided the necessary precursors for the asymmetric intramolecular alkylation reaction.

In their efforts to optimize the *in vitro* activities of several 4-methylsulfonamide antagonists to the transient receptor potential cation channel V1 (TRPV1), Lee and co-workers devised an asymmetric synthesis of **272** via the reductive amination of ketone **269** to probe the effect of substitution at the benzylic position of the aniline moiety (Scheme 74).[147] Both (*R*)- and (*S*)-*tert*-butanesulfinamide were used as the amine components for imine formation and $NaBH_4$ reduction,

Scheme 75. Synthesis of Tamsulosin



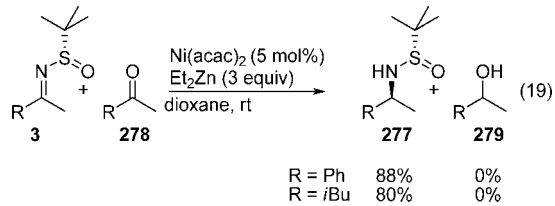
[a] The manuscript[148] reports 87% optical purity, while the Supporting Information indicates 85:15 dr. [b] 99% ee after two crystallizations with dibenzoyl-D-tartrate.

and (R_S,*R*)-**270** and (S_S,*S*)-**271** were synthesized in unoptimized 36% and 31% yields, respectively.

Reddy and co-workers at Suven Life Sciences developed a stereoselective synthesis of the antihypertensive drug Tamsulosin (**276**) employing a reduction of an in situ generated *N-tert*-butanesulfinyl ketimine (Scheme 75).[148] Several reductants were surveyed, and the best result was obtained when **1** and **273** were treated with Ti(O*i*Pr)$_4$ followed by reduction with $NaBH_4$, generating **274**. Removal of the sulfinyl group from crude **274** followed by two crystallizations with dibenzoyl-D-tartrate provided enantiomerically pure **275**, which was further converted to tamsulosin (**276**).

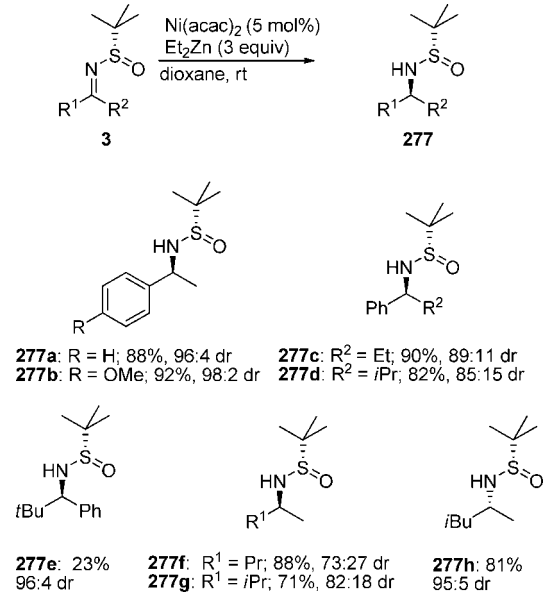
4.2.2. Transition Metal Catalyzed Reductions of Ketimines

The nickel-catalyzed diethylzinc reduction of *N-tert*-butanesulfinyl ketimines was developed by Qin and co-workers (Scheme 76).[149] The reaction conditions were optimized, revealing that 5 mol% Ni(acac)$_2$ and 3 equiv of Et_2Zn in dioxane at ambient temperatures provided **277a** in the highest yield and diastereoselectivity (88%, 96:4 dr). The nickel catalyst was essential for this transformation. No reaction was observed in a ^{1}H NMR study of ketimine **3** (R^1 = Ph, R^2 = Me) and diethylzinc in the absence of this catalyst. A number of aryl alkyl ketimines **3** were reduced employing these optimized conditions to generate **277b**−**d** in high yields (82−92%) and with diastereomeric ratios ranging from 85:15 to 98:2. While **277e** was generated with excellent diastereoselectivity (96:4 dr), the reduction was sluggish due to steric hindrance, resulting in a low isolated yield. The reductions of several *N-tert*-butanesulfinyl dialkyl ketimines also proceeded in good yields (**277f**−**h**). Selective reduction of a number of *N-tert*-butanesulfinyl ketimines in the presence of their corresponding ketones **278** was also demonstrated (eq 19).

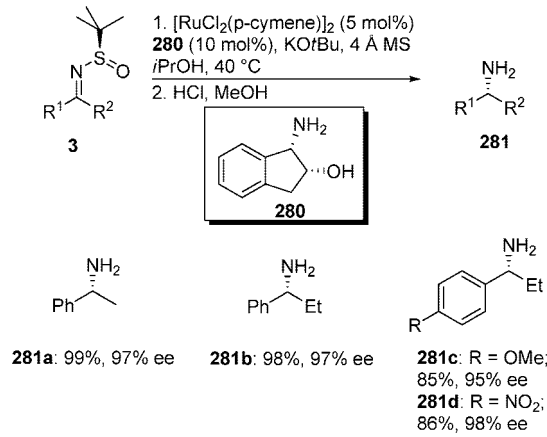


Recently, Yus and co-workers developed a ruthenium catalyzed asymmetric transfer hydrogenation of *N-tert*-butanesulfinyl ketimines, providing a new method for the rapid synthesis of α-branched amines (Scheme 77).[150] Several reaction parameters were examined using the ruthenium precatalyst [RuCl$_2$(*p*-cymene)]$_2$ and *i*PrOH as the hydride donor and solvent, including ligand, temperature, and additives. A number of chiral amino alcohol ligands were screened in conjunction with the ruthenium source, and ligand **280** was chosen due to its cost-effectiveness as well as the high level of selectivity obtained for **281a** when this ligand was employed. Under the optimized conditions of heating to 40 °C, use of KO*t*Bu as the base, and addition of 4 Å MS to suppress competitive hydrolysis, amine **281a** was obtained in quantitative yield and with 97% ee. The scope of the reaction was probed with three other *N-tert*-butanesulfinyl ketimines, and the resulting amines **281b**−**d** were produced in excellent yields (85−98%) and selectivities (95−98% ee).

Scheme 76. Diethylzinc Reduction of *N-tert*-Butanesulfinyl Ketimines 3 Catalyzed by Ni(acac)$_2$



Scheme 77. Ruthenium Catalyzed Asymmetric Transfer Hydrogenation of *N-tert*-Butanesulfinyl Ketimines



5. Synthesis of α,α-Dibranched Amines (Tertiary Carbinamines)

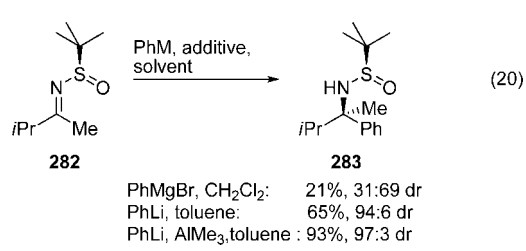
There are two significant challenges that limit the success and generality of many asymmetric additions of nucleophiles to ketimines. First, ketimines are much less reactive than

aldimines, and consequently, the propensity for side reactions, including competitive α-deprotonation to form enamides or competitive reduction by organometallics via β-hydride elimination, is greatly increased. Second, the level of diastereoselectivity for imine additions is dependent not only on the facial selectivity but also on the *E/Z*-isomer ratio of the imine. In contrast to aldimines where large steric differences inherently provide very high *E/Z*-isomer ratios, for ketimines the steric difference between the two ketimine substituents is often much smaller, resulting in lower selectivity.

The use of *N-tert*-butanesulfinyl imines **3** largely overcomes these challenges due to the activating nature of the sulfinyl group, which enhances the electrophilicity of the imine while at the same time minimizing undesired competitive α-deprotonation. Morever, as described previously (section 3.1.2), for these imines modest differences in sterics between the two imine substituents result in good *E/Z*-imine isomer ratios that enable highly diastereoselective additions to be achieved. A large variety of nucleophiles have been added to *N-tert*-butanesulfinyl ketmines **3** to give a variety of tertiary carbinamine products (see relevant sections of the review for specific addition products).

5.1. 1,2-Additions of Organometallic Reagents to Ketimines

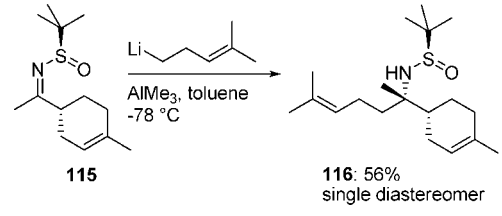
The addition of organolithium reagents to *N-tert*-butanesulfinyl ketimines **3** was first reported by Ellman and Cogan in 1999, providing a general method for the asymmetric synthesis of α,α-dibranched amines.[49] In the following full paper, details were provided on the effects of the organometallic reagent and Lewis acid additives on the yield and stereoselectivity of the transformation.[92] The addition of Grignard reagents to *N-tert*-butanesulfinyl ketimine **282** was first explored using the reaction conditions previously optimized for additions to *N-tert*-butanesulfinyl aldimines (see section 4.1.1). While the addition of allylmagnesium bromide to ketimines proceeded with high yield and excellent diastereoselectivity (see section 7.1), the addition of phenylmagnesium bromide proceeded poorly, providing **283** in 21% as a 31:69 mixture of diastereomers (eq 20). In contrast, the addition of phenyllithium to **282** provided more promising results, yielding **283** in 65% yield and 94:6 diastereomeric ratio, favoring the diastereomer opposite that observed for the Grignard addition. To enhance the product yield, a survey of Lewis acids was conducted, including Al(O*i*Pr)$_3$, trialkylaluminums, diethylzinc, $BF_3 \cdot OEt_2$, and magnesium and zinc salts. Trimethylaluminum ($AlMe_3$) had the most dramatic effect on the 1,2-addition of phenyllithium to **282**, providing **283** in high yield and diastereoselectivity. The stereochemistry of this addition was rationalized by chelated transition state **284** (Scheme 78).



(20)

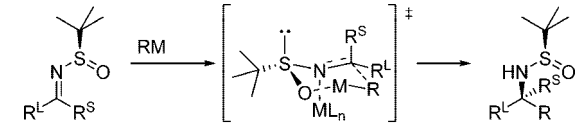
The $AlMe_3$-mediated addition of aromatic and alkyl organolithium reagents to a variety of *N-tert*-butanesulfinyl ketimines **3** was found to be very general (Scheme 79). To minimize the competitive side reaction of α-deprotonation, the *N-tert*-butanesulfinyl ketimines were first treated with $AlMe_3$ before slow addition of the complex to a solution of the desired aryl or alkyl lithium diluted in toluene at −78 °C. Under these conditions, the reactions proceeded in good to excellent yields (61%-quantitative) and with diastereoselectivities ranging from 89:11 to 99:1. Notably, product **287b** was isolated with a higher diastereoselectivity (89:11) than the *E/Z* ratio of the *N-tert*-butanesulfinyl ketimine precursor (5:1), which, given the high yield, suggests either that complexation with $AlMe_3$ perturbs the imine isomer ratio or that under the reaction conditions imine isomerization occurs at a rate competitive to 1,2-addition. Several additions were performed without the $AlMe_3$ additive, and marginally to dramatically lower yields and diastereoselectivities were observed. The assignments of the absolute configurations of **287a** and **287i** were established by chemical correlation, while a derivative of **287h** was analyzed by X-ray structural analysis. The configurations of the other adducts were assigned by analogy.

The utility of this chemistry was demonstrated in the synthesis of the marine natural product (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene (see section 3.2.5).[79] The $AlMe_3$-mediated addition of the organolithium to ketimine **115** produced **116** in 56% yield with perfect diastereoselectivity (eq 21).

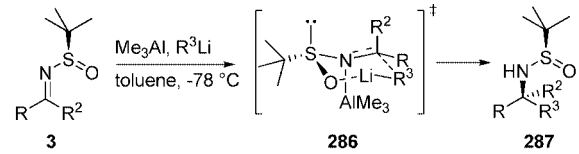


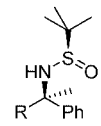
(21)

Scheme 78. Chelated Transition State for Additions to *N-tert*-Butanesulfinyl Ketimines 3

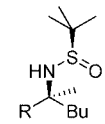


Scheme 79. Synthesis of α,α-Dibranched Amines from *N-tert*-Butanesulfinyl Ketimines

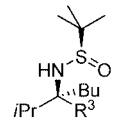




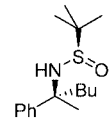
287a: R = *i*Pr; 93%, 97:3 dr
(no $AlMe_3$ 65%, 94:6 dr)
287b: R = Bu; 93%, 89:11 dr
(no $AlMe_3$ 67%, 63:37 dr)
287c: R = *i*Bu; 62%, 85:15 dr
287d: R = 2-naphthyl; 62%, 99:1 dr



287e: R = Ph; 86%, 98:2 dr
(no $AlMe_3$ 26%, 99:1 dr)
287f: R = *i*Pr; 61%, 99:1 dr

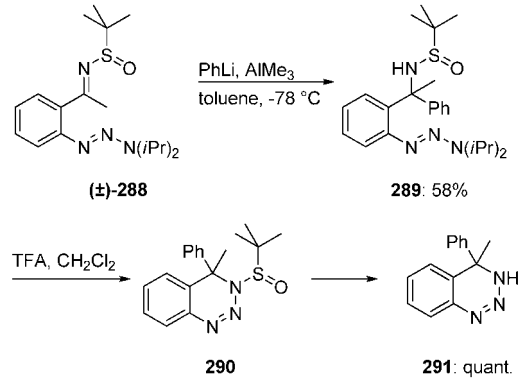


287g: R^3 = Ph; 82%, 91:9 dr
287h: R^3 = Me; 82%, 91:9 dr
(no $AlMe_3$ 54%, 82:18 dr)

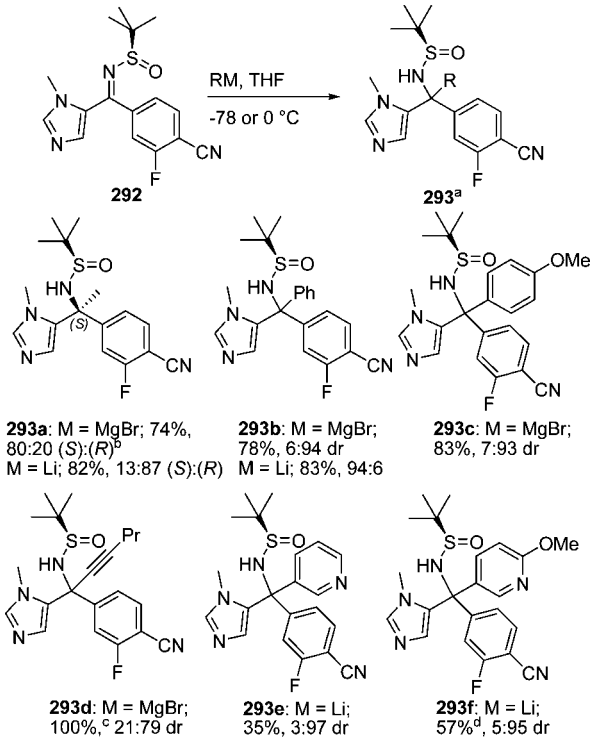


287i: quant., 99:1 dr

Scheme 80. Synthesis of Heterocycle 291 from *N-tert*-Butanesulfinyl Ketimine 288



Scheme 81. 1,2-Addition of Organometallic Reagents to 292

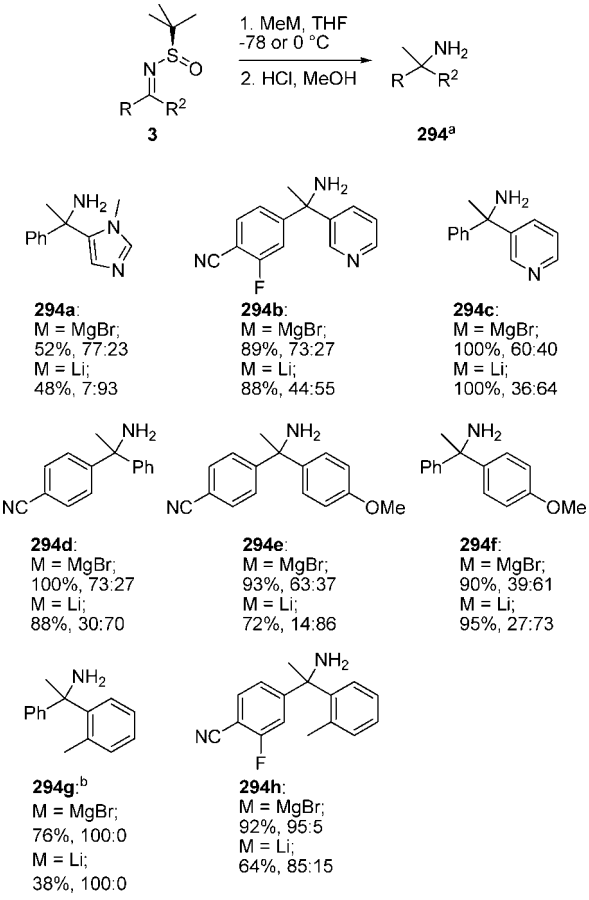


[a] Ratio of diastereomers given as (−):(+) enantiomers after deprotection of the sulfinyl group. [b] X-ray structural analysis established the absolute configuration of **293a** from the addition of MeMgBr as (*S*). [c] Crude yield of the *N-tert*-butanesulfinyl amine **293**. [d] Isolated yield of the amine salt after deprotection.

In an interesting application, Brase and co-workers added phenyllithium to ketimine **288** (Scheme 80).[151] Despite activation with the strong Lewis acid $AlMe_3$, the triazene present in **288** was stable to the reaction conditions, providing **289** in 58% yield. Further studies revealed that treatment of **289** with TFA promoted cyclization to the heterocycle **290**, which upon prolonged reaction times underwent complete deprotection to **291** in quantitative yield.[152]

In their work on the synthesis of protein farnesyl transferase (FTase) inhibitors, Shaw and DeSolms at Merck explored the addition of organometallic reagents to *N-tert*-butanesulfinyl aryl-heteroaryl and diaryl ketimines (Schemes 81 and 82).[153] Optimization of the reaction conditions revealed that THF was the solvent of choice due to the insolubility of the starting ketimines in Et_2O or CH_2Cl_2. To obtain the best yields, excess of the Grignard reagent was

Scheme 82. 1,2-Addition of Organometallic Reagents to Diaryl *N-tert*-Butanesulfinyl Ketimines

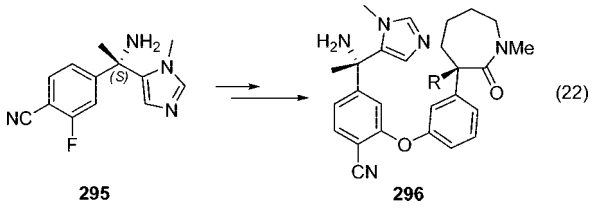


[a] Ratio of enantiomers given as (−):(+). [b] Reactions conducted at 0 °C.

necessary (6 equiv), and the reaction was conducted at 0 °C. When organolithium reagents were used as the nucleophile, the reactions were conducted at −78 °C. In the course of their studies, they determined that addition of a Grignard versus an organolithium reagent to the same imine proceeded with opposite diastereoselectivity. The scope of this method was investigated for addition of a variety of alkyl, alkynyl, and aryl organometallic reagents to ketimine **292**, providing sulfinyl amines **293a**−**f** in moderate to high yields (35−100%) and with good to excellent diastereomeric ratios (Scheme 81). The scope with respect to the *N-tert*-butanesulfinyl ketimine **3** was also explored using methylmagnesium bromide or methyllithium as the nucleophiles, providing amines **294** after methanolysis of the sulfinyl group (Scheme 82). While a reversal in diastereoselectivity depending on the type of organometallic reagent utilized was observed for additions to the aryl-heteroaryl ketimines and the diaryl ketimines with an electron-withdrawing substituent (products **294a**−**e**), no reversal was observed for electron-neutral or electron-rich substrates (products **294f**−**h**). Notably, an increase in diastereoselectivity was observed for additions to diaryl ketimines bearing an *ortho*-methyl substituent (products **294g**−**h**) similar to those shown in Scheme 81.

Graham and co-workers at Merck utilized compound **295**, obtained after methanolysis of the *tert*-butanesulfinyl group of **293a** in their synthesis of **296**, which was designed as a dual inhibitor of both protein farnesyltransferase (FTase) and protein geranylgeranyltransferase I (GGTase-I) (eq 22).[154]

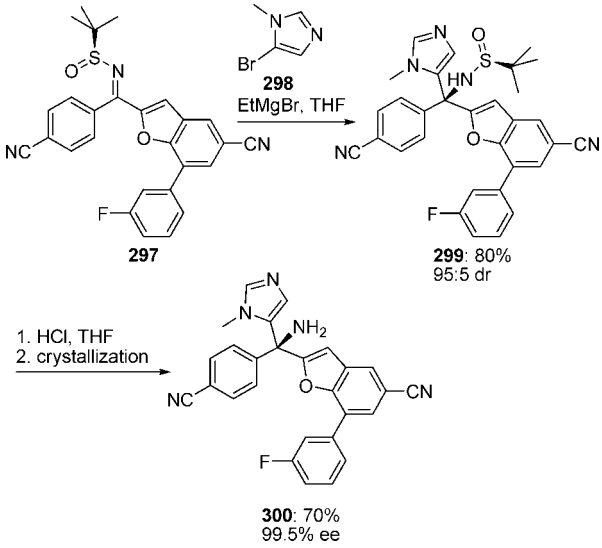
Sakaitani and co-workers at Chugai Pharmaceutical Co. prepared a large number of tertiary carbinamines in the



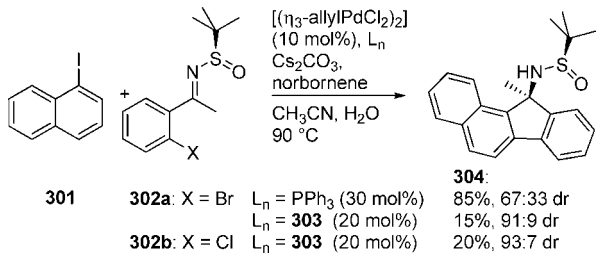
synthesis of potential protein FTase inhibitors that ultimately culminated in the development of inhibitor **300**, obtained by addition of a heterocyclic organometallic reagent prepared from **298** to *N-tert*-butanesulfinyl ketimine **297** (Scheme 83).[155] Notably, while the use of *n*BuLi as the base for addition of 1-methyl-2-TES imidazole to **297** afforded adduct **299** with low diastereoselectivity (2:1), treatment of **298** with ethylmagnesium bromide and subsequent addition to ketimine **297** proceeded with excellent diastereoselectivity (95:5). Removal of the sulfinyl group and recrystallization provided enantiomerically pure inhibitor **300**, which showed significant tumor regression *in vivo* for human nonsmall cell lung carcinoma xenografts in mice.

Recently, Lautens and co-workers developed a domino *ortho*-arylation and subsequent addition to a carbonyl group for the rapid synthesis of fluorene and phenanthrene derivatives.[156] While the majority of their study focused on additions to other carbonyl functionalities (ketene, aldehyde, and ester), *N-tert*-butanesulfinyl ketimines **302a** and **302b** were also explored (Scheme 84). For the initial reaction between **301** and **302a**, PPh_3 was used as the phosphine ligand, as it was optimal for related transformations, and **304** was generated in 85% yield but with moderate diastereoselectivity. When (2-biphenyl)di-*tert*-butylphosphine (ligand **303**) was used, ketimines **302a** and **302b** both provided product **304** in low yield but with high diastereoselectivity.

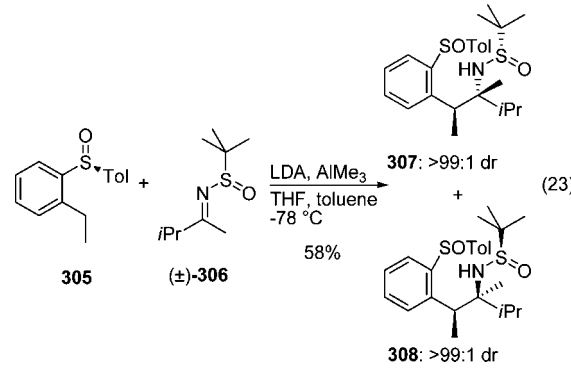
Scheme 83. Asymmetric Synthesis of FTase Inhibitor 300



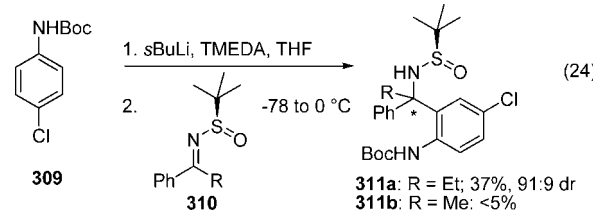
Scheme 84. Domino *ortho*-Arylation and Subsequent Addition to *N-tert*-Butanesulfinyl Ketimine



In their efforts to develop a new method for the synthesis of α,α-dibranched amines with adjacent stereocenters, Garcia Ruano and co-workers examined the addition of deprotonated **305** to *N-tert*-butanesulfinyl ketimine (±)-**306** (eq 23).[157] While the focus of the study was the addition of **305** to diverse *N-p*-toluenesulfinyl ketimines, the transformation failed due to imine decomposition when an *N-p*-toluenesulfinyl dialkyl ketimine was used as the substrate. In contrast, addition to the *N-tert*-butanesulfinyl dialkyl ketimine (±)-**306** using $AlMe_3$ as an additive proceeded smoothly, providing a 1:1 mixture of diastereomers, each arising from one of the sulfinyl enantiomers, which were separated by column chromatography to yield the diastereomerically pure **307** and **308**. Overall, the transformation proceeded with complete stereocontrol over the two newly formed chiral centers, where the configuration of the carbon adjacent to the amine was controlled by the *N*-sulfinyl group, and the configuration of the benzylic stereocenter was dependent on the configuration of the sulfoxide.

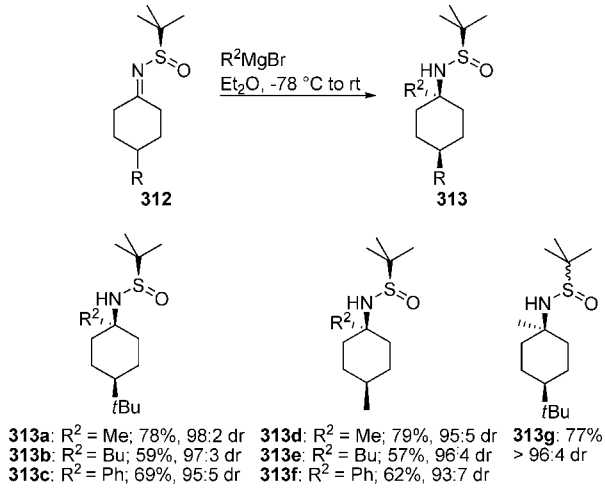


Rajapakse and co-workers at Merck examined the addition of *o*-lithiated anilines to *N-tert*-butanesulfinyl imines, but while additions to aldimines worked well (see section 4.1.2), low to moderate yields were obtained for the analogous addition to ketimines (eq 24).[123] Competitive deprotonation of the starting ketimine was found to be the primary nonproductive pathway, as determined by deuterium quenching experiments.

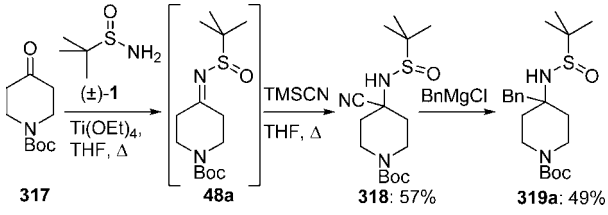


The first example of additions of organometallic reagents to cyclic *N-tert*-butanesulfinyl ketimines derived from substituted cyclohexanones was reported by Ellman and McMahon (Scheme 85).[13] The reaction conditions previously optimized for the addition of organometallic reagents to acyclic *N-tert*-butanesulfinyl ketimines were first evaluated (RLi, $AlMe_3$, toluene, −78 °C), but poor selectivity was observed when organolithium reagents purchased as solutions in Et_2O were utilized (MeLi, PhLi), presumably due to the aggregation state of the lithium species. However, unlike additions to acyclic *N-tert*-butanesulfinyl ketimines, additions of aryl or alkyl Grignard reagents to these cyclic ketimines **312** proceeded in good yields and with high diastereoselectivities. Given that the ketimines **312** were isolated as 1:1

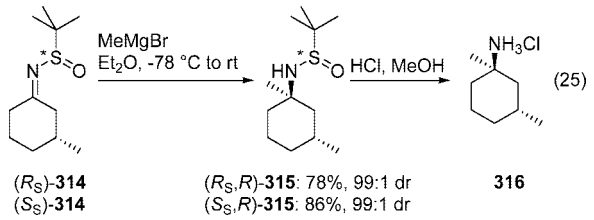
Scheme 85. Addition of Grignard Reagents to Cyclic *N-tert*-Butanesulfinyl Ketimines



Scheme 86. Synthesis of 4-Benzyl-4-aminopiperidine 319a



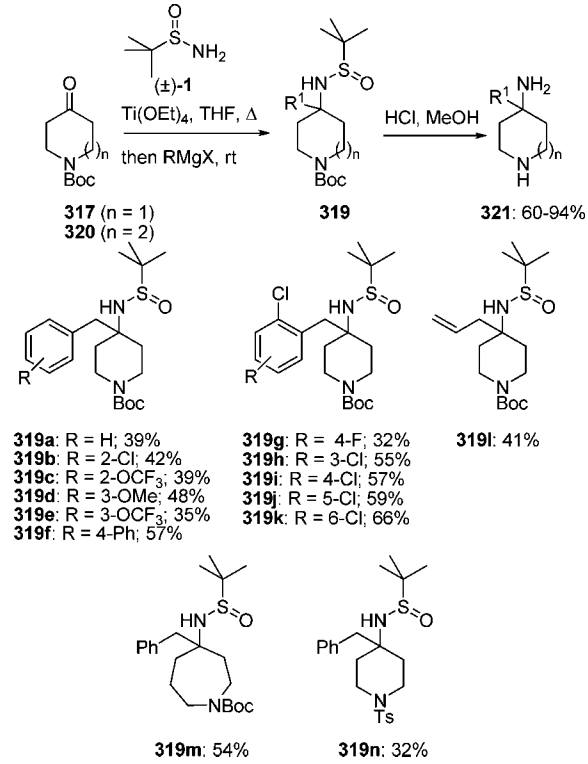
mixtures of imine isomers, the selectivity of this reaction was rationalized by equatorial attack of the nucleophile on the lowest energy chair conformation, with the sulfinyl group playing no role in addition selectivity. Indeed, when racemic *tert*-butanesulfinamide was employed, no loss in selectivity was observed (compare **313a** to **313g**). Good yields and diastereoselectivities were obtained for all compounds **313a**−**g**. Addition of methylmagnesium bromide to ketimines (R_S)-**314** and (S_S)-**314**, derived from (*R*)-3-methylcyclohexanone, was also examined, and regardless of the sulfinyl stereochemistry, the reaction proceeded with the same level of stereoselectivity relative to the methyl substituent on the cyclohexane ring, as confirmed after conversion of (R_S, *R*)-**315** and (S_S, *R*)-**315** to the same amine hydrochloride product **316** (eq 25).



Collins and Caldwell developed a method for the addition of Grignard reagents to *N-tert*-butanesulfinyl ketimine **48a**, derived from *N*-Boc-piperidin-4-one (**317**) and racemic *tert*-butanesulfinamide (**1**; Scheme 86).[6] Their initial route required trapping the *N-tert*-butanesulfinyl ketimine **48a** through a Strecker reaction with trimethylsilylcyanide (TMSCN) before workup to avoid facile hydrate formation. Subsequent treatment of the α-aminonitrile **318** with 2 equiv of benzylmagnesium chloride afforded adduct **319a** in 49% yield.

To shorten the overall synthetic sequence, an alternative synthesis of the 4-benzyl-4-aminopiperidine class of compounds was developed via addition of Grignard reagents to an *in situ* generated cyclic *N-tert*-butanesulfinyl ketimine (Scheme 87). Formation of the *N-tert*-butanesulfinyl ketimine from **317** followed by addition of excess benzylmagnesium chloride provided **319a** in an improved 39% yield compared to the 28% overall yield for the two-step procedure (see Scheme 86). This protocol was extended to include a variety of electronically diverse substituted benzylic nucleophiles, providing **319b**−**k** in moderate yields (32−66%). Allylmagnesium bromide was also added to provide **319l** in 41% yield, but the authors noted that a range of other Grignard reagents were not effective nucleophiles for this transformation. The effect of ring size was also briefly examined, and the sulfinyl protected 4-benzyl-4-aminoazepane **319m** was generated in 54% after purification. Variation of the *N*-protecting group was also tested, and **319n** was synthesized in 32% yield. Concomitant deprotection of both the sulfinyl and Boc protecting groups was demonstrated, providing amines **321** in 60−94% yield.

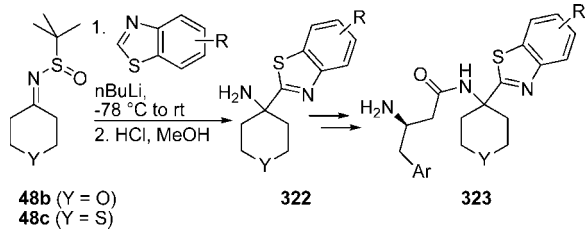
Scheme 87. *In Situ N-tert*-Butanesulfinyl Ketimine Condensation and Subsequent Grignard Addition



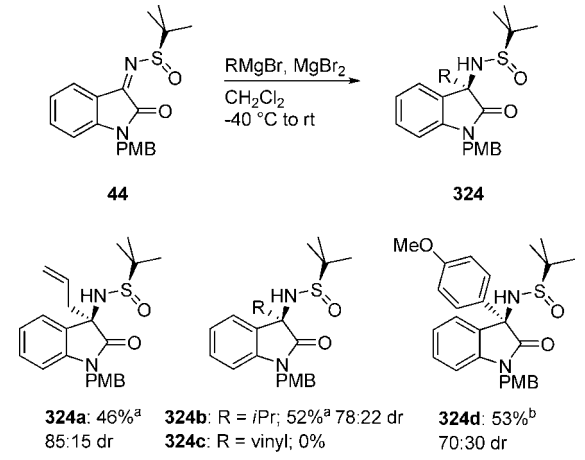
Nitta and co-workers at Toray Industries explored the addition of lithiated benzothiazole derivatives to racemic *N-tert*-butanesulfinyl cyclic ketimines **48b** and **48c**, which were utilized in the preparation of a novel class of dipeptidyl peptidase IV (DPP-IV) inhibitors for the treatment of type 2 diabetes (Scheme 88).[7]

Recently, Silvani and co-workers disclosed a method for the addition of Grignard reagents to the isatin-derived *N-tert*-butanesulfinyl imine **44**, providing a rapid route for the asymmetric synthesis of quaternary 3-aminooxindoles **324** (Scheme 89).[59] Optimization of the reaction conditions revealed that the highest yields and diastereoselectivities were obtained in the presence of the Lewis acid additive $MgBr_2$, using 5 equiv of the Grignard reagent. Addition of allyl, alkyl, or aryl Grignard reagents generated **324a**, **b**, and **d** in moderate diastereoselectivities (70:30 to 85:15). The major

Scheme 88. Addition of Benzothiazole Derivatives to *N-tert*-Butanesulfinyl Ketimines 48



Scheme 89. Additions of Grignard Reagents to *N-tert*-Butanesulfinyl Imine 44



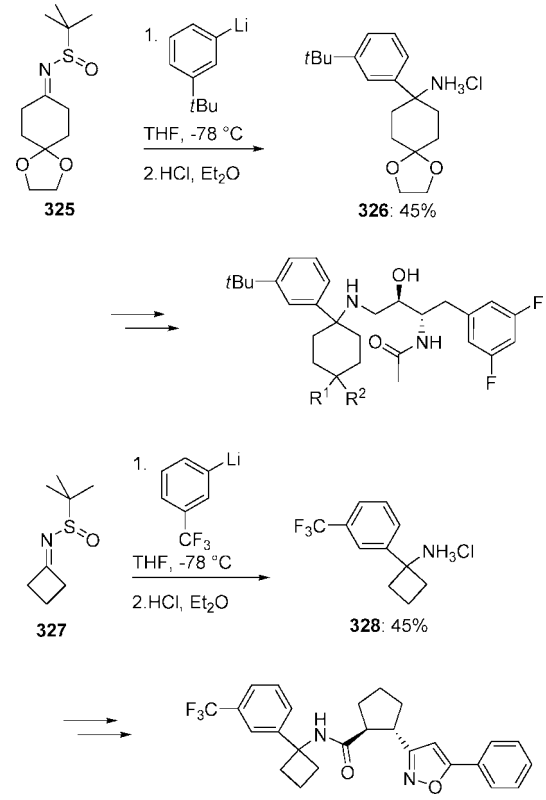
[a] Yield of the major diastereomer after purification. [b] Yield determined by mass balance of the reaction mixture.

diastereomers were isolated in 46−53% yield after column chromatography. Unfortunately, the addition of vinylmagnesium bromide to **44** did not provide any of the desired product **324c**.

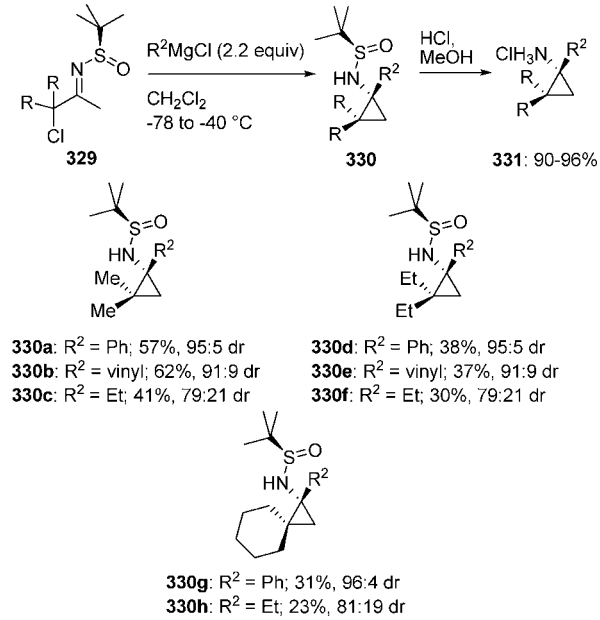
Probst, Hom, and co-workers and Elan Pharmaceuticals reported the addition of an aryl lithium reagent, prepared by lithium−halogen exchange from the corresponding aryl iodide, to *N-tert*-butanesulfinyl ketimine **325**, providing amine hydrochloride **326** after sulfinyl group cleavage (Scheme 90).[8] Further elaboration provided a series of compounds that were tested as β-secretase (BACE-1) inhibitors. Similarly, Shao and co-workers at Merck reported the addition of aryl lithium reagents to ketimine **327** to provide amines such as **328** after sulfinyl deprotection.[10] These amines were incorporated into novel isoxazole voltage gated sodium channel blockers.

A synthesis of cyclopropylamines via a proposed Favorskii-type rearrangement upon reaction of Grignard reagents with α-chloro *N-tert*-butanesulfinyl ketimines **329** was reported by De Kimpe and co-workers (Scheme 91).[68] Optimization of the reaction conditions revealed that addition of 2.2 equiv of the Grignard reagent to the ketimine at −78 °C followed by subsequent warming to −40 °C provided the highest yields and diastereoselectivities of this interesting class of compounds. Several Grignard reagents were tested, providing **330a**−**h** in moderate yields and with varying diastereoselectivities (79:21 to 96:4). While conversions were high for this reaction, yields dropped significantly upon isolation of the major diastereomer by column chromatography despite several attempts to improve the purification procedure. The absolute configuration was determined by X-ray structural analysis of **330b**. Removal of the sulfinyl group under acidic conditions was also demonstrated.

Scheme 90. Applications of Aryl Lithium Additions to Cyclic Ketimines



Scheme 91. Synthesis of *N-tert*-Butanesulfinyl Cyclopropylamines

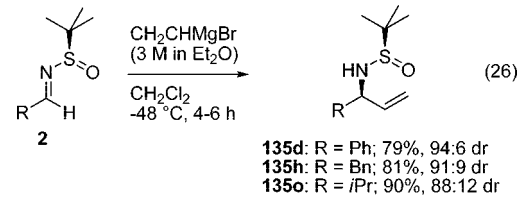


6. Synthesis of Allylic Amines

6.1. 1,2-Additions of Vinyl Reagents to Aldimines and Ketimines

The addition of vinyl Grignard reagents to *N-tert*-butanesulfinyl imines was first reported by Ellman and co-workers in their 1999 full paper (eq 26; for full substrate scope, see section 4.1.1).[92]

The utility of the addition of vinyl Grignard reagents to aldimines was demonstrated by Lee and Ellman in the develop-

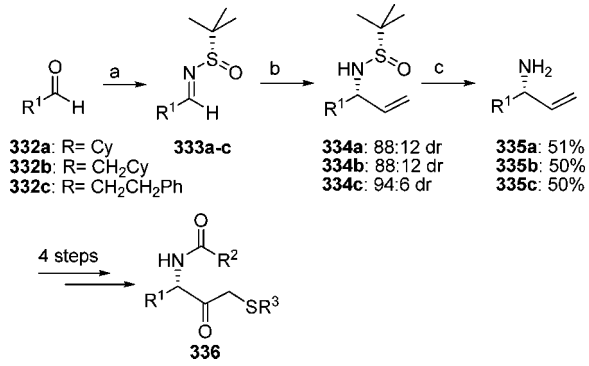


ment of a seven-step parallel solution-phase synthesis of cysteine protease inhibitors **336** (Scheme 92).[158] In this sequence, adaptations were made to eliminate the need for chromatographic purification of intermediates. Starting from diverse aldehydes **332**, *N*-*tert*-butanesulfinyl imines **333** were formed, utilizing $Ti(OEt)_4$ as a Lewis acid. Removal of titanium adducts was accomplished by incubating the mixture with a combination of sand and Na_2SO_4, followed by filtration and concentration. The crude imines were then dissolved in CH_2Cl_2 and treated with an excess of vinyl Grignard reagent in Et_2O, providing *N*-sulfinyl amines **334a**−**c** with 88:12 to 96:4 dr. After acidic methanolysis of the sulfinyl group, the allylic amine products were neutralized and scavenged on sulfonic acid resin, allowing purification by rinsing away undesired side products. Elution with ammonia and methanol provided the desired allylic amines **335** in 50−51% overall yields from *tert*-butanesulfinamide. A series of subsequent transformations allow access to diverse mercaptomethyl ketone cysteine protease inhibitors **336**.

Hashimoto, Nakata, and co-workers disclosed the highly diastereoselective addition of a vinylzinc reagent to heteroaryl imine **338** (Scheme 93).[159] Further elaboration of the product provided fragment **340**, which was used toward the total synthesis of siomycin A (**341**). A large excess (5 equiv) of the organozinc reagent was required to obtain high yields of the desired product. Attempted addition of the corresponding vinyllithium reagent was unsuccessful, resulting in decomposition of the imine. The stereochemistry of the newly formed stereocenter, confirmed by crystallographic analysis at a later stage in the synthesis, is consistent with addition to the imine via an open transition state.

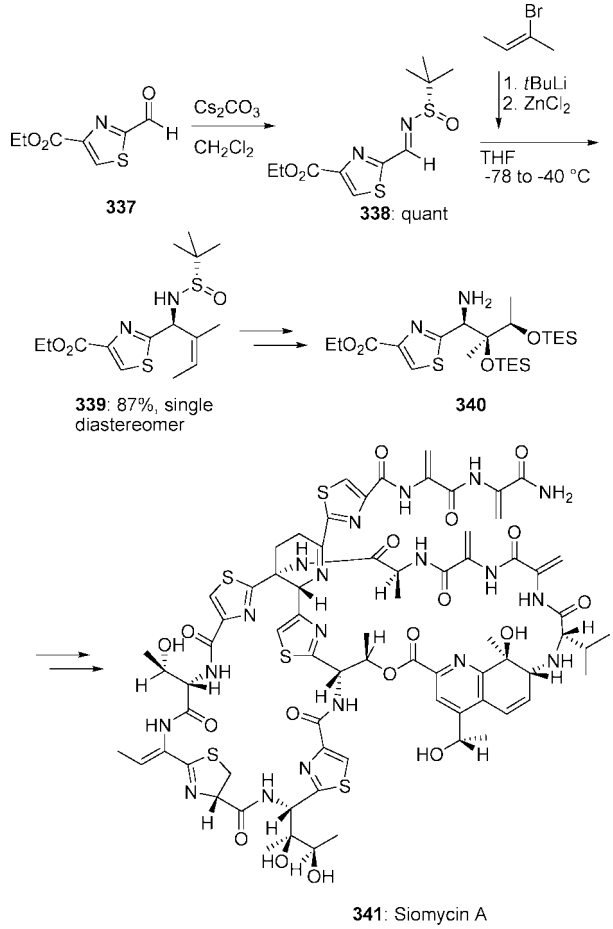
The ability of the *N*-*tert*-butanesulfinyl group to dominate the stereoselectivity of Grignard additions to chiral imines was demonstrated by Shuto and co-workers.[160] A series of eight α- and *β*-cyclopropyl imines **342** and **343** were prepared, representing the full range of stereochemical combinations with respect to both the sulfinyl stereocenter and the *cis*/*trans* cyclopropyl isomers. Treatment of these

Scheme 92. Parallel Solution-Phase Synthesis of Protease Inhibitors[a]

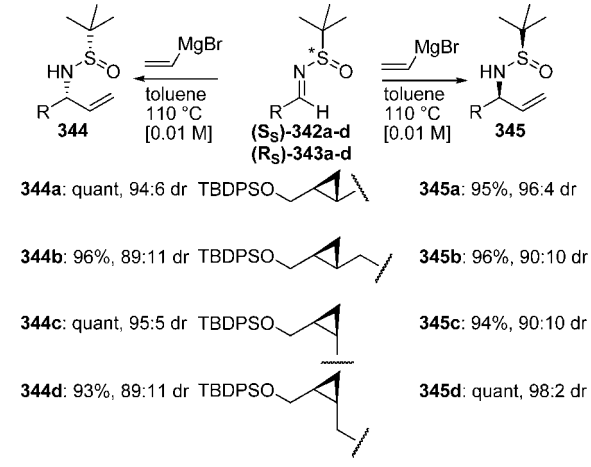


[a] (a) (i) (*S*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, CH_2Cl_2; (ii) 2:1 sand/$Na_2SO_4 \cdot 10H_2O$; (b) (i) vinyl Grignard/Et_2O, CH_2Cl_2; (ii) aqueous workup; (c) (i) 4 N HCl/dioxane, MeOH; (ii) 1 M KOH; (iii) sulfonic acid resin, CH_2Cl_2; (iv) saturated NH_3/MeOH.

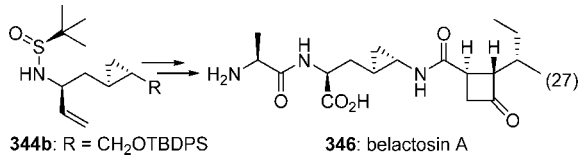
Scheme 93. Addition of a Vinylzinc Reagent to a Heteroaryl Imine



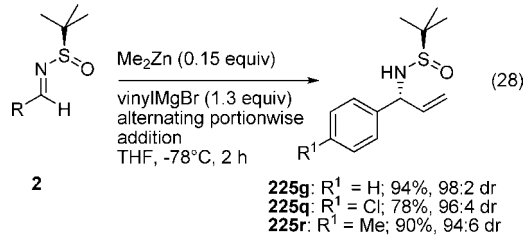
Scheme 94. Vinyl Grignard Additions to α- and *β*-Cyclopropyl *N*-*tert*-Butanesulfinyl Aldimines



imines with vinylmagnesium bromide provided the full range of *N*-sulfinyl amines **344a**−**d** and **345a**−**d** in excellent yields (Scheme 94). The major diastereomer in each case was formed with at least 89:11 diastereoselectivity, with the stereochemistry of the newly formed chiral center dictated by the sulfinyl stereochemistry, matching that predicted by a chelated transition state. Subsequent synthetic transformations allowed the synthesis of proteasome inhibitor belactosin A (**346**) from intermediate **344b** (eq 27). This chemistry was utilized for the synthesis of a series of systematically varied belactosin A stereo- and regioisomers, which were evaluated as proteosome inhibitors.[161]

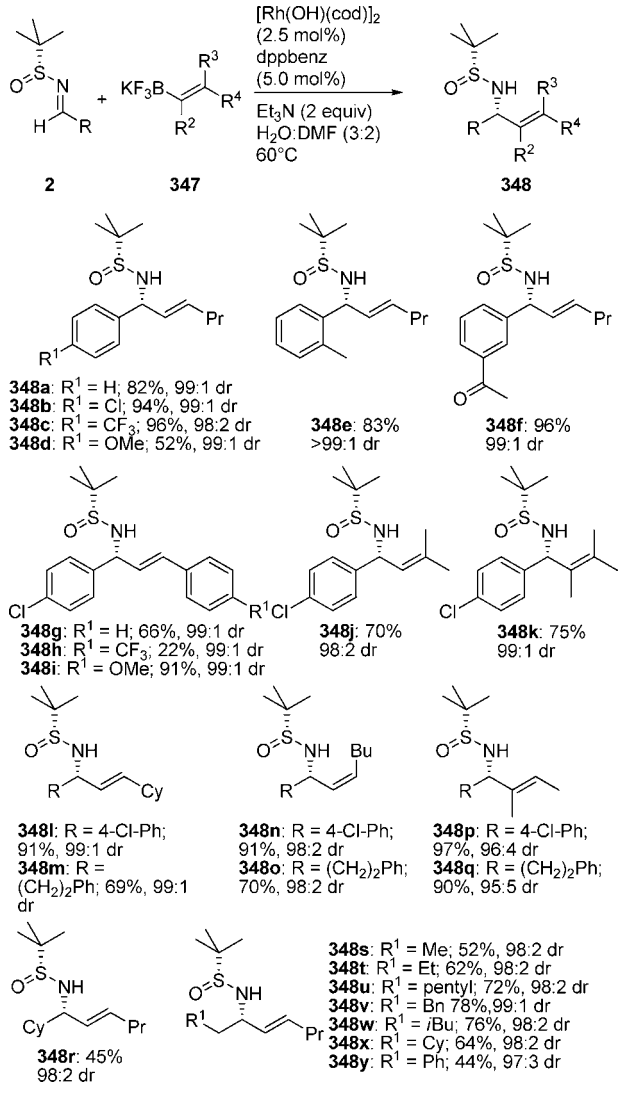


The asymmetric synthesis of allylic amines via addition of a vinyl triorganozincate reagent to aryl *N-tert*-butanesulfinyl aldimines **2** was recently demonstrated by Guijarro, Yus, and Almansa (eq 28).[131] A catalytic amount of dimethylzinc (0.15 equiv) is employed in the presence of an excess of Grignard reagent, providing **225g**, **q**, and **r** in high yields and with high diastereoselectivities (see section 4.1.3 for further details pertaining to this transformation).



The first example of a rhodium-catalyzed addition of an alkenylboron reagent to imines was recently reported by Ellman and Brak to provide a practical diastereoselective synthesis of allylic amines (Scheme 95).[162] For this transformation, the commercially available and air-stable precatalyst $[Rh(OH)(cod)]_2$, in conjunction with dppbenz as the ligand and Et_3N as an additive in a 3:2 ratio of H_2O/DMF at 60 °C, gave the highest yields and selectivities. It was also determined that, for this transformation, alkenyl trifluoroborates[163] were more effective coupling partners than the corresponding alkenylboronic acids. A range of different *N*-sulfinyl aromatic imines were tested with pentenyl trifluoroborate, demonstrating that the electronic nature of the imine had little effect on the transformation. Electron-donating, electron-withdrawing, and *ortho*-substituents were all tolerated, with the successful addition to the 3-acetylphenyl *N*-sulfinyl imine highlighting the functional group compatibility of this method (**348a**−**f**). The authors noted that the electronic effects on the trifluoroborate influenced the outcome of the reaction and lower yields were observed for the addition of highly electron-deficient trifluoroborates than for electron-rich trifluoroborates (**348h**−**i**). Several substitution patterns on the trifluoroborate species were also incorporated into the final products, including di-, tri-, and tetrasubstituted alkenyl inputs (**348j**−**q**). *cis*-Disubstituted alkenyl trifluoroborates could also be used without olefin isomerization at short reaction times (**348n**−**o**). Importantly, the scope of the reaction also included aliphatic *N*-sulfinyl imines. Unbranched, γ-, β-, and α-branched substrates could be utilized to obtain the allylic amines in good yields and diastereoselectivities (**348m**, **o**, **q**−**y**), including the *N*-sulfinyl imine derived from phenylacetaldehyde, which is a particularly challenging substrate due to imine tautomerization (**348y**). Overall, all additions proceeded in good yields and with very high diastereoselectivities (95:5 to 99:1 dr). Significantly, this reaction was demonstrated on a moderate scale (10 mmol) with only 1 mol% loading of the rhodium catalyst using standard Schlenk techniques, providing adduct **348v** in 75% yield and 99:1 dr.

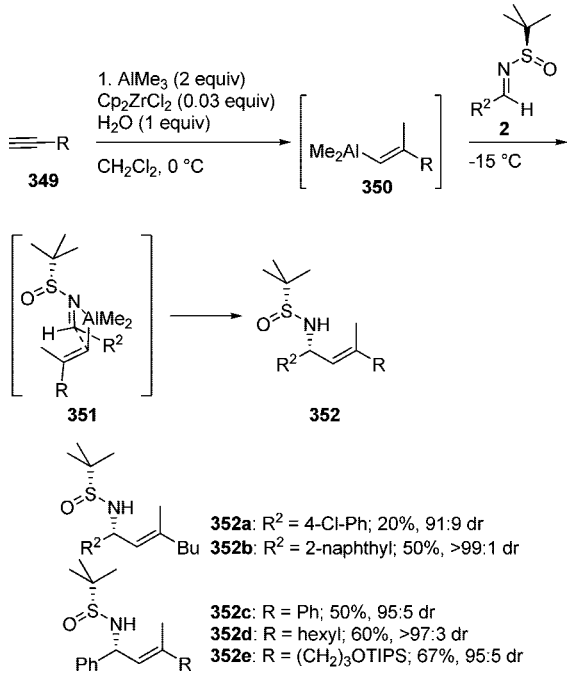
Scheme 95. Addition of Alkenyl Trifluoroborates to *N-tert*-Butanesulfinyl Imines



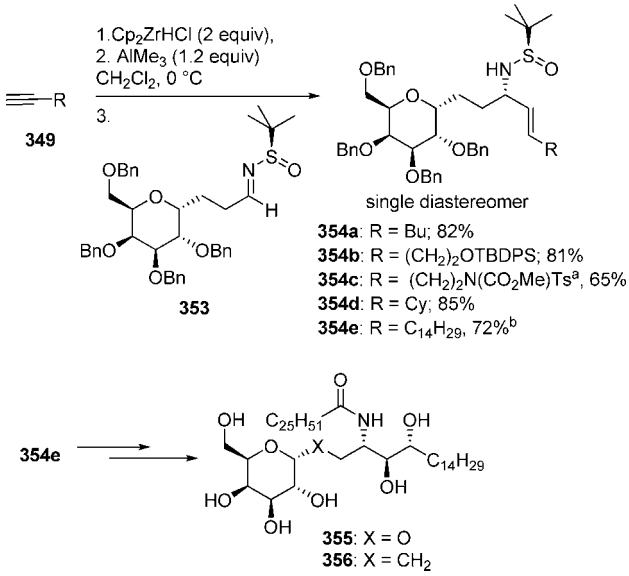
Wipf and co-workers reported the addition of the alkenylorganometallic intermediates **350**, prepared by carboalumination of alkynes **349** in the presence of water and catalytic Cp_2ZrCl_2, to *N-tert*-butanesulfinyl imines for the synthesis of allylic amines **352** (Scheme 96).[164] While the focus of this study was additions of **350** to *N-p*-toluenesulfinyl imines, a number of *N-tert*-butanesulfinyl imines **2** were investigated to probe the effects of the bulkier *tert*-butanesulfinyl group on the diastereoselectivity of the reaction. For analogous cases, comparable (**352c**) or superior (**352d**−**e**) facial selectivity was observed for the *N-tert*-butanesulfinyl adducts, but yields were lower (50−67% versus 75−85%). The absolute configuration of **352e** was established by chemical correlation experiments. The authors rationalized the stereochemical outcome by the four-membered chelate transition state model **351**, where the Lewis acidic aluminum coordinates to the imine nitrogen and addition of the nucleophile occurs opposite to the bulky *tert*-butyl group.

This methodology was later slightly modified and extended to additions to imine **353** (Scheme 97).[165] Additions of nucleophiles bearing alkyl, silyl ether, carbamate, and sulfonamide substituents were tolerated under the reaction conditions, providing adducts **354a**−**e** in good yields and with excellent diastereoselectivities. This method was applied to the synthesis of **356**, a more potent α-C-galactosylceramide analogue of the marine sponge glycolipid immuno-

Scheme 96. Asymmetric Synthesis of *N-tert*-Butanesulfinyl Allylic Amines via Organoaluminum Reagents



Scheme 97. Addition of Organoaluminum Reagents to *N-tert*-Butanesulfinyl Imine 353



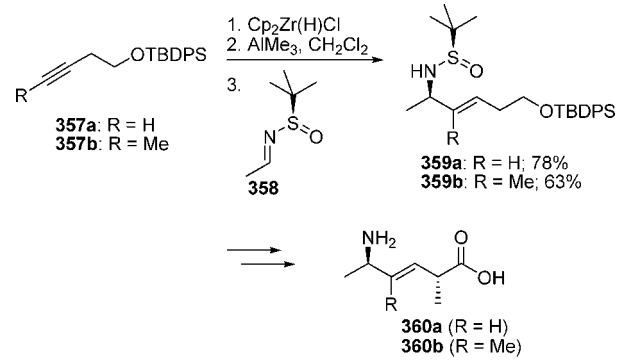
[a] A 93:7 diastereomeric ratio was obtained. [b] Isolated yield after sulfinyl deprotection.

stimulant **355**, which displays potent biological activity against various disease models.

This chemistry was also utilized in the synthesis of branched allylic amines **360** (Scheme 98).[166] Hydrozirconation of alkynes **357a** and **b** followed by transmetalation provided the corresponding alkenyl aluminum reagents, which underwent addition to enantiomerically pure *N-tert*-butanesulfinyl imines **358** to provide adducts **359**, which were isolated in diastereomerically pure form by chromatography. A series of subsequent reactions provided the desired products **360** in enantiomerically pure form, which were evaluated as β-turn mimetics for β-sheet nucleation.

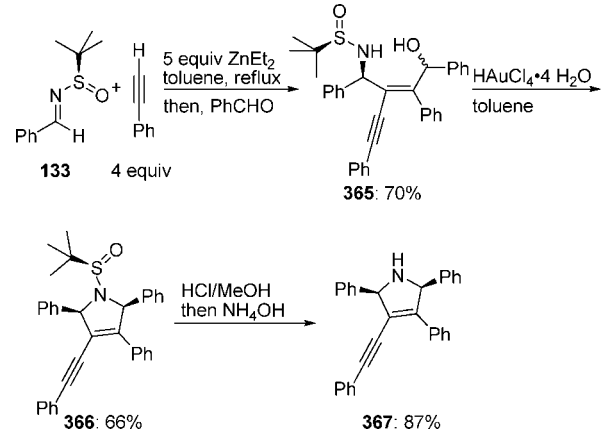
The synthesis of 1,3-enynamines was accomplished via the nucleophilic addition of an alkynylzinc species to *N-tert*-

Scheme 98. Synthesis of β-Turn Mimetics[a]



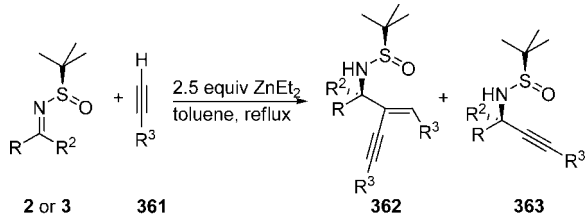
[a] The enantiomer of **360b** was prepared analogously from (*S*)-**358**.

Scheme 99. Synthesis of Dihydropyrrole 367



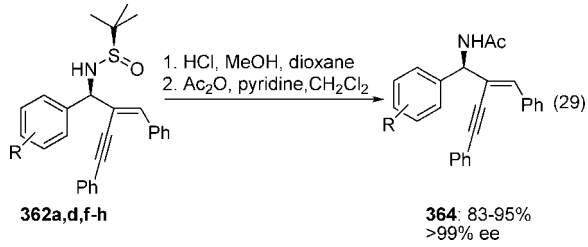
butanesulfinyl aldimines, as reported by Xu and co-workers.[167] Extensive screening of reaction conditions revealed that refluxing a 1:2.5:5 mixture of *N-tert*-butanesulfinyl imine **2**, diethylzinc, and acetylene **361** in toluene provided the best selectivity and yield of **362** (Table 10). The scope of the reaction was probed by surveying a number of different *N-tert*-butanesulfinyl aldimines **2**. Electronically diverse substituents on the aryl moiety could be incorporated into the final products in high yields and with excellent diastereoselectivites (entries 1−8). However, *ortho* substitution on the aryl ring resulted in lower diastereoselectivites (entries 9−11) except for the *N-tert*-butanesulfinyl 2-fluorobenzaldimine (entry 12). An alkyl *N-tert*-butanesulfinyl aldimine was also evaluated, and it provided the desired 1,3-enynamine **362m** in high yield (83%) and diastereoselectivity (>99:1, entry 13). The yields and diastereoselectivities were also excellent when a functionalized aryl alkyne and an aliphatic alkyne were used (entries 14 and 15). However, when an *N-tert*-butanesulfinyl ketimine **3** was examined, the *N-tert*-butanesulfinyl propargylamine product **363p** was obtained in low yield and with moderate diastereoselectivity (entry 16). The absolute stereochemistry for compounds **362** was determined by X-ray structural analysis of a derivative of **362a**. Sulfinyl group deprotection and amine acylation without racemization were also demonstrated for select adducts **362a**, **d**, and **f**−**h** (eq 29). Interestingly, when the reaction was quenched with benzaldehdye, compound **365** could be obtained in 70% yield (Scheme 99). Cyclization of **365** followed by removal of the sulfinyl group provided the highly substituted chiral dihydropyrrole **367**.

Table 10. Synthesis of Enynes



2 or 3 361 (5 equiv) 362 363

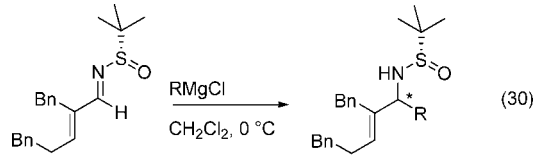
entry	R	R^2	R^3	362/363	isolated product	yield (%)	dr
1	Ph	H	Ph	50:1	**362a**	93	>99:1
2	4-Me-Ph	H	Ph	28:1	**362b**	92	>99:1
3	4-MeO-Ph	H	Ph	34:1	**362c**	91	>99:1
4	4-Et_2N-Ph	H	Ph	16:1	**362d**	60	>99:1
5	3-Cl-Ph	H	Ph	42:1	**362e**	91	97:3
6	4-Cl-Ph	H	Ph	24:1	**362f**	88	>99:1
7	3-F-Ph	H	Ph	40:1	**362g**	86	>99:1
8	naphthyl	H	Ph	20:1	**362h**	85	>99:1
9	2-MeO-Ph	H	Ph	28:1	**362i**	86	95:5
10	2-Cl-Ph	H	Ph	28:1	**362j**	88	95:5
11	2-Br-Ph	H	Ph	20:1	**362k**	78	90:10
12	2-F-Ph	H	Ph	40:1	**362l**	90	>99:1
13	Bu	H	Ph	40:1	**362m**	83	>99:1
14	Ph	H	4-Cl-Ph	99:1	**362n**	95	>99:1
15	Ph	H	pentyl	25:1	**362o**	81	>99:1
16	Ph	Me	Ph	1:99	**363p**	51	87:13



362a,d,f-h **364**: 83-95% >99% ee

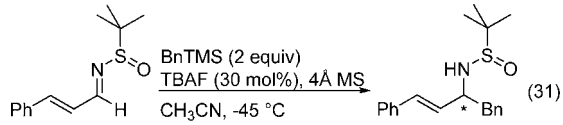
6.2. 1,2-Addition to α,β-Unsaturated Aldimines and Ketimines

Qin and co-workers reported the addition of several Grignard reagents to α,β-unsaturated imine **91c**, which was prepared via self-condensation of *N-tert*-butanesulfinyl phenylacetaldimine (see section 3.2.3).[88] High diastereoselectivity was obtained, but the isolated yield varied dramatically depending on the Grignard reagent (eq 30). Unfortunately, the absolute configurations of the product amines **368a**−**d** were not determined.



91c

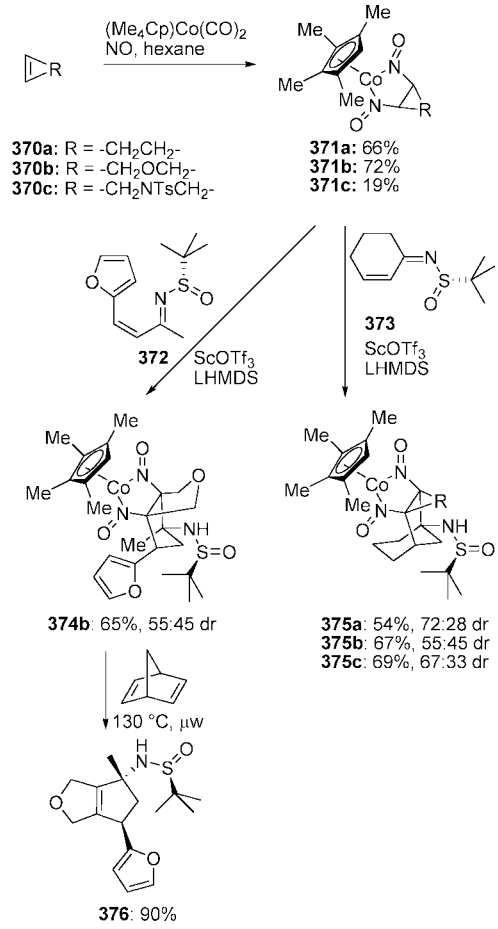
368a: R = Tol; 79% (93:7 dr)
368b: R = Me; 63% (99:1 dr)
368c: R = *i*Pr; 56% (99:1 dr)
368d: R = *t*Bu; 21% (99:1 dr)



369 **229f**: 68% 80:20 dr

The fluoride promoted reaction of benzyltrimethylsilane and *N-tert*-butanesulfinyl imine **369** to provide allylic amine **229f** was reported by Hou and co-workers (eq 31; for additions to other imines, see section 4.1.3).[133]

Scheme 100. Cobalt-Mediated Formal [3 + 2] Annulation of Alkenes with α,β-Unsaturated Imines

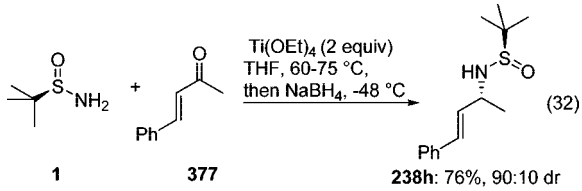


Bergman, Toste, and Schomaker reported that cobalt dinitrosyl complexes **371a**−**c**, prepared from the correspond-

ing 4- and 5-membered cyclic alkenes **370**, could be deprotonated with LHMDS and reacted with α,β-unsaturated *N-tert*-butanesulfinyl ketimines **372** and **373** in the presence of $Sc(OTf)_3$, providing adducts **374b** and **375a−c**, respectively (Scheme 100).[168] Yields for this reaction ranged from 54 to 69% with modest diastereoselectivities (55:45 to 72:28). Diastereomerically pure **374b** was obtained after isolation and treated with norbornadiene under microwave conditions to yield tertiary amine product **376** in 90% yield, constituting a formal [3 + 2] annulation reaction between alkene **370b** and imine **372**.

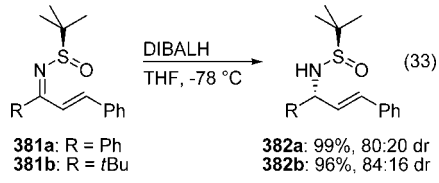
6.3. Reduction of α,β-Unsaturated Ketimines

Ellman and co-workers reported the one-pot stereoselective reductive amination of an α,β-unsaturated ketone in 1999 (eq 32; for reaction with other ketones, see section 4.2.1).[141] Significantly, only 1,2 reduction (and not 1,4 reduction) was observed.

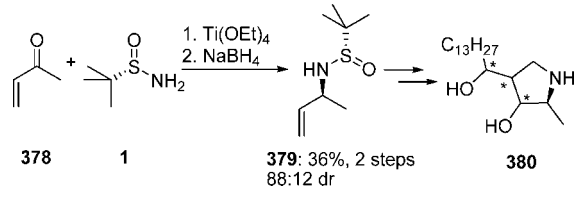


The reductive amination of the *N-tert*-butanesulfinyl ketimine derived from methyl vinyl ketone **378** was demonstrated by McDonald, Liotta, and co-workers in their synthesis of 1-deoxysphingolipid derivatives with conformationally restricted pyrrolidinediol head groups (**380**, Scheme 101).[169] Formation of the *N-tert*-butanesulfinyl ketimine and subsequent $NaBH_4$ reduction provided **379** in 36% yield over the two steps and an 88:12 diastereomeric ratio. Further elaboration provided several stereoisomers of **380**. The same synthetic route was also followed with **(*R*)-1** to access the enantiomers of these pyrrolidinediol derivatives.

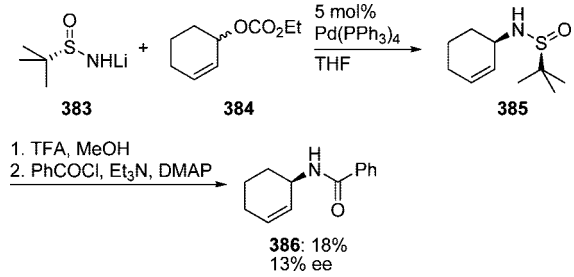
In the context of their work on the reduction of trifluoromethyl α,β-unsaturated *N-tert*-butanesulfinyl ketimines (see section 15.1.2), Liu and Liu reported the DIBALH-mediated reduction of α,β-unsaturated imines **381** to provide allylic amines **382** in high yield, but with moderate diastereoselectivity (eq 33).[77]



Scheme 101. Synthesis of Cyclic 1-Deoxysphingolipid Derivatives 380



Scheme 102. Palladium-Catalyzed Allylation Reaction of Allylic Carbonate 384 and Lithiated Sulfinamide 383



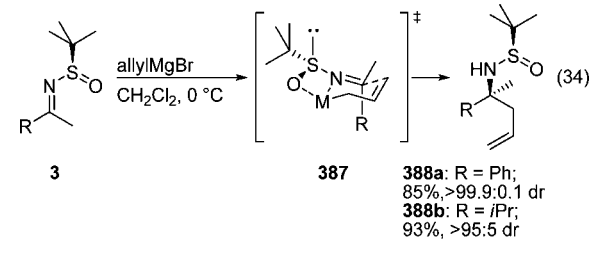
6.4. Palladium-Catalyzed Allylation of *tert*-Butanesulfinamide Anion

An alternative approach for the preparation of chiral allylic *N-tert*-butanesulfinyl amines from the palladium-catalyzed reaction of allylic carbonate **384** with lithiated *tert*-butanesulfinamide **383** was developed by Pyne and Dong (Scheme 102).[170] Treatment of **384** with $Pd(PPh_3)_4$ and subsequent nucleophilic addition of deprotonated (*S*)-*tert*-butanesulfinamide to the resulting (η^3-allyl)palladium(II) cationic species generated the unstable allylic amine **385**, which was further converted to benzamide **386**. Unfortunately, both the overall yield and enantiomeric purity of **386** were low for this synthetic sequence.

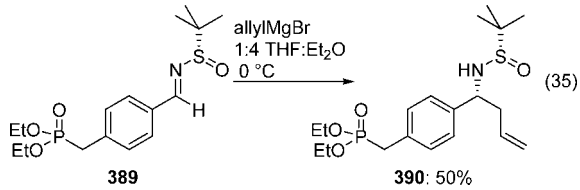
7. Synthesis of Homoallylic Amines

7.1. 1,2-Additions of Allyl Reagents to Aldimines and Ketimines

The first example of an addition of allylmagnesium bromide to an *N-tert*-butanesulfinyl imine was reported by Ellman and co-workers in their seminal report on additions of Grignard and organolithium reagents to *N-tert*-butanesulfinyl aldimines and ketimines.[92] Ketimines **3** were evaluated as substrates for the allylation reaction (eq 34). The noncoordinating solvent CH_2Cl_2, which had been optimal for the additions of Grignard reagents to *N-tert*-butanesulfinyl aldimines (see section 4.1.1), was employed, and **388a** and **b** were produced in excellent yields and with high diastereoselectivities (see section 5.1 for a more detailed discussion on the synthesis of tertiary carbinamines). The high level of diastereocontrol exhibited in this reaction was consistent with the chelated transition state **387**, previously proposed by Hua and co-workers for the allylations of *N-p*-toluenesulfinyl imines,[171] where addition to the imine occurs from the *si*-face and both the sulfinyl oxygen and imine nitrogen are coordinated to the metal. The coordination of the nitrogen to the metal could serve to activate the imine, which may explain the higher yields and diastereoselectivities observed for allylations relative to the additions of other Grignard reagents.



In their synthesis of ureapeptoid macrocycles, Burke and Wang reported the addition of allylmagnesium bromide to *N-tert*-butanesulfinyl aldimine **389** (eq 35).[172] This reaction was conducted in a 1:4 mixture of THF and Et_2O, providing **390** in a moderate 50% yield.

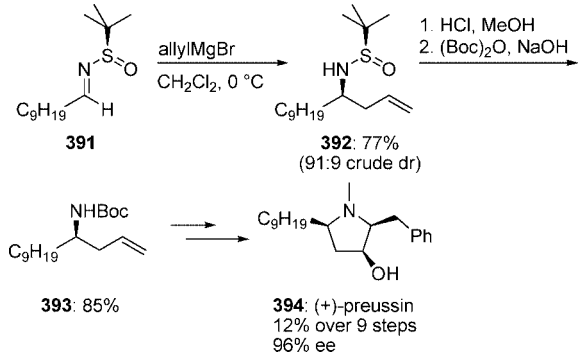


Wolfe and Bertrand utilized an allylation of *N-tert*-butanesulfinyl aldimine **391** in their asymmetric synthesis of (+)-preussin, a natural product that displays interesting biological properties, including antifungal, antiviral, and anticancer activity (Scheme 103).[173] A dropwise addition of allylmagnesium bromide to **391** in CH_2Cl_2 at 0 °C provided homoallylic amine **392** as a 91:9 mixture of diastereomers. Purification of **392** by silica gel chromatography provided diastereomerically pure material in a 77% isolated yield. Cleavage of the sulfinyl group and protecting group manipulation generated **393**, which was converted to (+)-preussin (**394**) over a number of subsequent synthetic transformations. The total synthesis of (+)-preussin was completed in nine steps and a 12% overall yield from commercially available decanal.

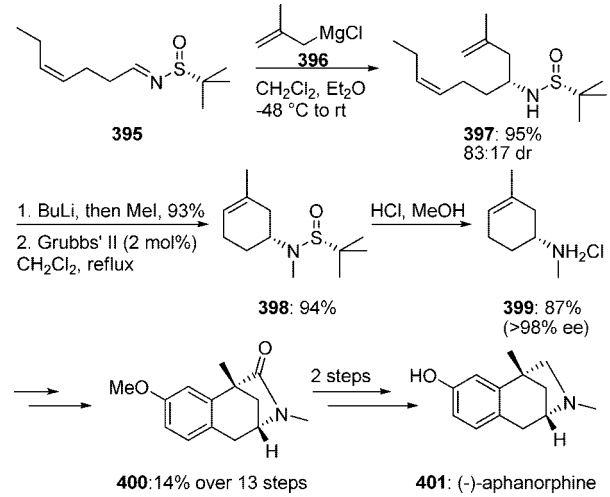
A formal asymmetric synthesis of (−)-aphanorphine (**401**), an alkaloid natural product, was completed by Grainger and Welsh (Scheme 104).[174] The introduction of the amine-substituted C4 stereocenter was achieved by addition of 2-methylallylmagnesium chloride (**396**) to *N-tert*-butanesulfinyl aldimine **395**, providing homoallylic *N-tert*-butanesulfinyl amine **397** in excellent yield (95%) as an 83:17 inseparable mixture of diastereomers. The stereochemical outcome of this addition was confirmed upon synthesis of the known intermediate **400** and was consistent with a chelated transition state (see **387**, eq 34). *N*-Methylation, ring-closing metathesis with Grubbs' second-generation catalyst, and removal of the sulfinyl group generated **399**, which was isolated in high yield as a single enantiomer after recrystallization. Further transformations provided **400**, completing the formal synthesis of (−)-aphanorphine (**401**) in 14% yield over 13 steps.

In their syntheses of the *Lycopodium* alkaloids (−)-cernuine (**404**) and (+)-cermizine D (**405**), Takayama and co-workers explored the addition of allylmagnesium bromide to *N-tert*-butanesulfinyl imine **402** (Scheme 105).[175] While the allylation and removal of the sulfinyl group to produce

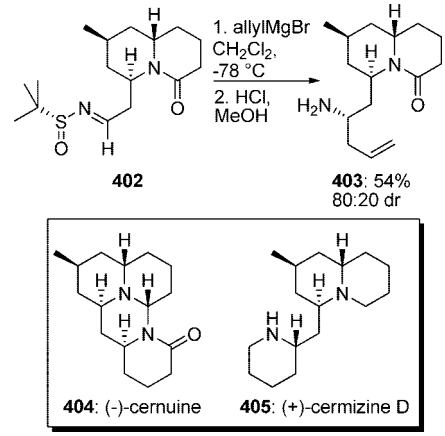
Scheme 103. Synthesis of (+)-Preussin



Scheme 104. Formal Synthesis of (−)-Aphanorphine

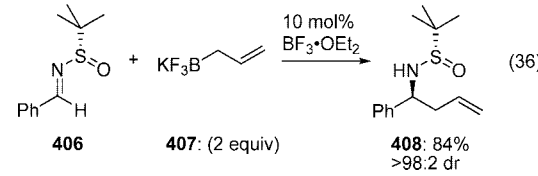


Scheme 105. Addition of Allylmagnesium Bromide to *N-tert*-Butanesulfinyl Imine 402



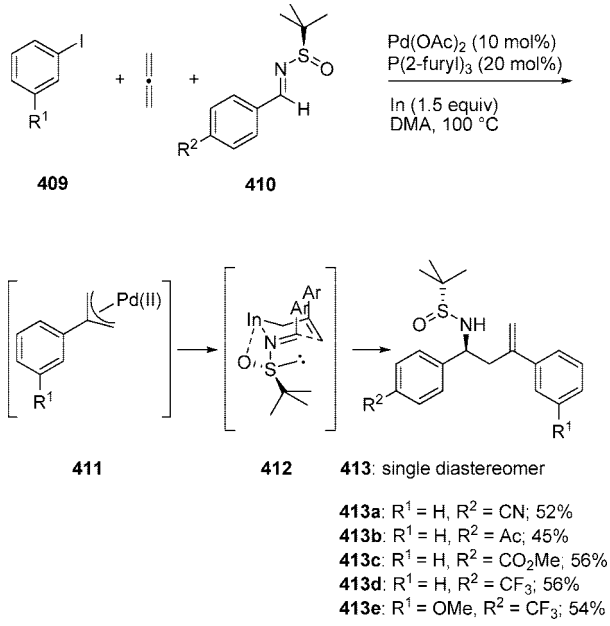
homoallylic amine **403** proceeded in an acceptable 54% overall yield for the two-step procedure, the diastereoselectivity was moderate (80:20). For this reason, an alternative sequence was employed to prepare these alkaloids.

Batey and Li demonstrated the addition of an allyltrifluoroborate **407** to the *N-tert*-butanesulfinyl imine **406** using a catalytic amount of $BF_3 \cdot OEt_2$ (eq 36).[176] Under these reaction conditions, the desired product **408** was obtained in 84% yield as a single diastereomer, as observed by ^1H NMR. The sulfinyl group could also be removed under acidic conditions to generate the homoallylic amine in high yield and without racemization.

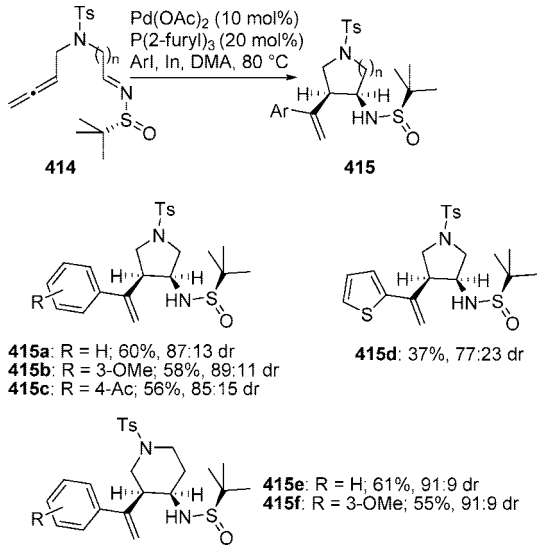


The addition of allyl indium reagents to *N-tert*-butanesulfinyl imines **410** was first described by Grigg and co-workers (Scheme 106).[177] For this methodology, the allyl indium species was prepared by transmetalation of a π-allyl palladium(II) complex **411** generated from 10 mol % $Pd(OAc)_2$, 20 mol % of the tris(2-furyl)phosphine ligand, aryl iodide **409**, and allene. The three-component cascade reaction provided sulfinyl-protected homoallylic amines

Scheme 106. Asymmetric Cascade Allylation of *N-tert*-Butanesulfinyl Imines



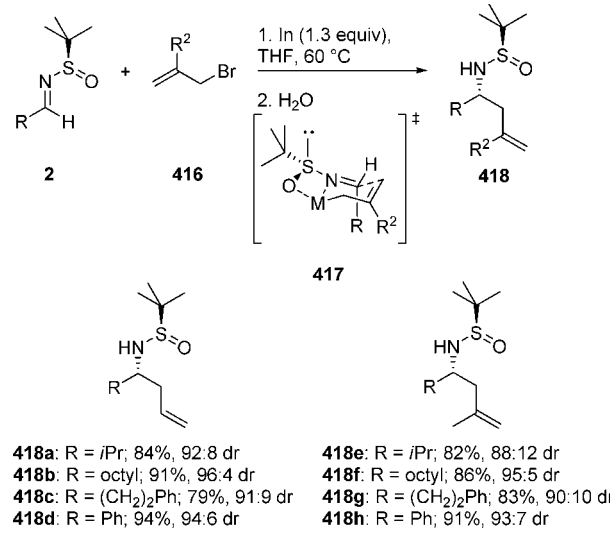
Scheme 107. Intramolecular Asymmetric Cascade Allylation of *N-tert*-Butanesulfinyl Imines



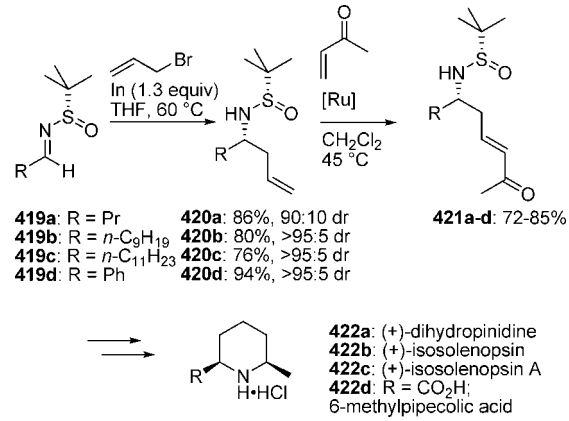
413a−**e** in 45−56% yield as single diastereomers. The stereochemical outcome was determined by X-ray structural analysis of **413c** and was consistent with the chelation controlled transition state **412**.

Grigg and co-workers extended this bimetallic cascade methodology to the intramolecular allylation of *N-tert*-butanesulfinyl imines **414** to produce highly functionalized amino-substituted pyrrolidine and piperidine products (Scheme 107).[178] Treatment of imine **414** with iodobenzene using the previously optimized catalytic system (*vide supra*) provided **415a** in 60% yield as an 87:13 mixture of diastereomers. Crystal structures of both the major and minor isomers confirmed the absolute stereochemistry of the two newly formed stereocenters, consistent with the previously proposed chelated transition state. Several aryl iodides were investigated, providing products **415a**−**f** in moderate yields and with diastereomeric ratios ranging from 77:23 to 91:9. The lowest diastereoselectivity was observed with 2-iodothiophene, potentially due to competitive coordination of the thiophene sulfur to the indium.

Scheme 108. Indium-Mediated Addition of Allyl Bromides to *N-tert*-Butanesulfinyl Imines



Scheme 109. Synthesis of 2,6-*cis*-Disubstituted Piperidines

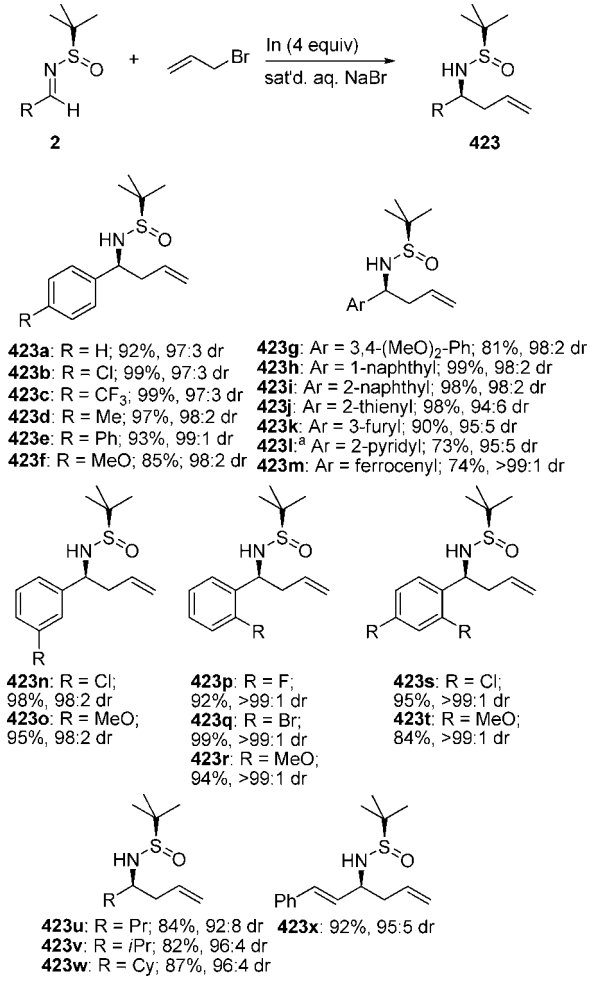


Foubelo and Yus developed an asymmetric synthesis of homoallylic amines by the indium-mediated addition of allyl bromides to *N-tert*-butanesulfinyl aldimines (Scheme 108).[179] The optimal reaction conditions were achieved with 1.3 equiv of indium in THF at elevated temperature (60 °C). The reaction was found to be general, allowing addition of allyl bromides **416** to a variety of *N-tert*-butanesulfinyl alkyl or aryl imines **2** to provide **418a**−**h** in high yields and diastereoselectivities. The absolute configuration of **418d** was determined by chemical correlation. The stereochemical outcome was consistent with the chelated transition state **417**.

Foubelo, Yus, and co-workers applied this methodology to the synthesis of four naturally occurring 2,6-*cis*-disubstituted piperidines **422a**−**d** (Scheme 109).[180] The allylations of (*S*)-*N-tert*-butanesulfinyl imines **419a**−**d** under the previously optimized reaction conditions provided homoallylic amines **420a**−**d** in 76−94% yields and with high diastereomeric ratios. The homoallyic amine products **420** were further functionalized by olefin cross-metathesis using the Hoveyda−Blechert ruthenium catalyst [Ru] to yield **421a**−**d**. Additional synthetic transformations then provided (+)-dihydropinidine, (+)-isosolenopsin, (+)-isosolenopsin A, and (2*R*,6*R*)-6-methylpipecolic acid.

The allylation of *N-tert*-butanesulfinyl imines in aqueous media was first reported by Lin, Xu, and co-workers (Scheme

Scheme 110. Indium-Mediated Allylation of *N-tert*-Butanesulfinyl Imines in Aqueous Media

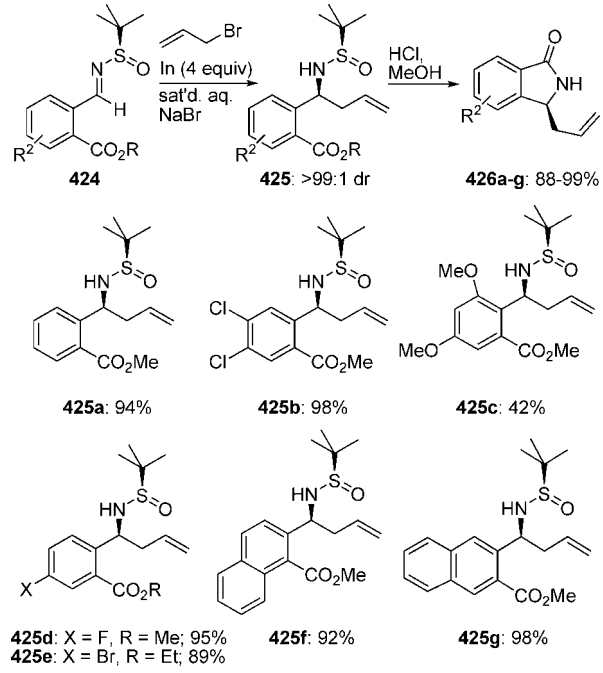


[a] Absolute stereochemistry not rigorously determined.

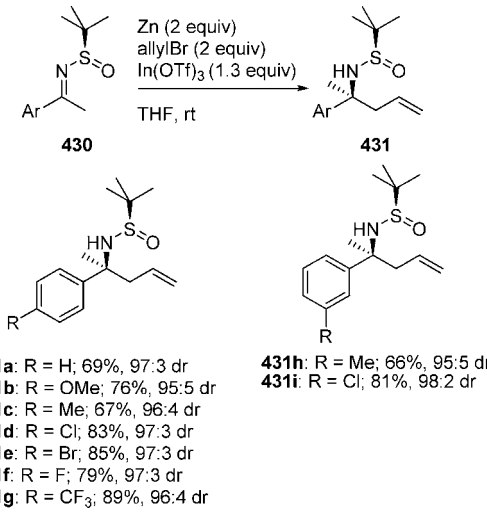
110).[181] When the indium-mediated reaction was conducted with water as the solvent, a low yield of the desired homoallylic amine product was observed. Yields were drastically improved when the solvent was changed to an aqueous saturated salt solution, with saturated aqueous NaBr being optimal. Notably, the use of 4 equiv of In was found to be necessary to achieve the highest yield. The scope of the reaction was explored employing these optimized reaction conditions, and additions to a wide variety of diverse aryl, heteroaryl, alkenyl, and alkyl substituted *N-tert*-butanesulfinyl aldimines **2** were investigated. In all cases, the desired *N-tert*-butanesulfinyl homoallylic amines **423a−x** were obtained in high yields (73−99%) and with diastereoselectivities ranging from 92:8 to >99:1. While electronic and steric factors did not seem to affect the yields of the products, the highest diastereoselectivities were observed for *ortho*-substituted aryl or bulky alkyl substituents. An attempt to extend this methodology to the allylation of the *N-tert*-butanesulfinyl ketimine of 4-bromoacetophenone resulted in a high diastereoselectivity (94:6) but a low yield (30%). The configurations of the homoallylic amine products were assigned as *S* based on the comparison of the minor diastereomers to the products synthesized by the zinc-mediated allylation of *N-tert*-butanesulfinyl imines in wet HMPA (*vide infra*).

Allylation of a number of *N-tert*-butanesulfinyl imine substrates **424** that were prepared from 2-formylbenzoates

Scheme 111. Asymmetric Synthesis of Allyl-Substituted Isoindolinones



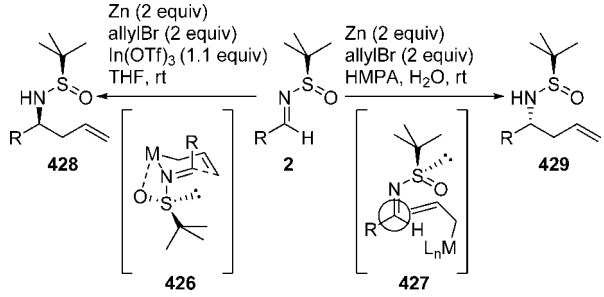
Scheme 112. Diastereoselective Allylations of *N-tert*-Butanesulfinyl Ketimines



was also achieved (Scheme 111).[181] As previously noted for imines bearing *ortho*-substituted aryl substituents, diastereoselectivities in all examples were extremely high (>99:1). The *N-tert*-butanesulfinyl protected homoallylic amines **425a−g** were mostly generated in high yields (89−98%), with **425c**, bearing two *ortho* substituents, being the notable exception (42%). The absolute configuration of **425e** was confirmed by X-ray structural analysis. Cleavage of the sulfinyl group under acidic conditions and subsequent lactamization provided a series of enantiomerically pure allyl-substituted isoindolinones **426a−g** in 89−99% yield.

The synthesis of both stereoisomers of chiral homoallylic amines from a common *N-tert*-butanesulfinyl imine precursor was achieved by Lin, Xu, and Sun (Table 11).[182,183] Allylzinc bromide, which was prepared *in situ*, was chosen as the allylation reagent. Optimization of the reaction conditions revealed that the addition of the Lewis acid $In(OTf)_3$ resulted in an increase in diastereoselectivity in THF, and the stereochemical outcome for product **428**, established by

Table 11. Diastereoselective Allylation of *N-tert*-Butanesulfinyl Aldimines

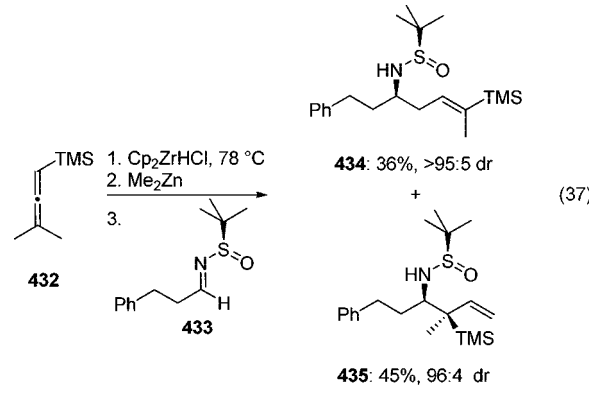


		THF conditions			HMPA, H_2O conditions		
entry	R	product	yield (%)	dr	product	yield (%)	dr
1	Ph	**428a**	93	98:2	**429a**	97	99:1
2	4-F-Ph	**428b**	98	98:2	**429b**	97	99:1
3	4-Cl-Ph	**428c**	98	98:2	**429c**	96	97:3
4	4-Br-Ph	**428d**	93	97:3	**429d**	99	98:2
5	4-Me-Ph	**428e**	95	96:4	**429e**	88	97:3
6	4-MeO-Ph	**428f**	91	95:5	**429f**	81	98:2
7	2-Cl-Ph	**428g**	91	97:3	**429g**	73	98:2
8	2-Me-Ph	**428h**	95	98:2	**429h**	89	97:3
9	3-Br-Ph	**428i**	98	98:2	**429i**	99	98:2
10	2-naphthyl	**428j**	81	95:5	**429j**	86	97:3
11	cyclopropyl	**428k**	98	86:14	**429k**	97	96:4
12	Cy	**428l**	99	97:3	**429l**	94	97:3
13	Et	**428m**	93	88:12	**429m**	92	95:5
14	*i*Pr	**428n**	96	94:6	**429n**	94	98:2
15	$(CH_2)_2Ph$	**428o**	92	90:10	**429o**	93	96:4
16	cinnamyl	**428p**	83	91:9	**429p**	87	94:6

chemical correlation, was consistent with the chelated transition state **426**. Notably, the opposite diastereomer **429** was obtained upon use of wet HMPA as solvent in the absence of additives, presumably due to the disruption of the chelation between zinc and the *N-tert*-butanesulfinyl imine as shown in the open transition state **427**. With reaction conditions to obtain either **428** or **429** identified, the scope of the reaction was evaluated. An array of different *N-tert*-butanesulfinyl aldimines **2** was surveyed, including aryl, vinyl, and various alkyl derivatives, and the desired products were obtained in high yields with excellent diastereoselectivities.

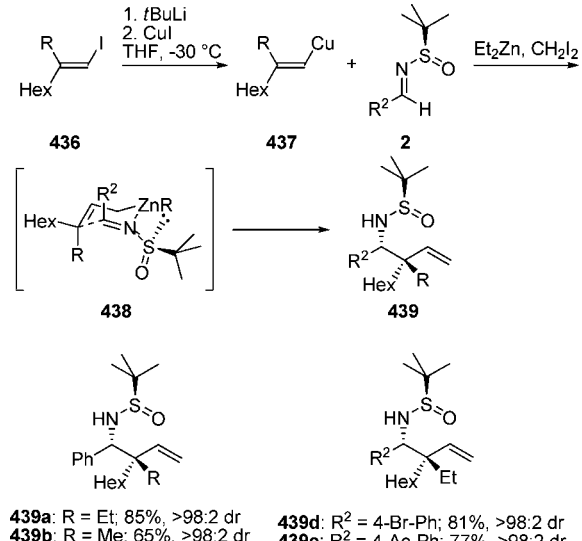
The allylation of *N-tert*-butanesulfinyl ketimines with allylzinc bromide in the presence of $In(OTf)_3$ as a Lewis acid was also demonstrated (Scheme 112). Again, yields and diastereoselectivities were high for a variety of acetophenone-derived imine precursors **430** (66−85% yield, ≥95:5 dr). However, when the optimized HMPA conditions were employed, no reaction was observed.

Wipf and Pierce demonstrated a method to access silyl-substituted homoallylic amines via hydrozirconation of allenylsilane **432**, transmetalation with Me_2Zn, and subsequent addition to *N-tert*-butanesulfinyl aldimine **433** (eq 37).[184] However, the regioselectivity of this transformation was low, producing **434** and **435** in a 1:1.3 ratio, albeit with high diastereoselectivities for each product. The authors attempted to modify the reaction conditions to improve the regioselectivity but were not successful. The mixture of **434** and **435** was separated by column chromatography, and the structures were assigned by NOE experiments.

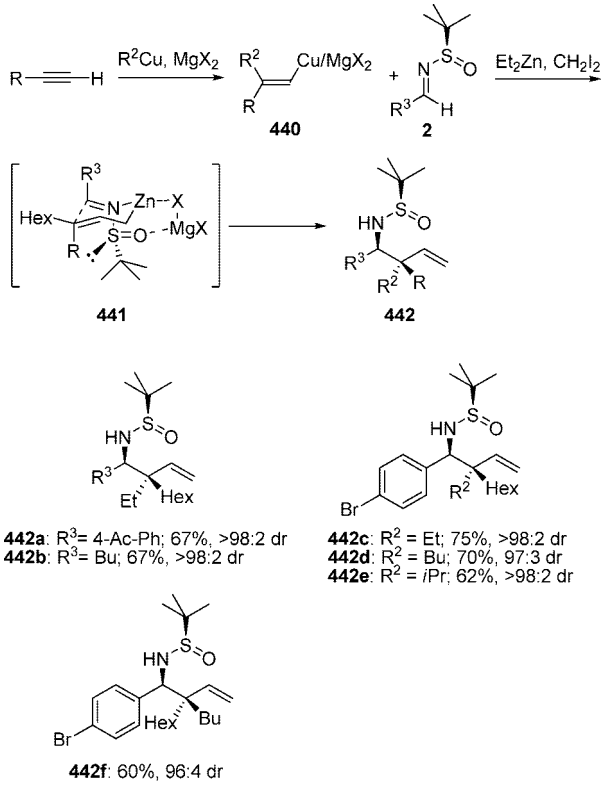


Marek, Knochel, and co-workers devised a novel synthesis of *N-tert*-butanesulfinyl protected homoallylic amines bearing a quaternary carbon stereocenter (Scheme 113).[185] Treatment of disubstituted vinyl iodides **436** with *t*BuLi at low temperature followed by addition of CuI provided intermediates **437**, which underwent homologation reactions with a

Scheme 113. Preparation of Homoallylic Amines 439 from Vinyl Iodides 436



Scheme 114. Carbocupration of Alkynes and Additions to *N-tert*-Butanesulfinyl Imines

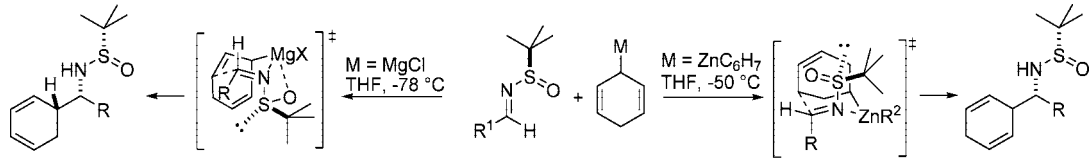


zinc carbenoid, prepared in situ from diethylzinc and diiodomethane, before addition to *N-tert*-butanesulfinyl imines **2**. This sequence provided homoallylic amines **439a**−**f** in good yields (65−87%) and diastereoselectivities (≥95:5). Primary and secondary alkyl substituents on the vinyl iodide and aromatic or alkenyl *N-tert*-butanesulfinyl imines were all tolerated. However, the authors noted that additions to aliphatic *N-tert*-butanesulfinyl imines gave poor diastereomeric ratios (70:30). The stereochemical outcome of this one-pot sequence was confirmed by X-ray structural analysis of **439d** and was rationalized by the chelated transition state **438** with the imine substituent occupying a pseudoaxial position.

Interestingly, a switch in diastereoselectivity was observed upon the addition of the metal salt $MgBr_2$ (Scheme 114). For this transformation, vinyl copper species **440** were prepared by direct carbocupration of alkynes with $R^2Cu/MgBr_2$ and were subjected to the same homologation with a zinc carbenoid, as described previously (*vide supra*). Nucleophilic addition to *N-tert*-butanesulfinyl imines **2** provided homoallylic amines **442a**−**f** in good yields (60−75%) and with excellent diastereoselectivities. The switch in facial selectivity was rationalized by invoking cyclic transition state **441**, where the sulfinyl oxygen is coordinated to the magnesium salt.

The synthesis of homoallylic amines **444** or **446** was recently described by Studer and co-workers in the desymmetrization of metalated cylohexadienes via addition to *N-tert*-butanesulfinyl imines **2** (Table 12).[186] The effect of the metal on the desymmetrization reaction was studied with MgCl, providing **444** as the major isomer in addition to varying amounts of **446**. When the metal was changed to the dicyclohexadienyl zinc derivative (M = ZnC_6H_7), a reversal in regioselectivity was observed, and the symmetrical diene **446** was obtained as the major isomer along with a mixture of other isomers. Excellent diastereoselectivities were observed for all additions of the cyclohexadienyl (M = MgCl) nucleophile to *N-tert*-butanesulfinyl aryl, heteroaryl, alkenyl, and aliphatic imines (**444a**−**k**, entries 1−11). However, small amounts of **446** were isolated in each case (1−13%), and for additions to the *N-tert*-butanesulfinyl aliphatic imines (entries 8−11), it could not be separated from the major isomer. Varying diastereoselectivities were observed when the dicyclohexadienyl zinc derivative was employed (M = ZnC_6H_7) with aryl or heteroaryl imine precursors, and **446a**−**f** were isolated in modest to good yields (entries 1−6). Conversely, good yields and excellent diastereoselectivities were obtained when *N-tert*-butanesulfinyl aliphatic imines were utilized (entries 9−10). The relative configurations of the major isomers **444a** (entry 1, M = MgCl) and **446b** (entry 2, M = ZnC_6H_7) were assigned by

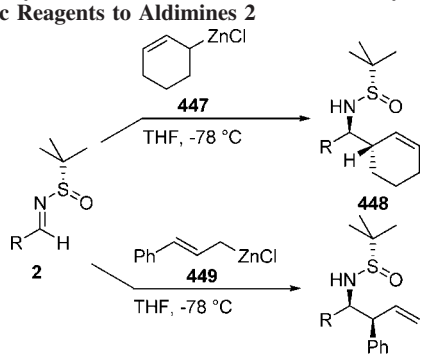
Table 12. Addition of Metalated Cyclohexadienes to *N-tert*-Butanesulfinyl Imines



		cyclohexadienyl-MgCl conditions			cyclohexadienyl-ZnC_6H_7 conditions		
entry	R	product	yield (%)	dr[a]	product	yield (%)	dr
1	Ph	**444a**	77	>99:1	**446a**	62	98:2
2	4-Me-Ph	**444b**	74	>99:1	**446b**	64	97:3
3	4-MeO-Ph	**444c**	86	>99:1	**446c**[b]	59	92:8
4	2-Me-Ph	**444d**	69	>99:1	**446d**	49	90:10
5	2-MeO-Ph	**444e**	72	>99:1	**446e**[b]	49	nd
6	2-furyl	**444f**	77	>99:1	**446f**	32	nd
7	(*E*)-CH=CHPh	**444g**	75	>99:1	**446g**		
8	Bn	**444h**[b]	48	>99:1	**446h**		
9	*i*Pr	**444i**[b]	79	>99:1	**446i**[b]	57	>99:1
10	Cy	**444j**[b]	74	>99:1	**446j**[b]	58	>99:1
11	*t*Bu	**444k**[b]	58	>99:1	**446k**		

[a] Diastereoselectivity with respect to the other three possible 1,3-diene isomers. [b] The other isomer(s) could not be separated.

Table 13. Asymmetric Addition of Substituted Allylic Organozinc Reagents to Aldimines 2



entry	R	R^2ZnCl	product	yield (%)	dr
1	4-Br-Ph	**447**	**448a**	98	≥98:2
		449	**450a**	95	≥98:2
2	4-F-Ph	**447**	**448b**	95	≥98:2
		449	**450b**	94	≥98:2
3	4-Me-Ph	**447**	**448c**	96	≥98:2
		449	**450c**	95	≥98:2
4	4-OMe-Ph	**447**	**448d**	93	≥98:2
		449	**450d**	94	≥98:2
5	2-Br,4-F-Ph	**447**	**448e**	96	≥98:2
		449	**450e**	94	≥98:2
6	furyl	**447**	**448f**	95	≥98:2
		449	**450f**	95	≥98:2
7	Et	**447**	**448g**	97	≥98:2
		449	**450g**	93	≥98:2
8	Cy	**447**	**448h**	92	97:3

X-ray structural analysis. The generation of **444** was rationalized by transition state **443**, in which the imine adopts a *Z*-conformation and the magnesium metal acts as a Lewis acid to complex both the sulfinyl oxygen and imine nitrogen. The formation of **446** was rationalized by cyclic transition state **445**, similar to the transition state proposed by Marek, Knochel, and co-workers (*vide supra*).

The addition of substituted racemic allylic zinc reagents to *N-tert*-butanesulfinyl aldimines was developed by Reddy and co-workers at Novartis, allowing the synthesis of a variety of homoallylic amines bearing adjacent stereogenic centers (Table 13).[187] Treatment of a variety of *N-tert*-butanesulfinyl aromatic imines with racemic cyclohexenylzinc chloride **447** at low temperature (−78 °C) afforded **448a**−**f** in high yields and diastereoselectivities (entries 1−6). Linear and branched aliphatic aldimines (entries 7−8) were also effective substrates. Likewise, the addition of the cinnamylzinc chloride **449** to aromatic (entries 1−5), heteroaromatic (entry 6), and alkyl (entry 7) imines proceeded smoothly, providing the corresponding homoallylic amines **450a**−**g** in excellent yields (93−95%) and with excellent diastereoselectivities (≥98:2). However, the authors noted that the method was not suitable for crotylation, as it resulted in a mixture of diastereomers. The absolute configurations of homoallylic amines **448a** and **450a** were determined by X-ray structural analysis.

This method was also amenable to reaction of organometallic reagents **447** and **451** with *N-tert*-butanesulfinyl ketimines **3** (Scheme 115). Adducts **452a**−**c** containing one quaternary center were produced in excellent yields and with very high diastereoselectivities upon addition of **447**. Likewise, addition of **451** to an *N-tert*-butanesulfinyl ketimine resulted in the regiospecific and diastereoselective reaction producing **452d** with two adjacent quaternary centers in 90% yield and with ≥98:2 dr.

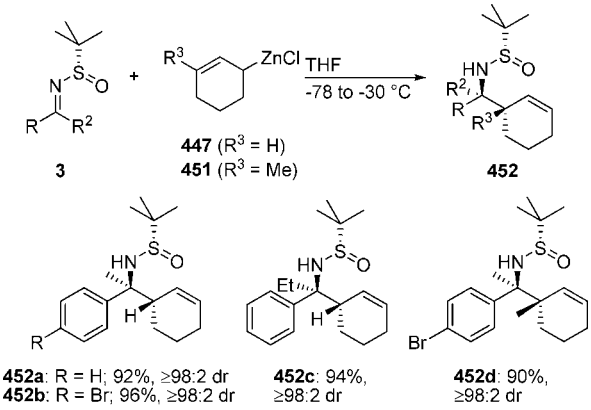
The tetrabutylammonium fluoride (TBAF) promoted addition of allyltrimethylsilane to *N-tert*-butanesulfinyl aldimines **2** was described by Zhang and co-workers (Scheme 116).[134] Racemic *N-tert*-butanesulfinyl imines **2** were employed, and the relative stereochemistry of the major isomer was unfortunately not determined. A screen of reaction conditions revealed that the optimal results were obtained when 30 mol % of TBAF was used and the reaction was conducted at −60 °C in THF. Molecular sieves were a necessary additive to remove any adventitious water. Both linear and α-branched aliphatic imines were examined. The moderate yields of **453a**−**d** were attributed to the presence of an α-proton on the imine precursor, which could be deprotonated under the reaction conditions, leading to the formation of byproducts. Yields were higher when *N-tert*-butanesulfinyl aromatic aldimines were used as substrates (70−80% yield, **453e**−**i**).

8. Synthesis of Propargylic Amines

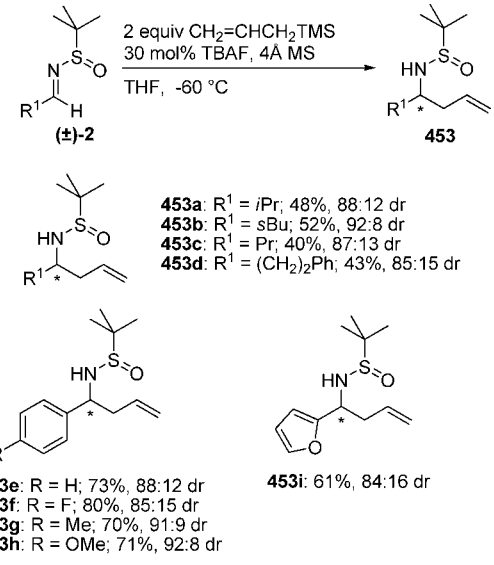
8.1. 1,2-Additions of Alkyne Reagents to Aldimines and Ketimines

The first report of the 1,2-addition of an alkyne nucleophile to an *N-tert*-butanesulfinyl aldimine was an isolated example from Barrow and co-workers in their study on the synthesis

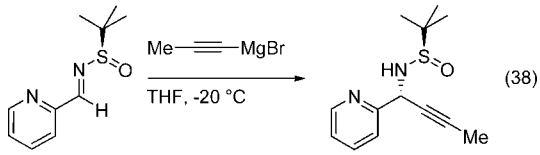
Scheme 115. Asymmetric Addition of Substituted Allylic Organozinc Reagents to Ketimines 3



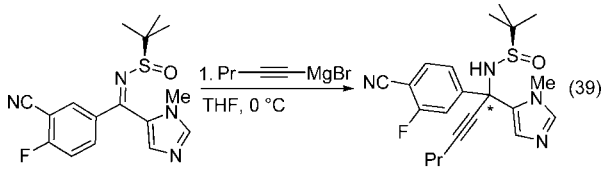
Scheme 116. Addition of Allyltrimethylsilane to *N-tert*-Butanesulfinyl Imines



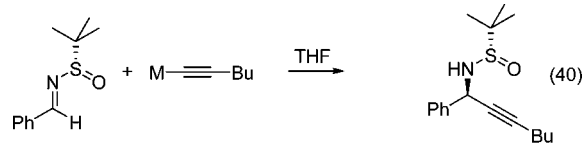
of 1,2-amino alcohols (see section 11.1).[62] Kuduk and co-workers also reported a single example of addition of an alkynyl Grignard reagent to the *N-tert*-butanesulfinyl 2-pyridyl imine **142**, providing **144e** in 90% yield and with 94:6 dr (eq 38, see section 4.1.1 for addition of other nucleophiles to this imine).[99]



An isolated example of the 1,2-addition of an alkyne nucleophile to an *N-tert*-butanesulfinyl ketimine was also disclosed by Shaw and deSolms (eq 39; see section 5.1 for more details).[153] The reaction proceeded smoothly, providing **293d** in 100% crude yield and with a 70:21 diastereomeric ratio.

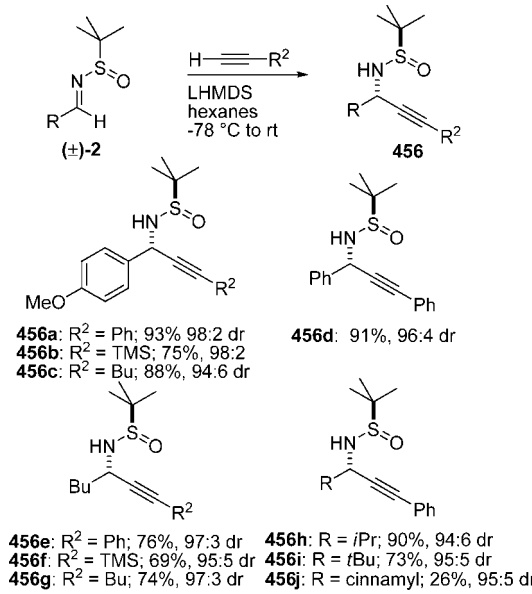


In their study of Lewis base catalyzed reactions, Scheidt and Lettan reported that the electron-deficient triethoxysilylalkyne **454a** could act as a nucleophile for additions into a variety of carbonyl compounds in the presence of a catalytic amount (20 mol %) of KOEt and 18-crown-6.[188] Addition of this nucleophile to *N-tert*-butanesulfinyl imine **133** at −78 °C provided the secondary propargylic amine **455** in 95% yield and 95:5 dr (eq 40). Interestingly, this method provided the opposite stereoisomer to the analogous reaction between imine **133** and alkynes **454b** or **c**, which were added at 0 °C.

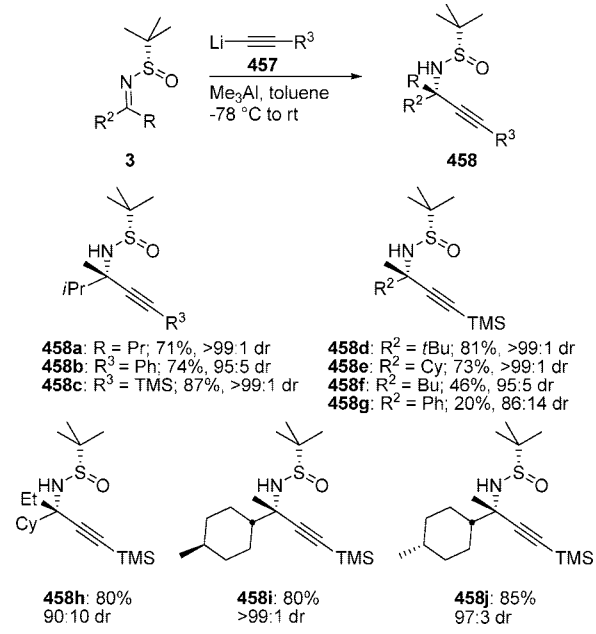


The first general method for the synthesis of propargylic amines via the addition of deprotonated alkynes to *N-tert*-butanesulfinyl aldimines **2** was developed by Hou and co-workers (Scheme 117).[189] Under the optimized conditions (LHMDS in hexanes), aromatic, aliphatic, or silyl substituted alkynes could be added to aromatic and aliphatic aldimines in high yields (69−93%) and diastereomeric ratios (≥94:6 dr, **456a**−**i**). While the diastereomeric ratio remained high for the addition of phenylacetylene to the *N-tert*-butanesulfinyl aldimine derived from cinnamaldehyde, the yield was low (26%, **456j**). The relative configuration of **456a** was determined by X-ray structural analysis. Very recently, Wang and co-workers published an extensive study on the highly

Scheme 117. Synthesis of *N-tert*-Butanesulfinyl Propargylic Amines

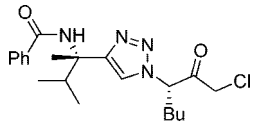


Scheme 118. Synthesis of α,α-Dibranched Propargylic Amines



diastereoselective addition of alkynyl Grignard reagents to *N-tert*-butanesulfinyl aldimines.[190]

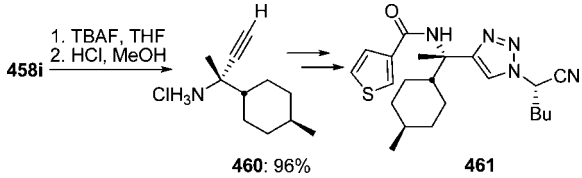
A general method for the synthesis of α,α-dibranched propargylamines via the addition of alkyne nucleophiles to *N-tert*-butanesulfinyl ketimines **3** was disclosed by Ellman and Patterson (Scheme 118).[191] For this transformation, high diastereoselectivities could be achieved by the dropwise addition of a solution of **3** and $AlMe_3$ in toluene at −78 °C to a solution of *in situ* generated lithium acetylides **457**. *N*-Propylethynyllithium, phenylethynyllithium, and (trimethylsilyl)ethynyllithium could all be added in high yields and with excellent diastereoselectivities (**458a**−**c**, Scheme 118). Several other alkyl and aryl ketimines also provided the desired adducts in high yields and diastereoselectivities (**458d**−**j**). Even the very sterically hindered product **458h** was obtained with only a minor drop in diastereomeric purity. A lower yield was observed for products **458f** and **g**, with



459

Figure 5. Chloromethyl ketone inhibitor of cathepsin S.

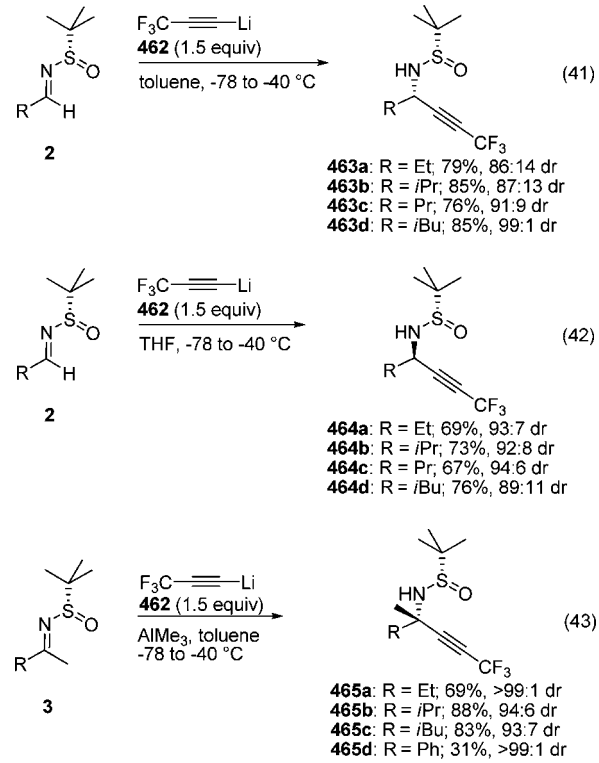
Scheme 119. Synthesis of Nitrile Inhibitor 461



competitive deprotonation of the imine substrate likely impeding reaction progress. Different reaction parameters were tested for these substrates, such as changing the solvent or omission of $AlMe_3$, but modifications that resulted in higher yields were not identified.

The utility of this method was demonstrated by the efficient synthesis of potent, nonpeptidic cathepsin S inhibitors.[192] A crystal structure of the chloromethyl ketone inhibitor **459** (Figure 5) in complex with cathepsin S established the sense of induction for alkyne additions to *N-tert*-butanesulfinyl ketimines and provided valuable insight for inhibitor optimization that led to the development of the highly potent and selective nitrile inhibitor **461** (Scheme 119).[192] Silyl and sulfinyl group removal from **458i** provided the enantiomerically pure propargyl amine **460**, which was then converted in four steps to the desired nitrile **461**.[193]

The scope with respect to the synthesis of *N-tert*-butanesulfinyl propargylamines was further extended to include trifluoromethyl alkyne nucleophiles by Qing and co-workers.[194] Dropwise addition of aldimines **2** in toluene to a solution of acetylide **462**, which was generated in situ from the deprotonation of 2-bromo-3,3,3,-trifluoropropane with LDA, provided adducts **463a**−**d** (eq 41). The observed stereochemical outcome was consistent with a chelated cyclic transition state (**128**, Scheme 33, section 4.1). However, the opposite diastereomer **464** was observed when THF was used as the solvent (eq 42), which by coordinating to the metal cation could promote an open transition state (**130**, Scheme 33, section 4.1). The addition of **462** to *N-tert*-butanesulfinyl ketimines **3** was also examined. In the presence of $AlMe_3$ as an additive in toluene, adducts **465a**−**c** were obtained in 69−88% yield and with ≥93:7 dr (eq 43). In the absence of $AlMe_3$, lower diastereoselectivity was observed. Addition of **462** to an aromatic *N-tert*-butanesulfinyl ketimine also proceeded with high diastereoselectivity but provided a low yield (31%) of **465d**. The absolute configurations of the products were determined by crystal structures of **463a** and **465b**. The sulfinyl groups were also cleaved using HCl in MeOH from select representative addition products to generate the corresponding enantiomerically pure trifluoromethylated propargylamines.



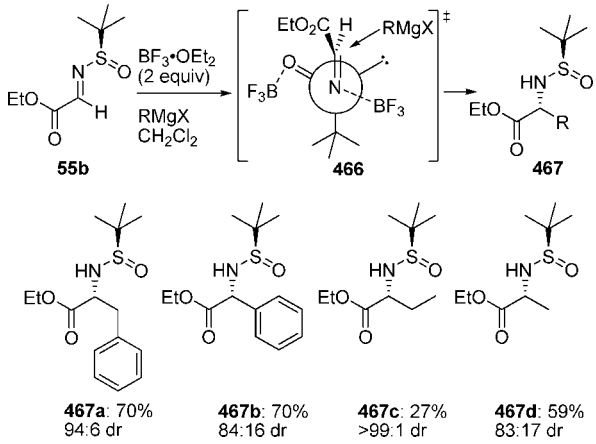
9. Synthesis of α-Amino Acid Derivatives

9.1. Nucleophilic 1,2-Additions to *N-tert*-Butanesulfinyl Imino Esters

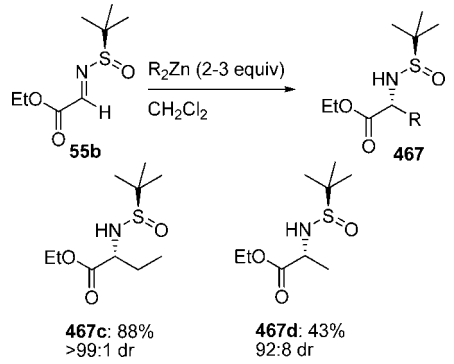
In 1999 Davis and co-workers published the first report on the additions of organometallic reagents to *N-tert*-butanesulfinyl imino esters, providing a direct route for the synthesis of *N-tert*-butanesulfinyl protected amino acid derivatives.[69] The addition of BnMgCl to the *N-tert*-butanesulfinyl aldimine (*R*)-**55b** proceeded with good diastereoselectivity (90:10) but poor yield (<30%). However, the precomplexation of the imine with 2 equiv of $BF_3 \cdot OEt_2$ followed by addition of the Grignard reagent provided **467a** in good yield and with high diastereoselectivity (Scheme 120). 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 **466**, 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 **467c** due to competitive imine reduction. However, in this case, Et_2Zn was found to be a suitable nucleophile, allowing isolation of **467c** in 88% yield with >99:1 dr (Scheme 121). The less reactive Me_2Zn provided only 43% yield of product **467d**, although with higher stereoselectivity than the corresponding Grignard addition.

Standaert and co-workers utilized the conditions developed by Davis and co-workers for addition of a cyclobutenyl Grignard reagent to imino ester (*S*)-**55c** in the asymmetric synthesis of unnatural amino acid **471** for incorporation into proteins using the *in vitro* protein biosynthetic machinery (Scheme 122).[70] While the imino ethyl ester **55b** 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 **55c** was used, providing **469** 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

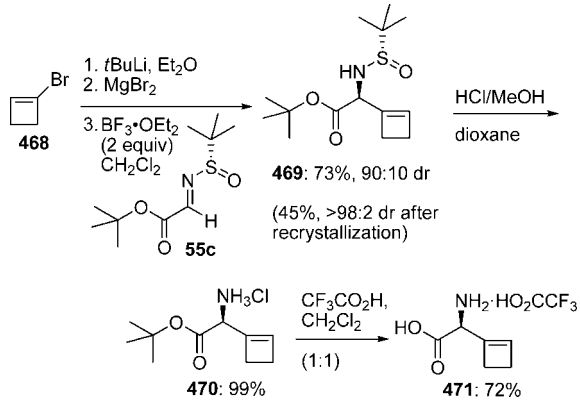
Scheme 120. Grignard Addition to α-Imino Esters



Scheme 121. Dialkylzinc Addition to α-Imino Esters

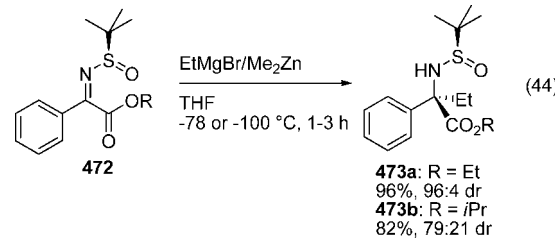


Scheme 122. Synthesis of 1-(1-Cyclobutenyl)glycine



tert-butyl ester then provided free amino acid **471** in 72% yield without epimerization.

A triorganozincate reagent, prepared by mixing EtMgBr with dimethylzinc, has been used as the nucleophile for the asymmetric synthesis of α,α-disubstituted amino acids from *N-tert*-butanesulfinyl imino esters, as reported by Yus and co-workers (eq 44; for addition to other imines, see section 4.1.3).[128,131] Dimethylzinc is used due to the inability of methyl groups to transfer from the triorganozincate reagents. The additions to imines **472** were carried out at low temperature in THF, and the desired ethylation products **473a** and **473b** were obtained in high yields (82−96%) and with good to excellent diastereoselectivities (79:21−96:4). 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 **473a** and **473b** in 15:85 and 21:79 dr, respectively.



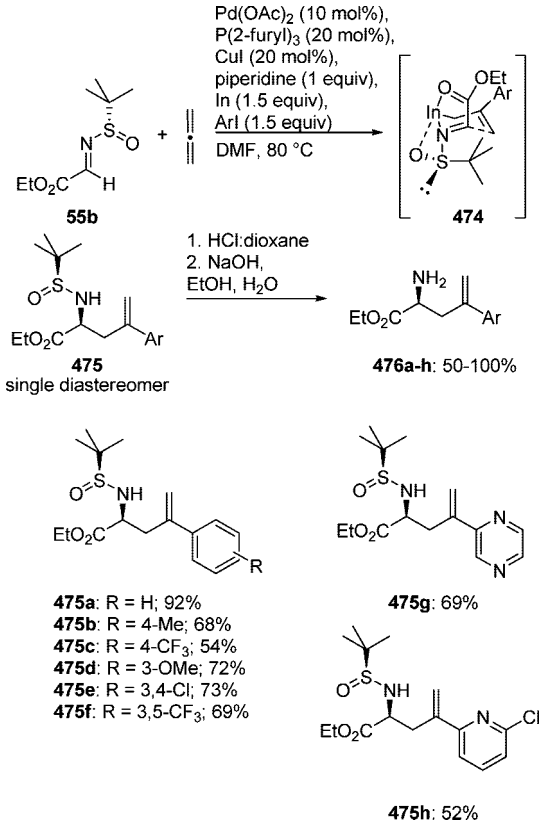
(44)

The addition of organoindium reagents to *N-tert*-butanesulfinyl imino esters has also been examined. Grigg and co-workers demonstrated allylations of *N-tert*-butanesulfinyl imino ester (*S*)-**55b** via a bimetallic Pd/In mediated cascade sequence for the synthesis of nonproteinogenic α-amino acid derivatives (Scheme 123).[195] With this *N-tert*-butanesulfinyl imine electrophile, slight modifications to their previously employed reaction conditions for the analogous transformation with *N-tert*-butanesulfinyl aryl or alkyl aldimines (catalytic $Pd(OAc)_2$, $P(2\text{-furyl})_3$, In, ArI, DME; see section 7.1) were implemented, including the addition of a catalytic amount of copper iodide, the addition of 1 equiv 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 they could not rule out the possibility of a copper allyl species. 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 **475a**−**h** as single diastereomers in yields ranging from 52 to 92%. The free amine products **476** were generated in 50−100% yield after a two-step deprotection sequence. The same synthetic sequence was also demonstrated with (*R*)- **55b**. The absolute configuration of **475e** was established by X-ray structural analysis. This outcome was rationalized by the chelated transition state **474**, which displayed the most exothermic heat of formation according to semiempirical calculations.

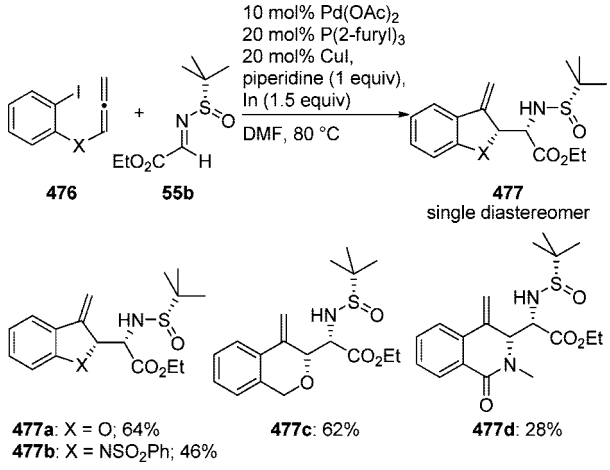
Tethered aryl iodide/allene substrates **476** were also employed to further extend the scope of this methodology (Scheme 124). Using the same reaction conditions (*vide supra*), **477a**−**d** were formed regioselectively in moderate yields (28−64%) with complete stereocontrol over the two new contiguous stereocenters. The absolute configuration of **477b** was determined by X-ray structural analysis, and a chelated transition state was proposed to account for the results. The authors also carried out the synthesis of the enantiomers of **477** by employing (*R*)-**55b**.

The allylation of *N-tert*-butanesulfinyl imino ester (*R*)-**55b** with an organoindium reagent in aqueous media was demonstrated for the first time by Lin, Xu, and co-workers (Scheme 125).[181] The effects of saturated aqueous salt solutions were probed, with NaBr providing the highest yield of the desired product (see section 7.1). Under these reaction conditions, the resulting homoallylic *N-tert*-butanesulfinyl amino ester **478** was produced in excellent yield and diastereoselectivity and was subsequently converted to D-allylglycine **479** 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 **474**, Scheme 123).

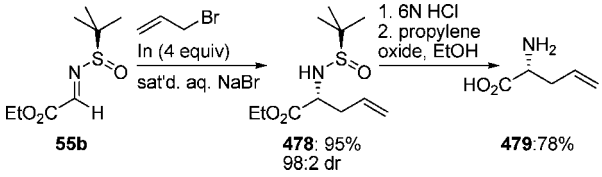
Scheme 123. Synthesis of Non-proteinogenic Amino Acids via the Bimetallic Cascade Allylation of *N-tert*-Butanesulfinyl Imino Esters



Scheme 124. Tandem Cyclization−Allylation Cascades with *N-tert*-Butanesulfinyl Imino Ester 55b

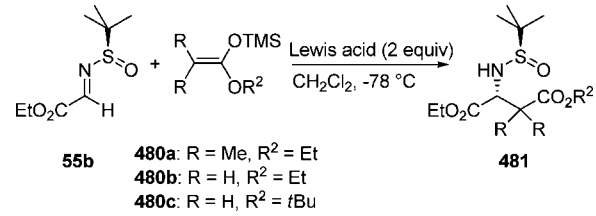


Scheme 125. Synthesis of D-Allylglycine (479)



The addition of silyl ketene acetals **480** to an *N-tert*-butanesulfinyl imino ester **55b** for the synthesis of aspartic acid derivatives **481** was explored by Skrydstrup and Jacobsen (Table 14).[196] 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 2 equiv of $BF_3 \cdot OEt_2$ were used for the

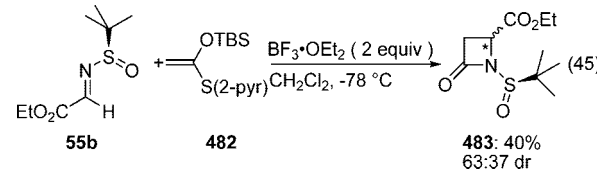
Table 14. Lewis Acid Promoted Addition of Silyl Ketene Acetals to 55b



entry	480	Lewis acid	product	yield (%)	dr
1	**480a**	$BF_3 \cdot OEt_2$	**481a**	81	87:13
2	**480a**	$AlMe_3$	**481a**	50	80:20
3	**480b**	$BF_3 \cdot OEt_2$	**481b**	67	90:10
4	**480b**	$AlMe_3$	**481b**	92	93:7
5	**480c**	$BF_3 \cdot OEt_2$	**481c**	17	96:4
6	**480c**	$AlMe_3$	**481c**	28	97:3
7[a]	**480c**	$AlMe_3$	**481c**	86	97:3

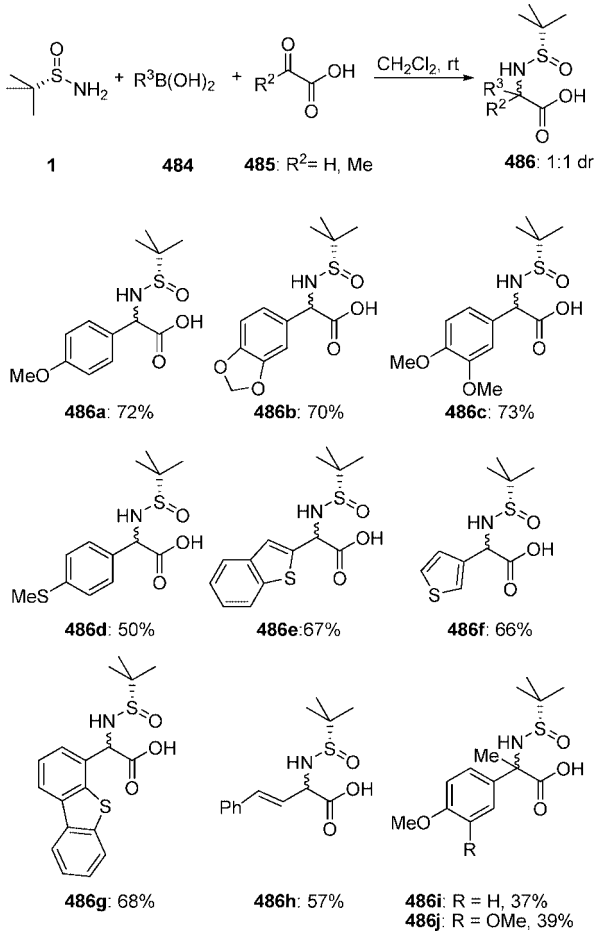
[a] Eight equivalents of **480c** were used.

reaction between **55b** and silyl ketene acetal **480a** (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 **480b** 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 **480c**, but 8 equiv of **480c** was required to obtain **481c** in high yield (entry 7). The absolute configurations of the major diastereomers of **481b** and **481c** were determined by chemical correlation experiments, and the major diastereomer of **481a** was assigned by analogy. The stereochemical outcome was rationalized by an open transition state model analogous to that proposed by Davis (**466**, see Scheme 120). A one-pot procedure for the synthesis of β-lactams was also developed using the silyl ketene acetal **482**, derived from 2-pyridyl thioacetate, and *N-tert*-butanesulfinyl imino ester **55b** (eq 45). However, product **483** was isolated in only a moderate yield and with poor diastereoselectivity.



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,[197] the norcardicin antibacterial agents,[198] and the cardiovascular drug Plavix.[199] Naskar and co-workers 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 126).[12] The one-pot, three-component coupling of *tert*-butanesulfinamide **1**, a boronic acid **484**, and glyoxylic acid monohydrate or pyruvic acid **485** took place under mild reaction conditions (ambient temperature in CH_2Cl_2), providing adducts **486a−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 **486a−g** in 50−73% isolated yields. An alkenyl boronic acid was also employed, providing **486h** in 57% yield. When pyruvic acid

Scheme 126. Synthesis of α-Arylglycines 486 by the Petasis Reaction



was used (**485**, R^2 = Me), the desired products **486i** and **486j** were generated, but yields were diminished (37−39%). Although this reaction is not diastereoselective, the authors demonstrated that the diastereomers of **486a** could be separated by preparative HPLC.

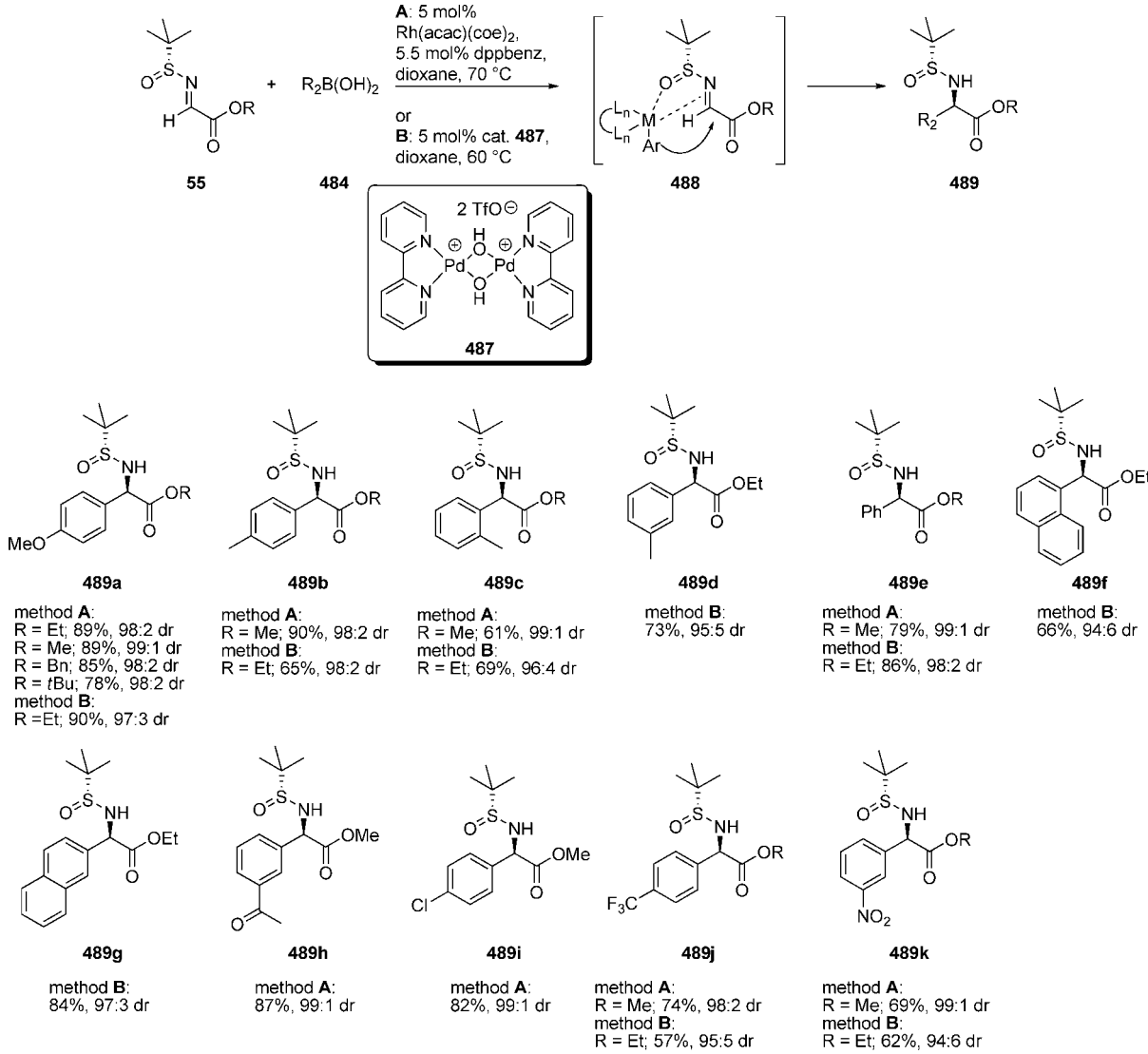
N-tert-Butanesulfinyl protected α-arylglycine derivatives have also been synthesized by the transition metal-catalyzed addition of arylboronic acids to *N-tert*-butanesulfinyl imino esters. The first example of this transformation was disclosed by Ellman and co-workers.[71] Building on their previous success with the Rh(acac)(coe)$_2$ and 1,2-bis(diphenylphosphinyl)benzene (dppbenz) catalyst system for additions to aromatic and aliphatic *N-tert*-butanesulfinyl aldimines (see section 4.1.4), these conditions were applied to additions to *N-tert*-butanesulfinyl imino esters **55** to provide access to diverse α-arylglycine derivatives (method **A**, Scheme 127). Methyl, benzyl, and *tert*-butyl esters **55** all provided high yields and selectivities, thereby maximizing flexibility in the choice of ester protecting group (**489a**, method **A**). High yields and diastereoselectivities were achieved for arylboronic acids with either electron-donating or electron-neutral substituents (**489a**−**c**, **e**), and ortho-substitution resulted in only a modest reduction in yield (**489c**). Importantly, arylboronic acids bearing electron-withdrawing substituents could also be incorporated (**489h**−**k**), which are ineffective coupling partners in the Petasis reaction (see Scheme 126).[200] It is notable that, for all of the ester derivatives of **55** and for all types of arylboronic acids, the products were obtained in ≥98:2 dr. Following this initial report, Lu and Dai published a cationic palladium-catalyzed addition of arylboronic acids to *N*-sulfinyl imino esters (catalyst **487**, method **B**, Scheme 127).[201] Similar yields and diastereoselectivities that approached those obtained for the rhodium-catalyzed additions were observed for a variety of arylboronic acid coupling partners (**489a**−**g**, **j**, and **k**). However, neither the Rh(0) nor Pd(0) catalyst systems, methods **A** and **B**, respectively, provided successful addition of pyridylboronic acids. The sense of induction observed for both methods is consistent with transition state **488**, in which addition of the aryl group adds to the *re*-face of the imine, opposite to the *tert*-butyl group.

Ellman and co-workers also demonstrated that the enantiomerically enriched *N-tert*-butanesulfinyl protected α-arylglycine esters could undergo subsequent, selective transformations such as sulfinyl deprotection (**490**), hydrolysis to the free carboxylic acid (**491**), and reduction to the β-amino alcohol (**492**), in each case with minimal to no racemization (Scheme 128). Moreover, they rigorously established that the *N-tert*-butanesulfinyl α-arylglycine **491** 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, which are the conditions developed by Carpino[202] for coupling *N*-Boc α-arylglycines without epimerization (Scheme 129).

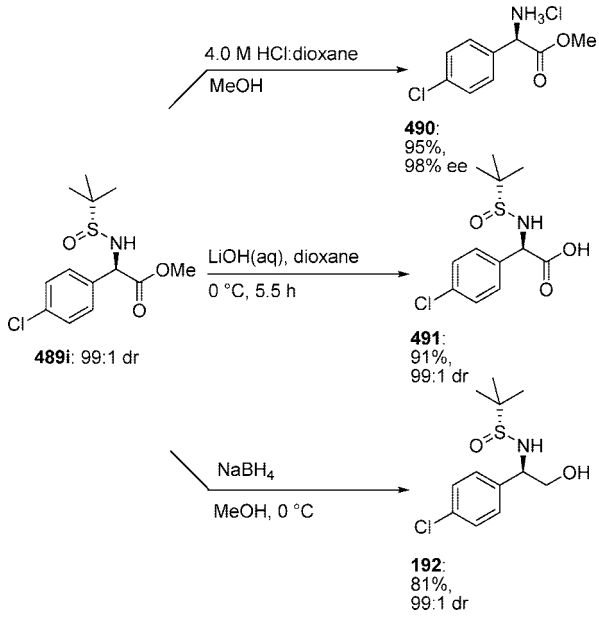
Recently, a trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoted addition of electron-rich arenes to *N-tert*-butanesulfinyl imino ester **55b** has also been demonstrated by Gautun and co-workers to furnish *N-tert*-butanesulfinyl protected heteroarylglycine esters (Scheme 130).[203] A series of heterocyclic aromatic compounds were tested, with addition of furan, pyrrole, and indole, generating **494a**, **b**, and **d** in moderate to high yields and diastereoselectivities. For the less reactive thiophene, an increase in reaction temperature to −20 °C was required, providing **494c** with poor diastereoselectivity and a modest 40% yield. The reaction between anisole and **55b** also required increased reaction temperatures (−20 °C) to give **494e** as a mixture of diastereomers in a combined 65% yield. In contrast, addition of pyridine to **55b** was unsuccessful, even upon increasing the reaction temperature. The C_2 symmetric adduct **494f** was obtained in 77% yield as a single diastereomer by treatment of pyrrole with 2 equiv of **55b**. The absolute configurations of **494d** and **f** were determined by X-ray structural analysis, and **494b** was assigned in accordance with **494f**. The absolute configurations of **494a** and **494e** were established by chemical correlation experiments. The observed stereochemical outcome for compounds **494a**, **b**, and **d** is consistent with an open transition state model (analogous to **466**, Scheme 120).

N-tert-Butanesulfinyl imino ester **55b** has been used as the electrophilic partner in the rhodium-catalyzed hydrogen-mediated reductive coupling of 1,3-enynes or 1,3-diynes to form α-amino ester products (Scheme 131).[204] Krische and co-workers disclosed that hydrogen-mediated coupling of a 1,3-enyne to **55b** 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 **55b** gave

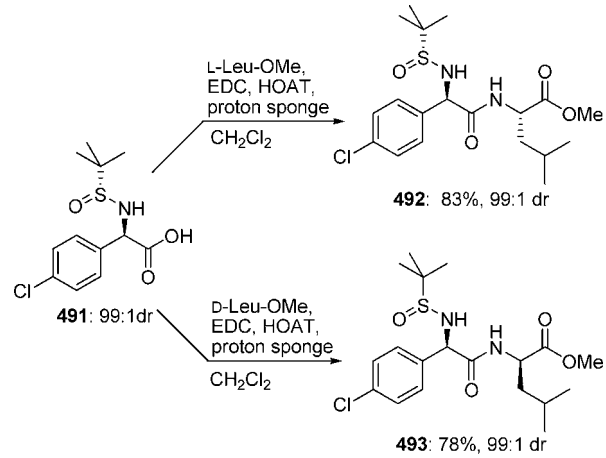
Scheme 127. Transition Metal Catalyzed Synthesis of *N-tert*-Butanesulfinyl Protected α-Arylglycines



Scheme 128. Further Synthetic Transformations of *N-tert*-Butanesulfinyl Protected Arylglycine Products

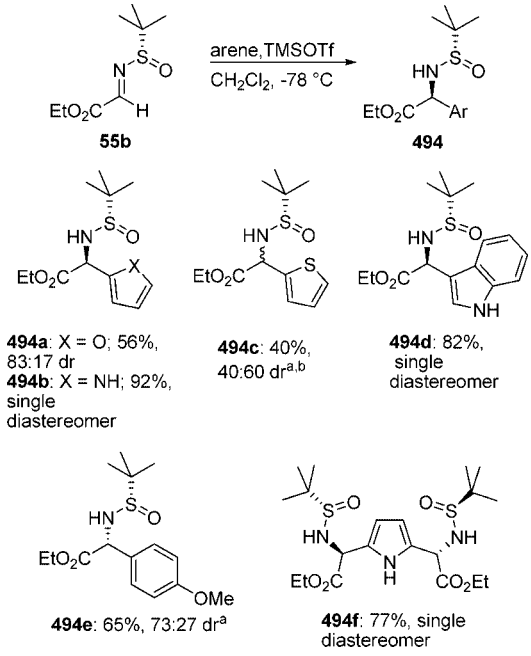


Scheme 129. Peptide Coupling of *N-tert*-Butanesulfinyl Arylglycine 491



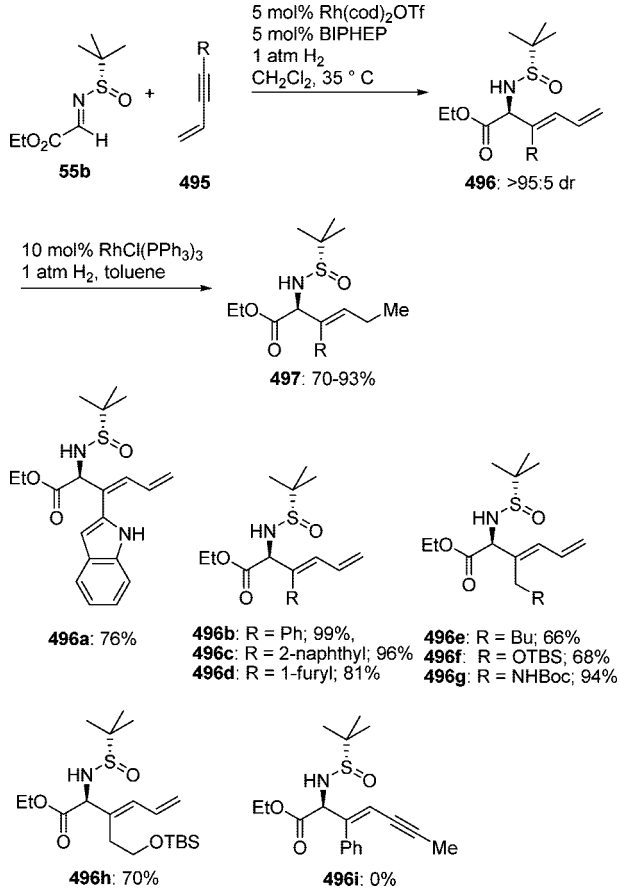
the expected coupled adducts **496** in good yields (66−99%) and >95:5 diastereomeric ratio (**496a**−**h**). Attempts to couple 1-phenyl-1,3-pentadiyne to **55b** under the reaction conditions optimized for enyne reductive couplings failed to give any of the desired product **496i**. For this transformation, the *N*-2,4,6-triisopropylbenzenesulfinyl imino ester was a more effective coupling partner. Regioselective hydrogenations of

Scheme 130. Synthesis of Heteroaromatic *N-tert*-Butanesulfinyl Protected α-Amino Esters



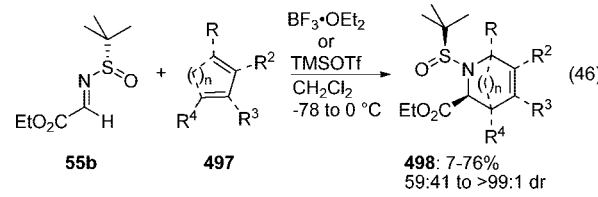
[a] The reaction was conducted at −20 °C. [b] The configuration of the major diastereomer was not determined.

Scheme 131. Hydrogen-Mediated Reductive Coupling of Conjugated Alkynes with *N-tert*-Butanesulfinyl Imino Ester 55b



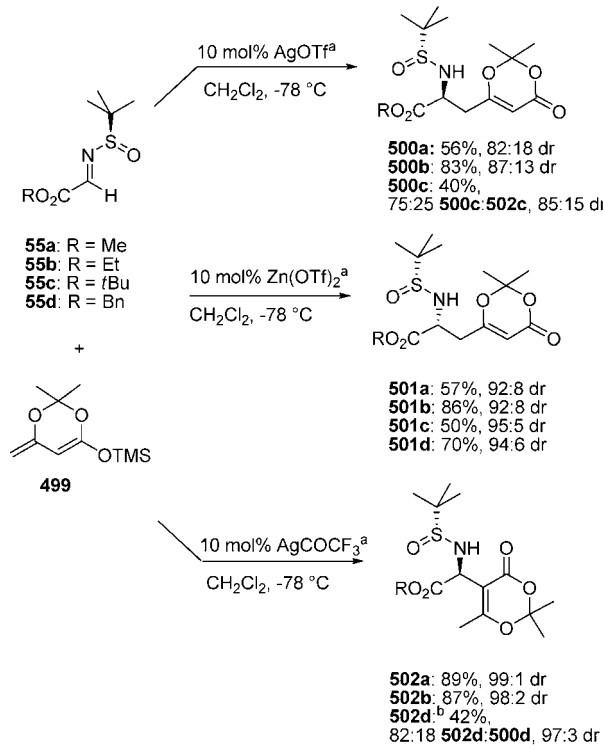
the terminal alkenes were achieved in 70−93% yield in the presence of Wilkinson's catalyst (Scheme 131). Exhaustive hydrogenation of the diene side chain was also achieved using Crabtree's catalyst, but replacement of the sulfinyl group with a carbamate protecting group was necessary.

Gautun and co-workers have demonstrated that *N-tert*-butanesulfinyl imino ester **55b** can act as a dieneophile in the Lewis acid mediated aza-Diels−Alder reaction, providing a number of heterocyclic adducts in varying yields and diastereoselectivities (eq 46; see section 18.3 for a more detailed discussion of this transformation).[205]



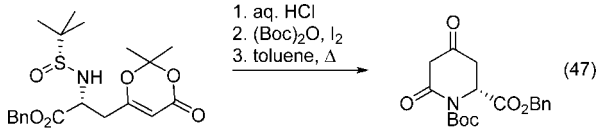
Liu, Chen, and co-workers reported a Lewis acid catalyzed vinylogous Mannich reaction between *N-tert*-butanesulfinyl imino esters **55a−d** and dioxinone-derived silyl dienolate **499** (Scheme 132).[206] Careful tuning of the Lewis acid catalyst provided access to either diastereomer of the γ-product (**500a−c** and **501a−d**) or the α-regioisomer (**502a**, **b**, and **d**). Using Ag(OTf) as the Lewis acid catalyst, γ-selectivity was observed, and **500a−c** were obtained in varying yields and with moderate diastereoselectivities. The $Zn(OTf)_2$ catalyzed reactions of **55a−d** with **499** provided excellent γ-selectivity but with a reversal of the diastereoselectivity, and **501a−d** were obtained in moderate to good yields and with excellent diastereoselectivities. The authors also noted that the counterion of the Ag(I) salt had a profound effect on the regioselectivity, where $AgOCOCF_3$ or AgOAc provided good yields (42−89%) of the α-regioisomers **502** with high diastereoselectivities (97:3 to 99:1).

Scheme 132. Vinylogous Mannich Reaction



[a] Regioselectivity was ≥25:1 as determined by ^1H NMR unless otherwise noted. [b] AgOAc was used as the Lewis acid catalyst.

The vinylogous Mannich product **501d** was converted to piperidinedione **503**, a known precursor to 4-hydroxypipecolic acid, in 59% over three steps (eq 47).



501d **503**: 59%

Several transition state models were proposed to account for the different selectivities observed between catalysts (Figure 6). For the Ag(OTf) catalyzed reaction, the diastereomeric outcome was rationalized by transition state **504**, while, for the $Zn(OTf)_2$ catalyzed reaction, transition state **505** was proposed. To account for the observed effect of the counterion on promoting α-selectivity, the authors proposed transition state **506**, where the counterion interacts with the TMS group of **499**, enhancing the coordination between Ag^+ and the oxygen of the silyl dienolate.

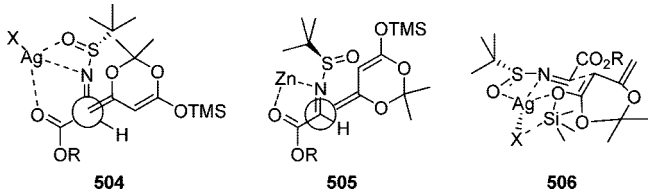
9.2. 1,2-Addition of Nucleophilic Carboxylic Acid Precursors

9.2.1. 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.[207] 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,[208,209] 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 of ethylaluminum cyanoisopropoxide [EtAl(O*i*Pr)CN] (eq 48) or TMSCN with **507** (Table 15).[210] 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.[208] When [EtAl(O*i*Pr)CN] was used with the *N-tert*-butanesulfinyl aldimine **507** in THF, the reaction took place in high yield and with high diastereoselectivity (eq 48). Similar results were obtained in other solvents of diverse polarity and chelating ability. The absolute configuration of the newly formed chiral center was determined by X-ray structural analysis of **508**.

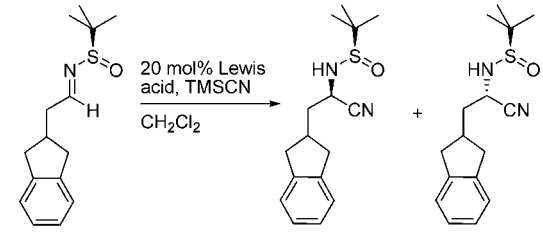
The reaction between imine **507** and TMSCN did not proceed in the absence of a Lewis acid or when the temperature was below 10 °C. A large variety of Lewis acids were screened, revealing that the nature of the metal as well



504 **505** **506**

Figure 6. Transition state models for the addition of **499** to *N-tert*-butanesulfinyl imino esters.

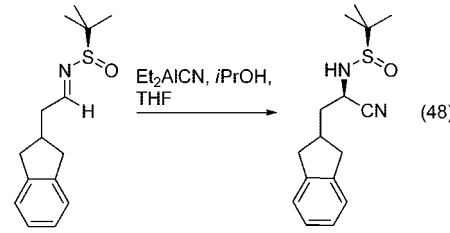
Table 15. Evaluation of Several Lewis Acids



507 **508** **509**

entry	catalyst	yield (%)	dr (**508**/**509**)
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

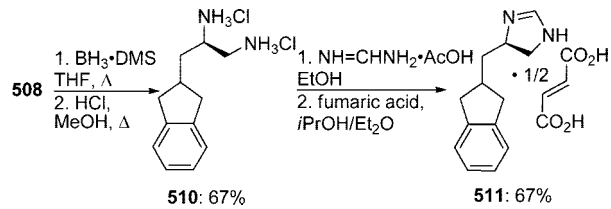
as the salt form of the metal had a significant influence on the yield and diastereoselectivity of the reaction (Table 15). The use of ZnI_2, $SnCl_4$, $BF_3 \cdot OEt_2$, or $Yb(OTf)_3$ generated mixtures of **508** and **509** in moderate to good yield with diastereoselectivites of up to 80:20 favoring **509** (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 **508** in moderate to good yield and with very high diastereoselectivities (entries 5−7). Other Lewis acids evaluated also favored the formation of **508**, albeit with inferior diastereomeric ratios. The utility of this product was demonstrated by the conversion of **508** to imidazoline **511** (Scheme 133). Treatment of **508** 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 **510** as the bis-hydrochloride salt in 67% yield. Cyclization of the diamine with formamidine acetate afforded **511**, which was isolated as the hemifumarate in 67% yield after crystallization.



507 **508**: 95% 97:3 dr

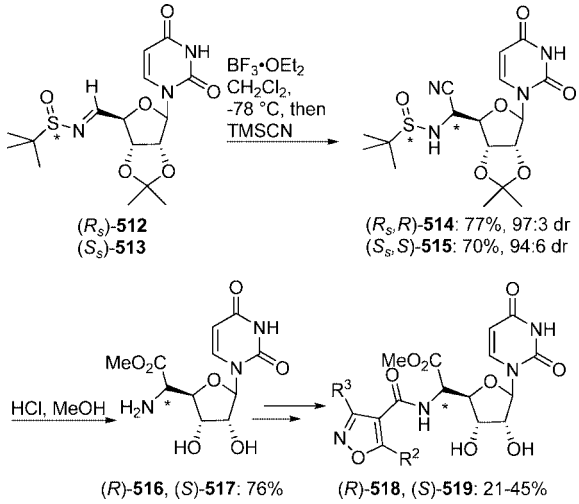
The Lewis acid catalyzed addition of TMSCN to an *N-tert*-butanesulfinyl aldimine was exploited by Plant, Williams, and Thompson (Scheme 134).[211] The *N-tert*-butanesulfinyl imine derivatives of uridine **512** and **513** were examined as precursors to novel chitin synthase inhibitors, which could

Scheme 133. Synthesis of 511 from *N*-Sulfinyl-α-aminonitrile 508



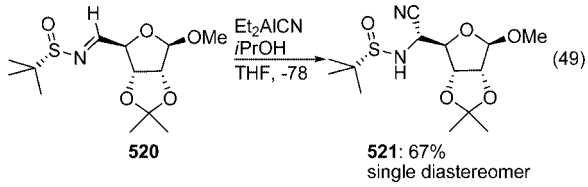
508 **510**: 67% **511**: 67%

Scheme 134. Stereoselective Cyanide Addition to *N-tert*-Butanesulfinyl Imines



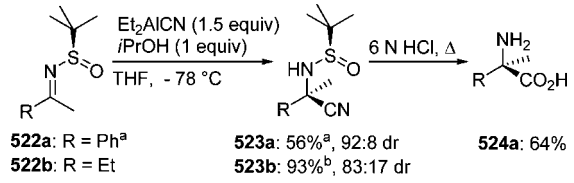
be utilized as potential pesticidal agents. Contrary to Cordi and Mabic's findings (*vide supra*), with these more electrophilic imines, high yields and diastereoselectivities were achieved when the reactions were conducted at low temperature (−78 °C) using $BF_3 \cdot OEt_2$ as the Lewis acid. Under these conditions, (R_S,*R*)-**514** was generated in 77% yield and 97:3 dr (Scheme 134). Comparable results were obtained when imine (S_S)-**513** was utilized, providing (S_S,*S*)-**515** in 70% yield and 94:6 dr. Treatment of (R_S,*R*)-**514** or (S_S,*S*)-**515** with HCl in MeOH produced the corresponding methyl esters (*R*)-**516** and (*S*)-**517** with concomitant removal of the sulfinyl and isopropylidene protecting groups. Coupling of the free amine (*R*)-**516** or (*S*)-**517** with isoxazole carboxylic acid analogues provided several derivatives of (*R*)-**518** and (*S*)-**519** in 21−45% yield.

Recently, Xu and co-workers demonstrated that the *N-tert*-butanesulfinyl imine **520**, derived from D-ribose, was an excellent substrate for the asymmetric Strecker reaction following the Et_2AlCN/*i*PrOH protocol developed by Davis and co-workers (*vide supra*), providing adduct **521** in 67% yield as a single diastereomer (eq 49).[212] Unfortunately, all attempts to hydrolyze the nitrile to furnish the desired carboxylic acid under acidic conditions failed due to the instability of the substrate under the reaction conditions.



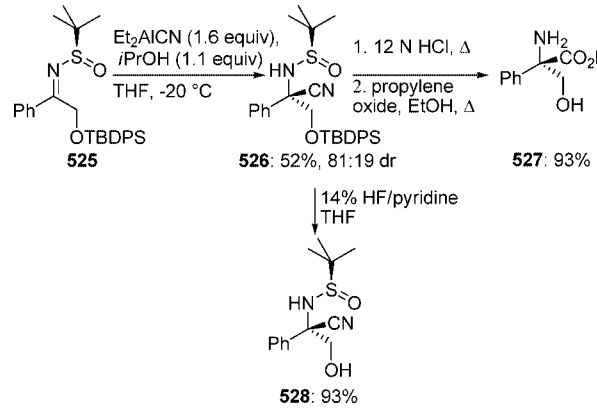
The first example of an asymmetric Strecker reaction utilizing an *N-tert*-butanesulfinyl ketimine was reported by Davis and co-workers in 2000 (Scheme 135).[213] While the primary focus of Davis's study was the use of his Et_2AlCN/*i*PrOH protocol for additions to *N-p*-toluenesulfinyl ketimines, the *N-tert*-butanesulfinyl ketimines **522** were also tested to probe the effects of the bulkier *tert*-butanesulfinyl group on the diastereoselectivity of the reaction. Ketimine **522a**, which exists as a single imine isomer, was converted to the corresponding amino nitrile **523a** in a 92:8 diastereomeric ratio, and a 56% yield of the major diastereomer was obtained after recrystallization. A lower diastereomeric ratio (83:17 dr) was observed for additions to the more challenging

Scheme 135. Addition of Et_2AlCN/*i*PrOH to Ketimines 522



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

Scheme 136. Synthesis of α-Phenylserine

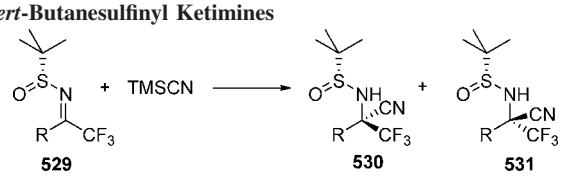


N-tert-butanesulfinyl ketimine substrate **522b**, and compound **523b** could not be purified to diastereomeric purity. The diastereoselectivity observed for **523a** and **523b** was higher than that obtained for the corresponding *N-p*-toluenesulfinyl amino nitriles (80:20 and 75:25 dr, respectively). The free amino acid **524a** could be generated in good yield (64%) without epimerization by hydrolysis of **523a** in refluxing 6 N HCl (Scheme 135).

Later, Davis' protocol was utilized by Avenoza, Peregrina, and co-workers for the synthesis of α-phenylserine **527** (Scheme 136).[214] Treatment of ketimine **525** with ethylaluminum cyanoisopropoxide [EtAl(O*i*Pr)CN] at −20 °C provided **526** 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 **526** was obtained after column chromatography. Selective cleavage of the silyl group by treatment with HF in pyridine provided alcohol **528** in high yield. A crystal structure was obtained to unambiguously establish the (*R*)-configuration at the newly formed stereocenter. Treatment of diastereomerically pure **526** 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 (**527**) was then achieved in high yield (93%) by treatment with propylene oxide in EtOH under reflux conditions (Scheme 136). The opposite enantiomer of **527** was also generated in the same manner by utilizing (S_s)-*N-tert*-butanesulfinyl ketimine **525**, constituting an efficient route to either enantiomer of α-phenylserine.

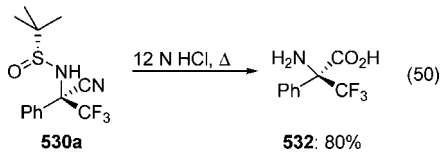
The asymmetric Strecker reaction for the synthesis of α-trifluoromethyl α-amino acids from CF_3-substituted *N-tert*-butanesulfinyl ketimines **529** was demonstrated by Lu and co-workers (Table 16).[76] The reaction conditions were optimized for the addition of TMSCN to the *N-tert*-butanesulfinyl ketimine **529a**. A panel of solvents was investigated, revealing that hexanes provided the desired

Table 16. Addition of TMSCN to CF_3-Substituted *N-tert*-Butanesulfinyl Ketimines



			hexanes, rt		DMF, −35 °C	
entry	imine	R	dr of **530**:**531**	yield of **530** (%)	dr of **531**:**530**	yield of **531** (%)
1	**529a**	Ph	99:1	85	86:14	72
2	**529b**	4-Me-Ph	92:8	87	88:12	69
3	**529c**	4-MeO-Ph	93:7	89	90:10	78
4	**529d**	4-Cl-Ph	89:11	83	86:14	71
5	**529e**	Me	96:4	69	95:5	71
6	**529f**	Et	88:12	77	91:9	76
7	**529g**	hexyl	93:7	88	92:8	84
8	**529h**	$(CH_2)_2Ph$	88:12	92	94:6	89

adduct **530a** in the highest yield and diastereoselectivity, while the reaction in DMF provided the opposite diastereomer **531a** (entry 1, Table 16). A variety of aromatic and aliphatic derivatives were evaluated (entries 2−8). While the asymmetric Strecker reaction proceeded in high yields for a range of ketimines **529**, the authors noted that *N-tert*-butanesulfinyl ketimines without a CF_3 substituent were not compatible coupling partners under these conditions. Compound **530a** was then hydrolyzed to (*S*)-2-amino-2-phenyl-1,1,1-trifluoropropanoic acid **532** in 80% yield (eq 50).



The stereochemical outcome of this reaction was established by X-ray structural analysis of **530a** and **530e**. Based upon the observed sense of induction, the authors rationalized the solvent dependence of the stereochemical outcome by proposing divergent reaction pathways (Figure 7). In hexanes, a chelated transition state (**533**) 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 **530** 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 (**534**). Under these conditions, the major product **531** has an (R_s,*R*) configuration.

9.2.2. 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

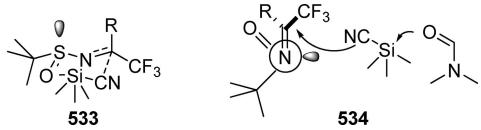
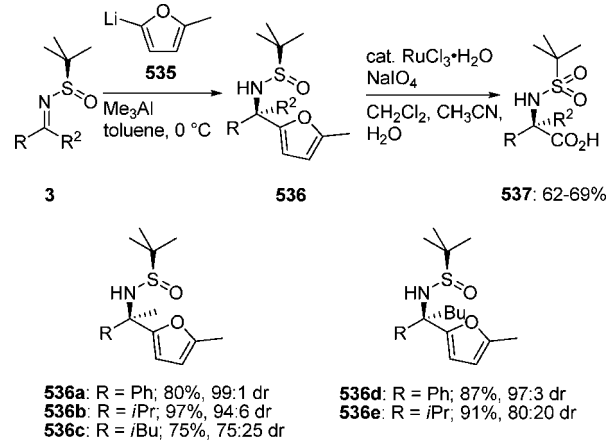
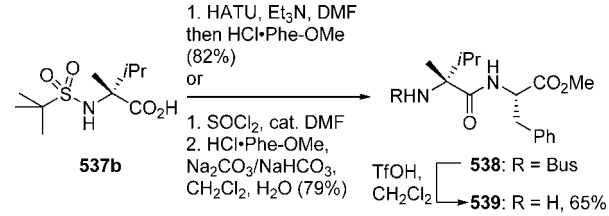


Figure 7. Proposed transition states for the asymmetric Strecker reaction.

Scheme 137. 1,2-Addition of 535 to *N-tert*-Butanesulfinyl Ketimines



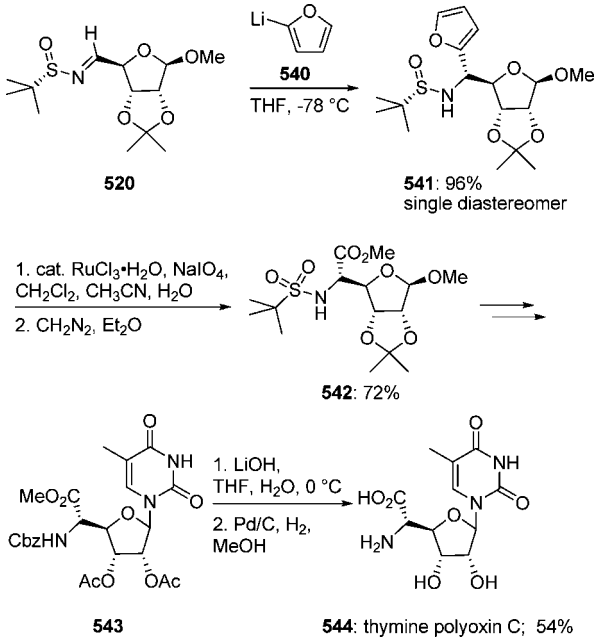
Scheme 138. Use of 537b as a Reagent for Peptide Synthesis



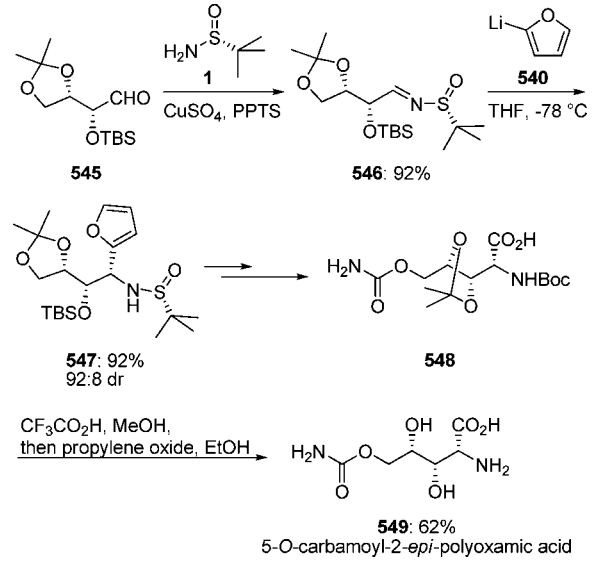
group. Ellman and co-workers first developed this approach for the expedient synthesis of α,α-disubstituted amino acids by the 1,2-addition of 5-methylfuryllithium **535** to *N-tert*-butanesulfinyl ketimines **3** (Scheme 137).[215] The conditions previously optimized for the addition of other organolithium reagents to *N-tert*-butanesulfinyl ketimines were employed ($AlMe_3$, toluene, −78 °C; see section 5.1), 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 **3** was probed, and high yields with moderate to high diastereoselectivities were obtained for α,α-dialkyl and α-aryl-α-alkyl amines **536a**−**e**. Oxidation of the resulting *N-tert*-butanesulfinyl amines **536** to the *N-tert*-butanesulfonyl (Bus)-protected amino acids **537** 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 the application of **537b** as a protected amino acid in peptide synthesis (Scheme 138). The coupling of **537b** 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 **538** using TfOH/CH_2Cl_2 provided the free amine **539** in 65% yield.

Xu and co-workers utilized the nucleophilic addition of 2-lithiofuran **540** to *N-tert*-butanesulfinyl aldimine **520** in their total synthesis of thymine polyoxin C, a core structure of the polyoxin and nikkomycin antibiotics (Scheme 139).[212,216] The reaction proceeded in high yield and provided **541** as a single diastereomer. The absolute configuration of the newly set stereocenter was confirmed by X-ray structural analysis of **541** and was consistent with addition via 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

Scheme 139. Synthesis of Thymine Polyoxin C



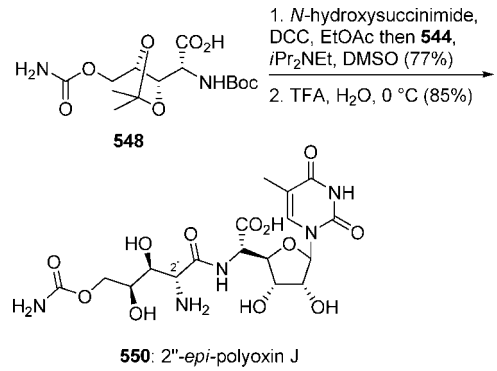
Scheme 140. Synthesis of 5-*O*-Carbamyl-2-*epi*-polyoxamic Acid (549)



to the methyl ester using diazomethane provided **542** in 72% yield over two steps. Further synthetic transformations provided intermediate **543**,[212] which was then globally deprotected, providing thymine polyoxin C (**544**) in reasonable yield over the two-step deprotection sequence.[216]

In order to facilitate the synthesis of polyoxin analogues, Xu and co-workers synthesized 5-*O*-carbamyl-2-*epi*-polyoxamic acid (**549**), a common side chain in many members of the polyoxin family (Scheme 140).[216] A modified procedure for the condensation of (*R*)-*tert*-butanesulfinamide with aldehyde **545** was developed, where addition of 1 equiv of PPTS in the presence of anhydrous copper sulfate provided the desired imine **546** in excellent yield. Subsequent nucleophilic addition of **540** to imine **546** under the previously optimized reaction conditions (*vide supra*) provided **547** in 92% yield and with 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

Scheme 141. Synthesis of 2″-*epi*-Polyoxin J



experimentally confirmed by the inferior diastereoselectivity obtained for addition of **540** to the (*S*)-*N*-*tert*-butanesulfinyl imine diastereomer. Subsequent synthetic transformations provided **548**, which afforded 5-*O*-carbamyl-2-*epi*-polyoxamic acid **549** after facile deprotection.

Xu and co-workers then developed a convergent synthesis of 2″-*epi*-polyoxin J (**550**) via amide bond coupling of the two intermediates prepared via *tert*-butanesulfinamide chemistry, **548** and **544**, followed by deprotection (Scheme 141).[216]

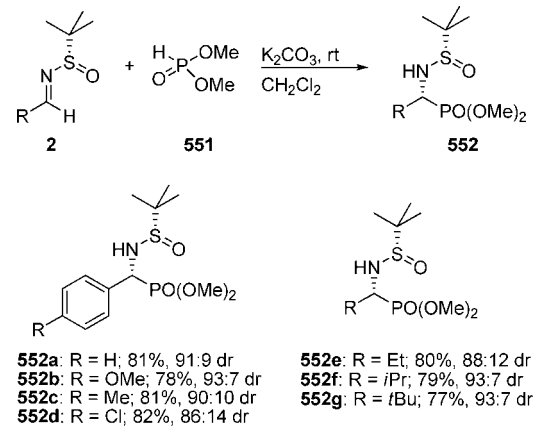
9.3. Synthesis of α-Amino Phosphonic Acids

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.[217]

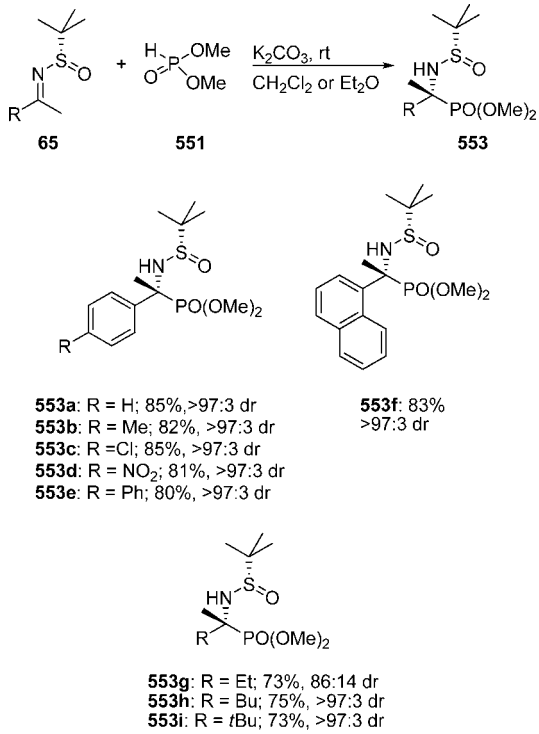
Yuan and Chen reported the first addition of dimethyl phosphite **551** to *N*-*tert*-butanesulfinyl imines **2**, affording α-aminophosphonates **552** (Scheme 142).[218,219] A screen of temperature, solvent, and base with the *N*-*tert*-butanesulfinyl imine derived from benzaldehyde revealed that the best yield and diastereoselectivity for the desired adduct **552a** were 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 *N*-*tert*-butanesulfinyl aryl and alkyl aldimines **2**, generating the *N*-*tert*-butanesulfinyl α-aminophosphonates **525a**−**g** in good yields and with good diastereoselectivities. In each case, the major diastereomer was isolable by column chromatography.

The synthesis of quaternary α-aminophosphonates from *N*-*tert*-butanesulfinyl ketimines **65** was also demonstrated

Scheme 142. Synthesis of *N*-Sulfinyl α-Aminophosphonates from Aldimines

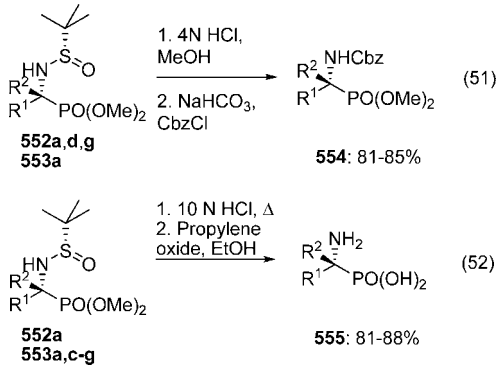


Scheme 143. Synthesis of Quaternary α-Aminophosphonates from *N-tert*-Butanesulfinyl Ketimines



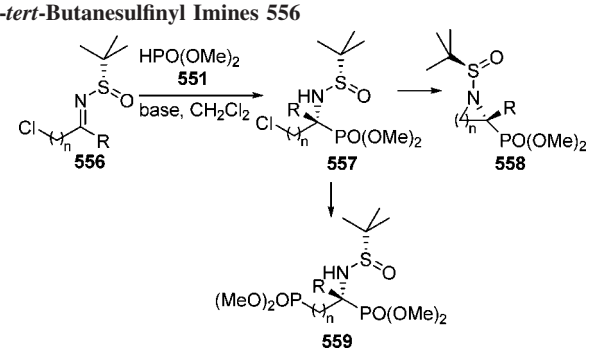
(Scheme 143). Using the reaction conditions optimized for the addition of **551** to *N-tert*-butanesulfinyl aldimines (*vide supra*), a variety of *N-tert*-butanesulfinyl quaternary alkyl and aryl α-aminophosphonates **553a**−**i** were synthesized in good yields (73−85%).[218] The addition of **551** to all of the *N-tert*-butanesulfinyl ketimines **65** surveyed proceeded with >97:3 dr except for the addition to the particularly challenging substrate **65** (R = Et), which gave α-aminophosphonate **553g** in a quite respectable 86:14 diastereomeric ratio.

Nitrogen protecting group manipulation was demonstrated by selective cleavage of the sulfinyl group and replacement with a Cbz group to give products **554** in high yields (eq 51). The free aminophosphonic acids **555** were also obtained by refluxing **552** or **553** in 10 N HCl followed by addition of propylene oxide (eq 52). The absolute configurations of the α-aminophosphonic acids were determined by correlation to known compounds, thus establishing the stereochemical outcome of the addition reaction.



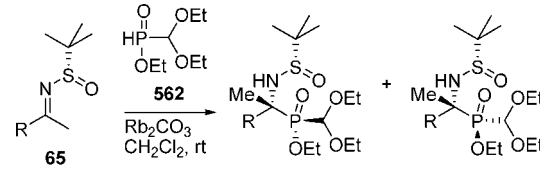
Yuan and co-workers also explored the addition of dimethyl phosphite **551** to chloro-substituted *N-tert*-butanesulfinyl aldimines and ketimines **556**.[220] For these substrates, they found that the product obtained depended on the choice of base

Table 17. Addition of 551 to Chloro-Substituted *N-tert*-Butanesulfinyl Imines 556



entry	*n*	R	base	yield of **557**	yield of **558**	yield of **559**	dr
1	1	Me	K_2CO_3		84		80:20
2	1	Me	KF		75		92:8
3	1	H	K_2CO_3			86	>97:3
4	2	Ph	K_2CO_3		82		89:11
5	2	Ph	Cs_2CO_3			87	61:39
6	3	Me	K_2CO_3	85			93:7
7	3	Ph	Cs_2CO_3		83		71:29

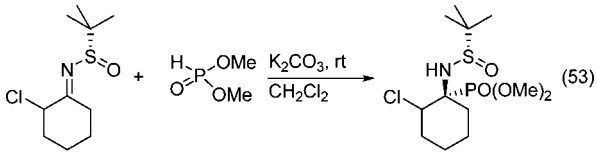
Table 18. Synthesis of α-Amino Phosphinates 563 and 564



entry	R	**563**	yield (%) of **563**	**564**	yield (%) of **564**
1	Ph	**563a**	46	**564a**	50
2	4-Me-Ph	**563b**	37	**564b**	48
3	4-MeO-Ph	**563c**	48	**564c**	50
4	4-CH_3S-Ph	**563d**	37	**564d**	34
5	4-morpholino-Ph	**563e**	29	**564e**	36
6	2-F-Ph	**563f**	37	**564f**	36
7	4-F-Ph	**563g**	43	**564g**	50
8	4-Cl-Ph	**563h**	46	**564h**	48
9	4-Br-Ph	**563i**	41	**564i**	35
10	1-furyl	**563j**	35	**564j**	49
11	1-thienyl	**563k**	45	**564k**	47
12	3-pyridyl	**563l**	50	**564l**	35
13	2-naphthyl	**563m**	43	**564m**	49
14	4-biphenyl	**563n**	49	**564n**	49
15	4-CN-Ph	**563o**	41	**564o**	48
16	4-NO_2-Ph	**563p**	32	**564p**	38
17	hexyl	**563q**	45	**564q**	30

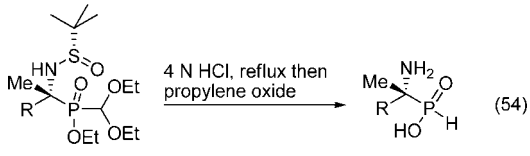
used as well as the structure of the starting *N-tert*-butanesulfinyl imine (Table 17). For the *N-tert*-butanesulfinyl ketimine **556** (R = Me, *n* = 1), the aziridine product (**558**) was obtained in the presence of either K_2CO_3 or KF, but the diastereoselectivity was highest with the latter base (entries 1 and 2). However, when the corresponding aldimine was examined with K_2CO_3 as the base, the 2-phosphoryl-1-aminophosphate **559** was generated with very high diastereoselectivity (entry 3). When the alkyl chain length was increased (*n* = 2), the azetidine product was obtained in the presence of K_2CO_3 (entry 4), but Cs_2CO_3 promoted the formation of the diphosphonate **558**, albeit with poor selectivity (entry 5). Further extension of the alkyl side chain to *n* = 3 on the *N-tert*-butanesulfinyl chloroalkyl methyl ketimine **556** (R = Me) provided the 4-chloro-1-methyl-1-aminophosphonate **557** when K_2CO_3 was employed (entry 6) whereas cylization to the pyrrolidine **558** occurred for the

N-tert-butanesulfinyl chloroalkyl phenyl ketimine **556** (R = Ph) when Cs_2CO_3 was used as the base (entry 7). The reaction conditions were also applied to the addition of **551** to cyclic *N-tert*-butanesulfinyl ketimine **560**, providing **561** in good yield and with moderate diastereoselectivity (eq 53). While not rigorously determined, the absolute configurations of products **557**, **558**, or **559** were predicted by analogy to the previous study conducted by Yuan and Chen on the addition of **551** to *N-tert*-butanesulfinyl aldimines and ketimines (*vide supra*).



560 **551** **561**: 78% 86:14 dr

Yuan and Zhang have also reported the synthesis of α-amino phosphinates (**563** and **564**) via the addition of ethyl diethoxymethyl phosphinate **562** to *N-tert*-butanesulfinyl imines **65** (Table 18).[221] Based on their previous conditions for the addition of dimethyl phosphite to *N-tert*-butanesulfinyl ketimines (*vide supra*), 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 addition of **562** to several aryl, heteroaryl, and alkyl ketimines (entries 1−17). The products were obtained as a mixture of phosphorus stereoisomers **563** and **564**, which were separable by column chromatography. A crystal structure of each isomer was obtained, revealing that **563** with S_P stereochemistry and **564** with R_P stereochemistry both displayed *R* stereochemistry at the newly formed stereogenic carbon center. High imine diastereofacial selectivity was observed, as demonstrated by single peaks in each ^{31}P NMR for **563a**−**q** and **564a**−**q** and by chiral HPLC analysis of selected oxidized derivatives. The free α-amino-H-phosphinic acids **565** were obtained by refluxing **563** or **564** with 4 N HCl (eq 54). 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.

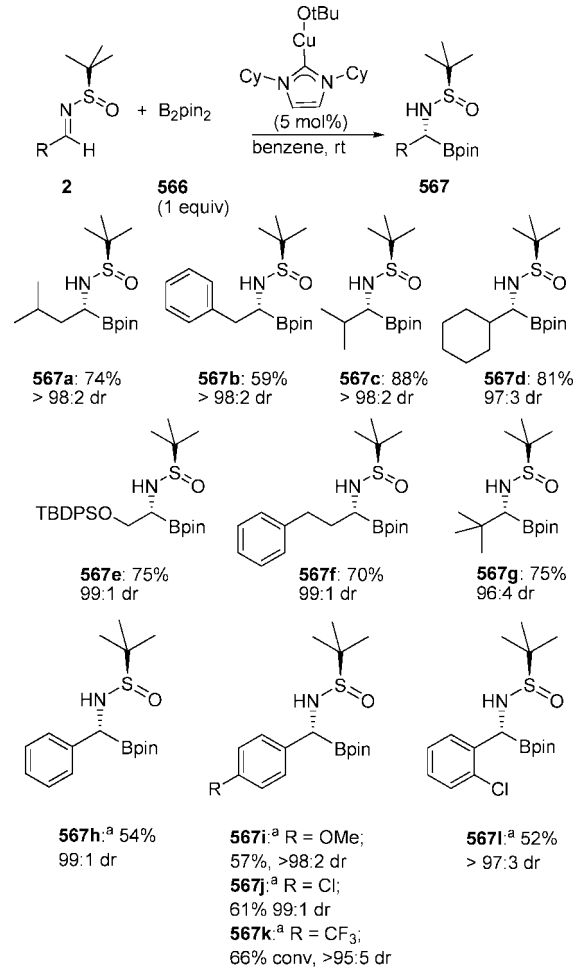


563 or **564** **565**: 61-94% >95% ee

9.4. 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.[222] Ellman and co-workers have recently developed a method for the copper-catalyzed addition of bis(pinacolato)-diboron **566** to *N-tert*-butanesulfinyl aldimines **2** for the synthesis of α-aminoboronate esters **567** (Scheme 144).[223] The optimal catalyst for this transformation was (1,3-dicyclohexylimidazol-2-ylident)copper(I) *tert*-butoxide, which was developed by Sadighi and co-workers[224] for the addition of bis(pinacolato)diboron across aromatic and aliphatic

Scheme 144. Synthesis of Functionalized α-Amino Boronate Esters



[a] Reactions carried out with 2 equiv of **566**, 10 mol % catalyst, toluene, 0 °C.

aldehydes. Additions to unbranched and branched aliphatic aldimines proceeded in good yields and with high diastereoselectivites (**567a**−**g**). Aryl aldimines could also be used, 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 an excess of **566** was used (**567h**−**j**). 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. Sulfinyl deprotection of adduct **567a** provided amine hydrochloride **568,** and subsequent peptide coupling reactions afforded bortezomib (**469**) in 41% yield from **568** (Scheme 145).

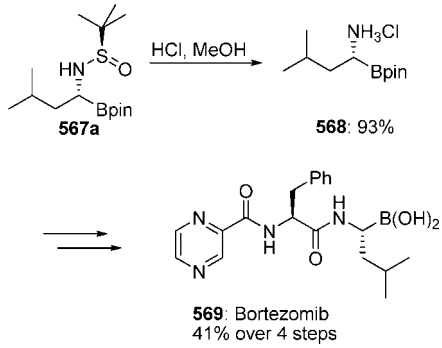
10. Synthesis of β-Amino Acid Derivatives

10.1. Synthesis of β-Amino Esters

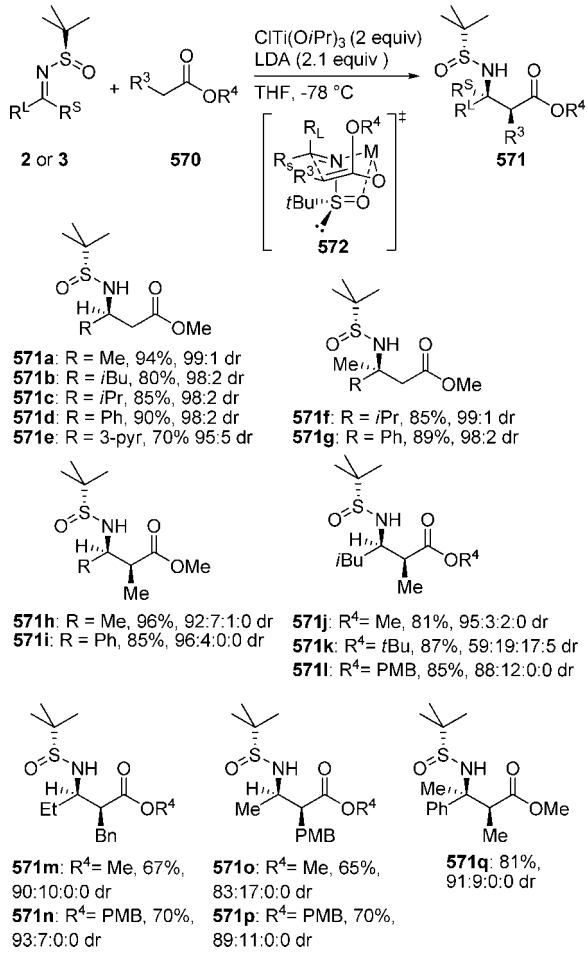
10.1.1. Methods for 1,2-Addition of Ester Enolates to N-tert-Butanesulfinyl Imines

The asymmetric synthesis of β-amino acids via enolate addition to *N-tert*-butanesulfinyl imines was first evaluated by Ellman and Tang in 1999[225,226] and was later expanded in a full report.[227] Optimization of the reaction conditions revealed that the highest yields and diastereoselectivities were

Scheme 145. Synthesis of Bortezomib

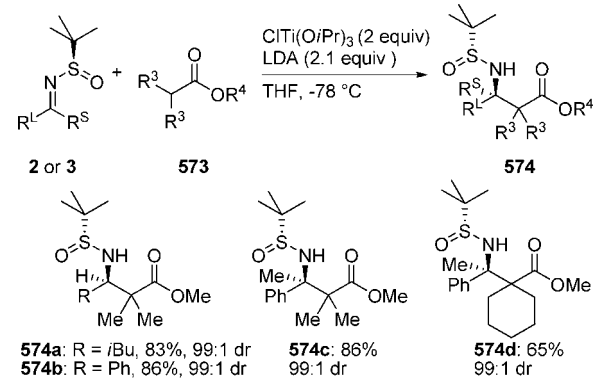


Scheme 146. Additions of Titanium Enolates to *N-tert*-Butanesulfinyl Imines



obtained with titanium enolates, which were prepared by transmetalation of a lithium enolate with $ClTi(OiPr)_3$ at low temperature in THF. Diastereoselectivities were further improved by increasing the $ClTi(OiPr)_3$ stoichiometry from 1 to 2 equiv. Under these optimized conditions, additions of the titanium enolate of methyl acetate **570** to a wide variety of *N-tert*-butanesulfinyl aldimines **2** were explored, providing products **571a**−**e** in 70−94% yield and with ≥95:5 dr (Scheme 146). Enolate additions to *N-tert*-butanesulfinyl ketimines **3** were also conducted, and **571f** and **g** were synthesized in 85% and 89% yields and with 99:1 and 98:2 diastereomeric ratios, respectively. This constitutes one of the few available methods for the preparation of β,β-disubstituted β-amino acids. The scope with respect to the enolate coupling partner was also explored. α-Substituted *N-tert*-butanesulfinyl-β-amino esters **571h**−**p** were produced with aryl or alkyl

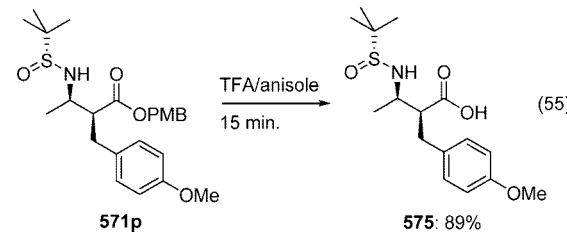
Scheme 147. Synthesis of α,α,*β*-Trisubstituted and α,α,*β*,*β*-Tetrasubstituted *β*-Amino Esters



substituents at the β-position and alkyl or benzyl groups at the α-position and various ester protecting groups. The synthesis of an α,β,β-*N-tert*-butanesulfinyl β-amino ester **571q** was also demonstrated. In addition, alternative ester protecting groups were evaluated. While the use of an acid labile *tert*-butyl ester provided low stereoselectivity (**571k**), the comparably acid labile *p*-methoxybenzyl (PMB) ester provided selectivity similar to that observed for the methyl ester (**571l**, **n**, and **p**). α,α-Disubstitutions on the enolates **573** were also competent with both *N-tert*-butanesulfinyl aldimines and ketimines as electrophiles to provide tri- and even tetrasubstituted β-amino acid products (**574a**−**d**, Scheme 147).

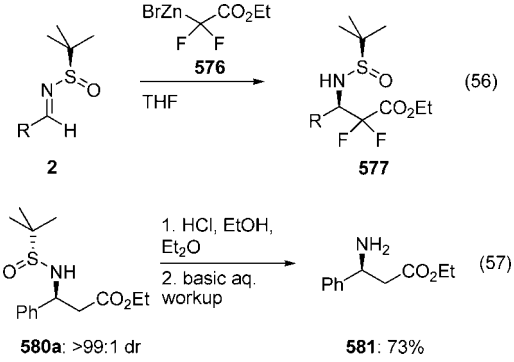
The absolute configurations of **571a**, **e**, **g**, **h**, and **j** were determined by chemical correlation. The absolute configuration of **571m** was determined by X-ray structural analysis, and the absolute configurations of other α-substituted β-amino acid derivatives were assigned by analogy. The observed diastereoselectivity was rationalized by the chelated transition state **572**. In this transition state the predominating *E*-isomer of the starting *N-tert*-butanesulfinyl imine serves to define the relative stereochemistry of the β-substituents of the product.

Selective acidic cleavage of the PMB-ester protecting group in the presence of an *N-tert*-butanesulfinyl group was also demonstrated by treatment of substrate **571p** with TFA/anisole to afford the free carboxylic acid **575** in 89% yield with minimal (<5%) cleavage of the *tert*-butanesulfinyl group (eq 55). This use of the PMB protecting group is of practical importance for the preparation of α-substituted β-amino acids because considerable epimerization at the α-stereocenter is known to occur under the basic conditions required for saponification of α-substituted β-amino esters.[228]

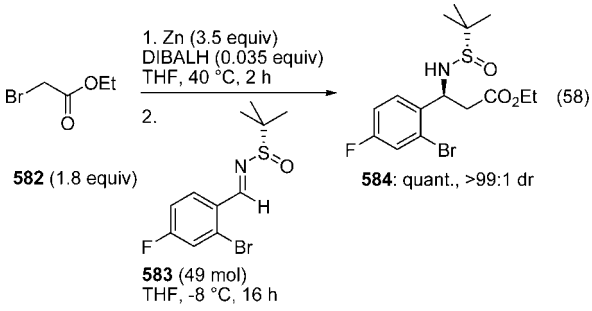


The first example of an addition of Reformatsky reagent to *N-tert*-butanesulfinyl imines was achieved by Staas and co-workers at Merck in their synthesis of α,α-difluoro β-amino esters **577** (eq 56; for details, see section 15.4).[229] More recently, the Reformatsky addition of unsubstituted acetate enolates to *N-tert*-butanesulfinyl aldimines **2** and ketimines **3** has been developed by Brinner and co-workers at Novartis (Scheme 148).[230,231] Notably, this reaction is conducted at

convenient temperatures (0 °C or rt versus −78 °C for titanium enolate additions) and is amenable to large scale synthesis (*vide infra*). Reactions using the Reformatsky reagent **578** derived from ethyl bromoacetate (R^3 = Et) were conducted at 0 °C to prevent Claisen condensation with the resulting β-amino ester products. Under these conditions, **580a**−**c** were generated in good yields (75−97%) and with excellent diastereoselectivities (94:6 to >99:1). When *tert*-butyl bromozinc acetate was employed, self-condensation was suppressed and the reaction could be performed at room temperature, providing **580d** and **e** in comparable yields and diastereoselectivities. The Reformatsky reaction was also applied to *N-tert*-butanesulfinyl ketimines **3**, providing quaternary substituted β-amino esters **580f**−**h** in good yields and with high diastereoselectivities. The absolute configuration was determined by chemical correlation experiments and is consistent with the cyclic transition state **579**. Removal of the sulfinyl group to convert crude **580a** to **581** was also demonstrated (eq 57).

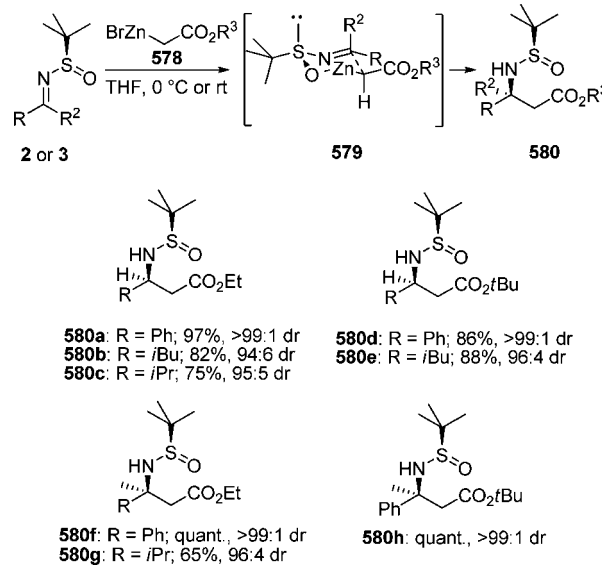


Girgis, Prasad, and co-workers at Novartis recently reported the optimization of this Reformatsky reaction for use on the pilot-plant scale (eq 58).[232] In paticular, reaction calorimetry experiments were utilized to determine an optimal method for activation of the zinc in the formation of the Reformatsky reagent. Activation of the zinc using DIBALH is carried out in the presence of a small amount of the starting bromoester **582**, followed by slow addition of the remainder of the bromoester while maintaining the reaction temperature at 40 °C. The imine **583** is slowly added to this preformed reagent at −10 °C. After quenching and an extractive reaction workup, the desired product **584** is obtained as a 22% MTBE solution in >99% yield, and with >95% purity and >99:1 dr, as determined by HPLC analysis, and is used without further purification in the next step of the synthetic sequence. Six batches of the process shown in eq 58 were performed on pilot plant scale (15 kg of **583** per batch) as part of a development effort.

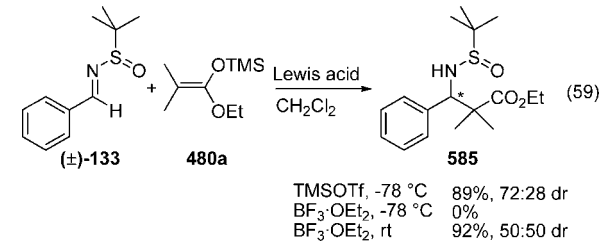


The addition of silyl ketene acetal **480a** to *N-tert*-butanesulfinyl imine **133** was explored by Skrydstrup and

Scheme 148. Reformatsky Reaction with *N-tert*-Butanesulfinyl Imines

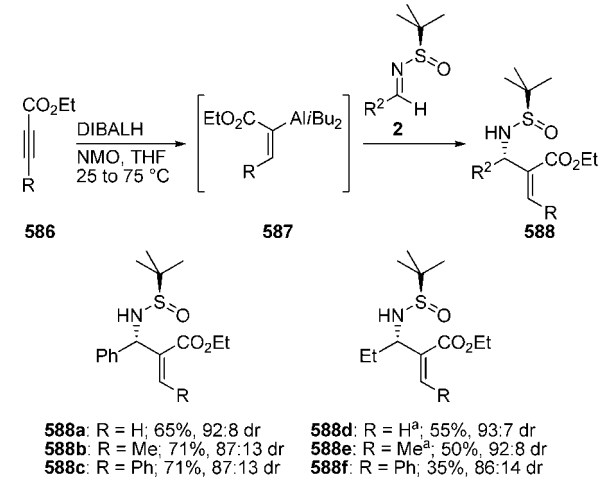


Jacobsen (eq 59).[196] Unfortunately, low stereoselectivity was observed for this reaction. Better results were obtained when the same silyl ketene acetal was added to an *N-tert*-butanesulfinyl imino ester, allowing synthesis of aspartic acid derivatives (see section 9.1).



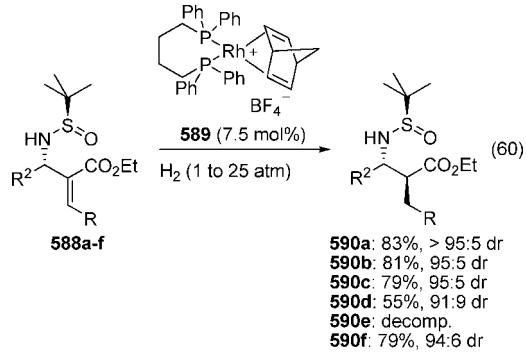
Davis and co-workers reported the synthesis of α-substituted β-amino esters via the addition of vinylaluminum reagent **587** to *N-tert*-butanesulfinyl aldimines (Scheme 149).[233] The vinylaluminum reagents were prepared from DIBALH, 4-morpholine *N*-oxide (NMO), and α-acetylenic esters **586**. Preliminary studies had focused on the use of

Scheme 149. Addition of Vinylaluminum Reagents to *N-tert*-Butanesulfinyl Imines



[a] Inseparable mixture of diastereomers.

N-*p*-toluenesulfinyl imines as the electrophile, but higher diastereoselectivities were obtained when the analogous *N*-*tert*-butanesulfinyl imines were employed, and the scope of the reaction was assessed with the latter nitrogen protecting group. The vinylaluminum reagent **587** (R = H) was evaluated, and moderate yields and high diastereoselectivities were observed for products **588a** and **d**. Additions of β-substituted vinylaluminum reagents to *N*-*tert*-butanesulfinyl aryl (R^2 = Ph) or alkyl (R^2 = Et) aldimines provided adducts **588b**, **c**, **e**, and **f** with moderate to good diastereoselectivities. Isolation of the major diastereomer was achieved in most cases by column chromatography. The absolute configuration of **588a** was determined by chemical correlation experiments and was consistent with addition via an open transition state. The *Z* olefin geometry was established by NOE experiments. Hydrogenation of the alkene moiety was accomplished in the presence of a catalytic amount of the cationic rhodium complex **589**, providing *anti*-α-substituted *N*-*tert*-butanesulfinyl β-amino esters **590a**−**d** and **f** (eq 60). However, hydrogenation of **589e** provided β-amino ester **590e** as a mixture of diastereomers and starting material, and prolonged exposure to the reaction conditions resulted in decomposition.



Grigg and co-workers developed a method for the synthesis of β-amino acid derivatives via a Pd- and In-mediated allylation of 2-pyridyl *N*-*tert*-butanesulfinyl imine **142** (Scheme 150).[234] Addition of both copper iodide and ascorbic acid was necessary, and the yields of the desired products were

Scheme 150. Synthesis of Chiral β-Amino Acid Derivatives via a Pd/In Transmetalation Cascade Reaction

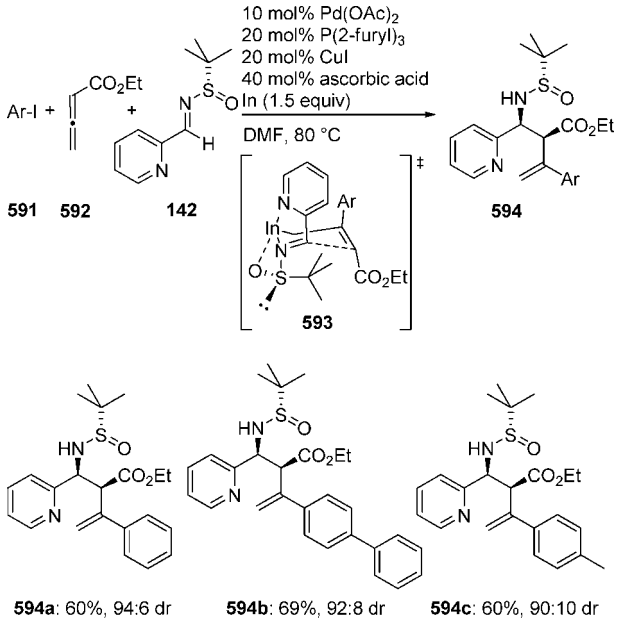
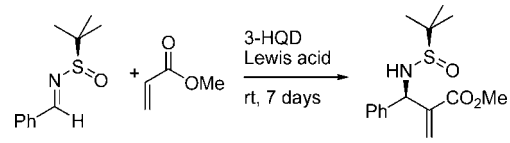


Table 19. Baylis−Hillman Reaction with *N*-*tert*-Butanesulfinyl Imine 133



entry	Lewis acid	yield (%)	dr
1	none	8	88:12
2	$La(OTf)_3$	12	96:4
3	$Zn(OTf)_2$	27	89:11
4	$Sc(OTf)_3$	10	92:8
5	$Yb(OTf)_3$	10	91:9
6	$In(OTf)_3$	17	82:18

depressed in the absence of these components. The authors propose that the copper iodide promotes formation of InI, facilitating transfer of indium from the solid to the solution phase. The role of ascorbic acid is unclear, but it is suggested that it could help to recycle unproductive higher valence states of Pd, Cu, or In. Three aryl iodides **591** were examined for the cascade reaction with functionalized allene **592** and imine **142**, providing **594a**−**c** in moderate yields and with good diastereoselectivities (≥90:10). The absolute stereochemistry of the major diastereomer of **594b** was determined by X-ray structural analysis and is consistent with the proposed chelated transition state **593**.

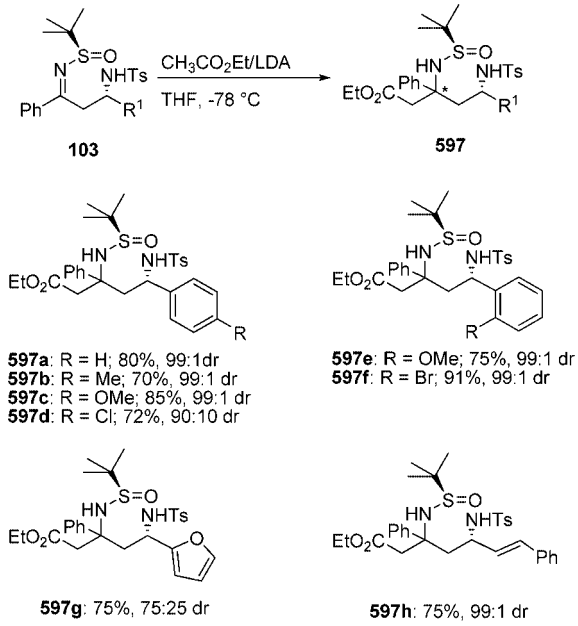
A Baylis−Hillman reaction using stoichiometric 3-hydroxyquinuclidine (3-HQD) between methyl acrylate (**595**) and *N*-*tert*-butanesulfinyl imine **133** was reported by Aggarwal and co-workers (Table 19).[235] In the absence of Lewis acid, only 8% yield of the desired product **596** was obtained (entry 1). Addition of several Lewis acids in catalytic amounts (5 mol %) provided only modest improvement in conversion, despite the prolonged reaction time (entries 2−6). While the diastereoselectivity for this reaction was higher when the *tert*-butanesulfinyl group was used (up to 96:4 dr), acceptable yields of the desired product were only obtained with *p*-toluenesulfinyl imines.

Wang, Chen, and co-workers demonstrated the addition of the enolate derived from ethyl acetate and LDA to β-amino imines **103** (Scheme 151; for synthesis of these imines, see section 3.2.3).[90] In most cases, products **597** were obtained with high diastereoselectivity. Unfortunately, the configuration of the newly formed stereocenter was not determined.

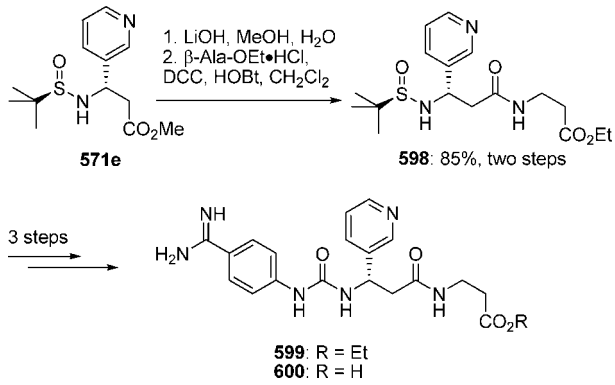
10.1.2. Synthetic Applications of Ester Enolate Additions to N-tert-Butanesulfinyl Imines

Ellman and Tang applied *N*-*tert*-butanesulfinyl β-amino ester **571e** to the formal synthesis of **600** which had been patented by Monsanto Co. (St. Louis)[236] as a GPIIbIIIa antagonist (Scheme 152).[225] Hydrolyis of the methyl ester of enantiomerically pure **571e** with LiOH followed by coupling the resulting free β-amino acid to β-alanine ethyl ester under standard peptide coupling conditions proceeded in 85% overall yield for the two-step process. These transformations demonstrate that the *N*-sulfinyl group is an effective protecting group for both β-amino acid saponification and amide bond coupling. Subsequent removal of the *tert*-butanesulfinyl group under acidic conditions, and introduction of the urea and amidine provided **599**, constituting the formal synthesis of **600**.

Scheme 151. Enolate Additions to β-Amino Imines



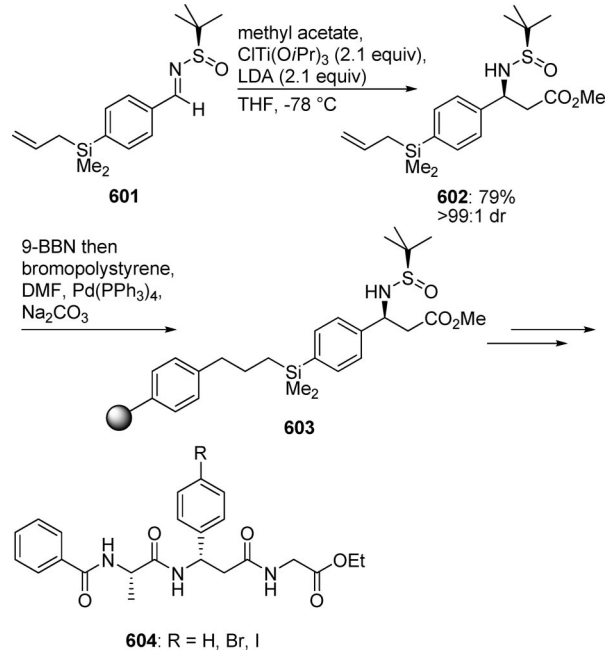
Scheme 152. Formal Synthesis of the GPIIbIIIA Antagonist 600



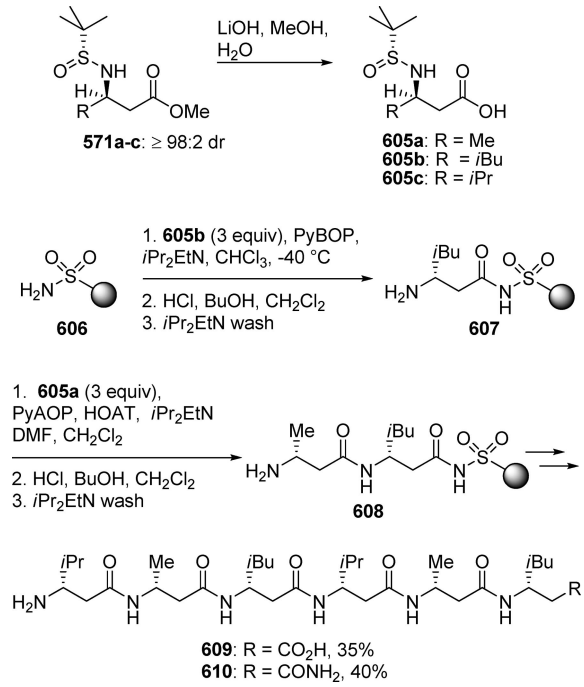
Silverman and Lee demonstrated that the addition of an enolate to the aromatic *N-tert*-butanesulfinyl aldimine **601** could be used in a traceless solid-phase synthesis of β-amino acid-containing peptides (Scheme 153).[237] Following the conditions reported by Tang and Ellman,[225] β-amino ester **602** was generated in 79% yield. The high diastereoselectivity of this transformation was confirmed by conversion of **602** to its Mosher amide, revealing a 99:1 diastereomeric ratio. Hydroboration of the terminal olefin followed by Suzuki coupling of the resulting borane compound with bromopolystyrene resin provided the support-bound β-amino ester derivative **603**. Compound **603** was further transformed to several β-amino acid containing tripeptide analogues, which upon cleavage from the polymer support with either TFA, Br_2, or ICl replaced the silyl support linkage with a hydrogen, bromide, or iodide, respectively.

In complementary work, Ellman and Tang also demonstrated the utility of the *N-tert*-butanesulfinyl-β-amino acids **571** as appropriately protected building blocks for the solid-phase synthesis of β-peptides such as **609**, known to adopt a helical conformation, and the corresponding amide **610** (Scheme 154).[227] β-Amino esters **571a−c** were first hydrolyzed to the corresponding β-amino acids **605a−c**. The unpurified saponification product **605b** was loaded onto 4-sulfamylbutyryl resin **606**.[238] Removal of the sulfinyl group, followed by washing with *i*Pr_2NEt, yielded the support-bound

Scheme 153. Solid Support Synthesis of Peptides Containing a β-Amino Acid



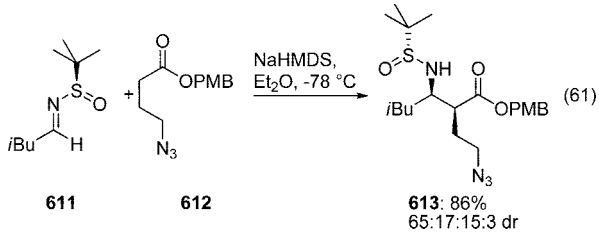
Scheme 154. Solid-Phase Synthesis of β-Peptides



amine **607**, which was next coupled with β-amino acid **605a**, yielding **608** after deprotection and neutralization. Subsequent introduction of the other residues, cleavage of the *N*-terminal *tert*-butanesulfinyl group, and removal from the polymer support yielded the desired foldamer peptides **609** and **610** in 35% and 40% overall yields, respectively.

Ellman and Tang also devised a synthesis of the α,β-disubstituted-β-amino ester **613** containing an azide as a masked primary amine functional group (eq 61). The standard reaction conditions for the addition of titanium enolates to *N-tert*-butanesulfinyl imines (*vide supra*) resulted in decomposition due to the presence of the azide functional group. However, formation of the sodium enolate of **612** followed by addition to imine **611** provided **613** in 86% yield

and 65:17:15:3 diastereomeric ratio. While the reaction proceeded with only modest selectivity, diastereomerically pure material was isolated by preparative HPLC. A method for the synthesis of constrained β-substituted-β-amino acids was also achieved (Scheme 155). Although the addition of the titanium enolate of **614** to imine **611** yielded **615** with poor diastereoselectivity, removal of the silyl protecting group and Mitsunobu cyclization to **617** proceeded in good yields.



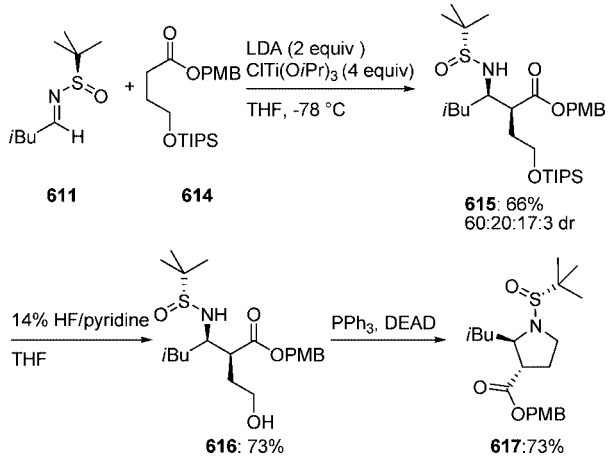
611 **612** **613**: 86%
65:17:15:3 dr

The incorporation of a β-amino acid into a phosphotyrosine mimetic was demonstrated by Burke and co-workers. Titanium enolate addition to *N-tert*-butanesulfinyl imine **618** provided the *N-tert*-butanesulfinyl protected β-amino phosphonomethyl-phenylalanine analogue **619** in 83% yield and >95:5 dr (Scheme 156).[239] Compound **619** was then successfully incorporated into the model tripeptide **620** and macrocyclic compound **621**, which were designed as β-amino phosphotyrosyl mimetics based upon scaffolds that had been previously shown to function as Grb2 SH2 domain-binding ligands.[240]

Ganesan and co-workers employed a titanium enolate addition of **623** to the β,γ-unsaturated *N-tert*-butanesulfinyl imine **622** in order to install the β-amino ester moiety in their total syntheses of the marine natural products azumamides A and E (Scheme 157).[241] The desired adduct **624** was obtained in a moderate 52% yield and then was converted to **625** by selective removal of the PMB-group followed by coupling with D-Val-D-Ala-OAll. Cleavage of the sulfinyl group followed by coupling with Boc-D-Phe provided intermediate **626** in 53% yield. Subsequent synthetic transformations and macrolactamization generated azumamide E (**627**). Azumamide E was converted to azumamide A (**628**) in one step via an EDC promoted amide bond formation reaction, completing the synthesis in 15 steps for the longest linear sequence.

Based on the success of the dipeptidyl peptidase IV (DPP-4) inhibitor Januvia used for the treatment of diabetes, Merck

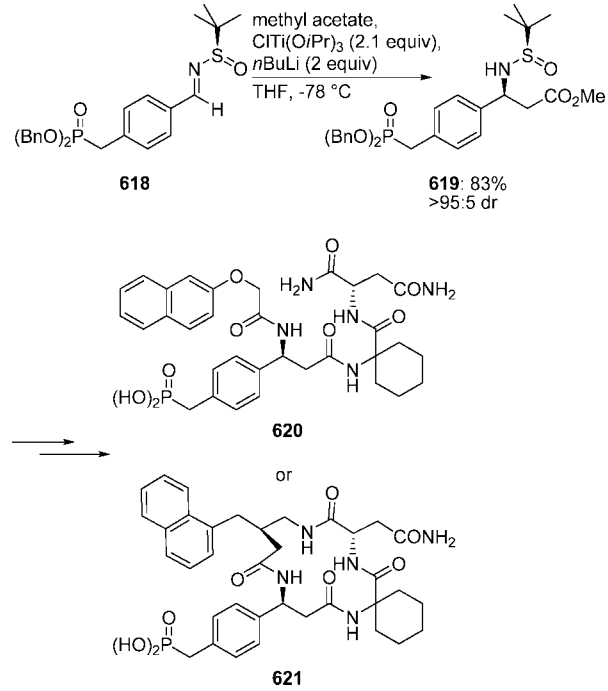
Scheme 155. Synthesis of Cyclic β-Amino Ester 617



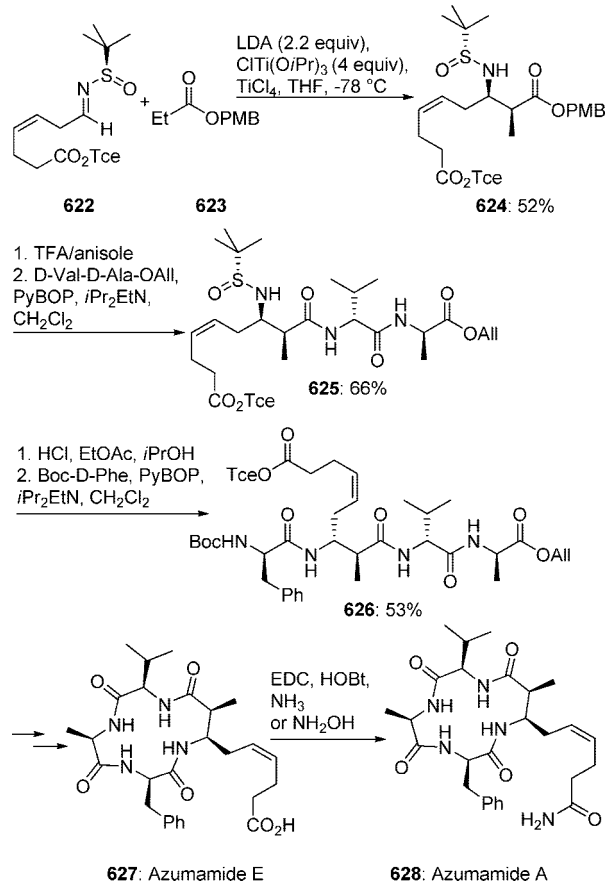
611 **614** **615**: 66%
60:20:17:3 dr

616: 73% **617**:73%

Scheme 156. Synthesis of β-Amino Phosphotyrosyl Mimetic

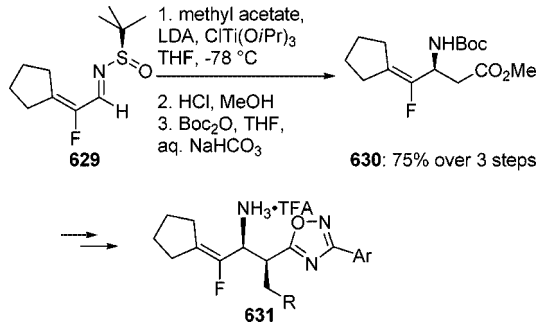


Scheme 157. Total Syntheses of Azumamides A and E

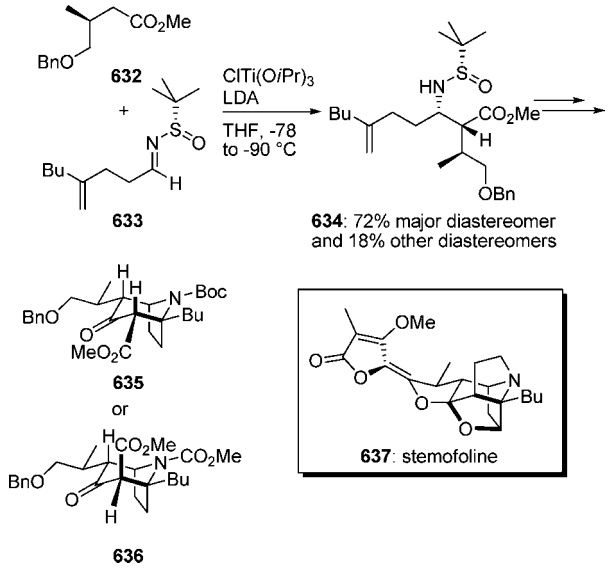


& Co. Inc. evaluated other classes of DPP-4 inhibitors. Toward this goal, a series of DPP-4 inhibitors incorporating a fluoroolefin were synthesized by Edmondson and coworkers.[242] The embedded β-amino acid was generated by the addition of the titanium enolate of methyl acetate to the *N-tert*-butanesulfinyl aldimine **629** bearing the fluoroolefin amide isostere (Scheme 158). Removal of the sulfinyl group

Scheme 158. Synthesis of Fluoroolefin DPP-4 Inhibitors



Scheme 159. Approach to the Asymmetric Synthesis of Stemofoline via Enolate Addition to 633

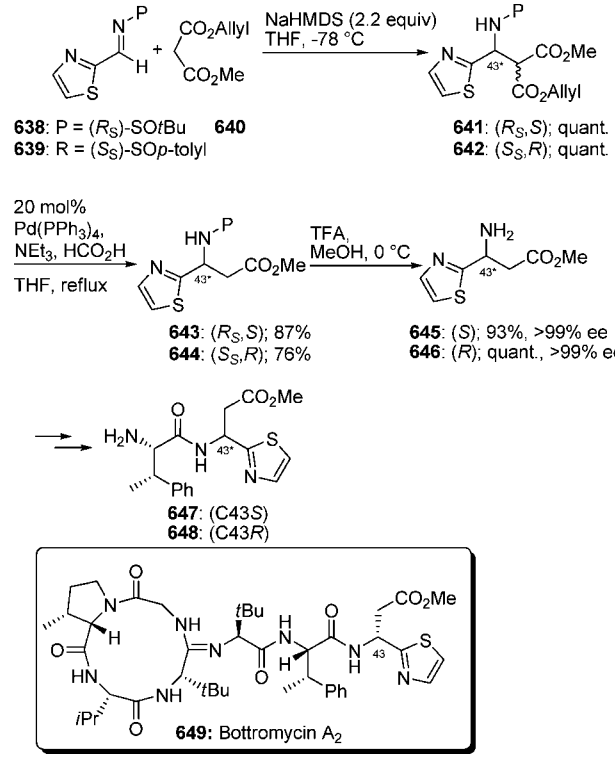


and introduction of the carbamate protecting group provided **630** in 75% yield over three steps. The β-amino ester **630** was converted to a series of oxadiazoles **631**, which were evaluated for their potency against DPP-4.

An enolate addition to *N-tert*-butanesulfinyl imine **632** was employed by Thomas and Vickers to install the requisite β-amino ester in **634**, an intermediate in their approach to the asymmetric synthesis of the alkaloid stemofoline (**637**) (Scheme 159).[243] For this transformation both the imine **633** and the enolate **632** were chiral, and although experiments were not conducted to identify the matched or mismatched scenarios under the reaction conditions employed (ClTi(O*i*Pr)$_4$, LDA, THF), the desired diastereomer **634** was obtained as the major product in 72% yield along with 18% yield of undesired diastereomers. Diastereomerically pure **634** was obtained after column chromatography, and the absolute stereochemistry was determined by X-ray structural analysis of a more advanced intermediate and was consistent with the chelated transition state proposed by Ellman and co-workers (see **572**, Scheme 146). Further synthetic transformations provided either tropinone **635** or **636**, potentially useful intermediates for the synthesis of this complex natural product.

The first total synthesis of bottromycin A$_2$, an antibiotic natural product, was reported in 2009 by Omura, Sunazuka, and co-workers (Scheme 160).[244] In order to complete the synthesis of the natural product, it was necessary to determine the configuration of the C43 stereocenter. Therefore, stereoselective syntheses of both enantiomers, **645** and **646**, were

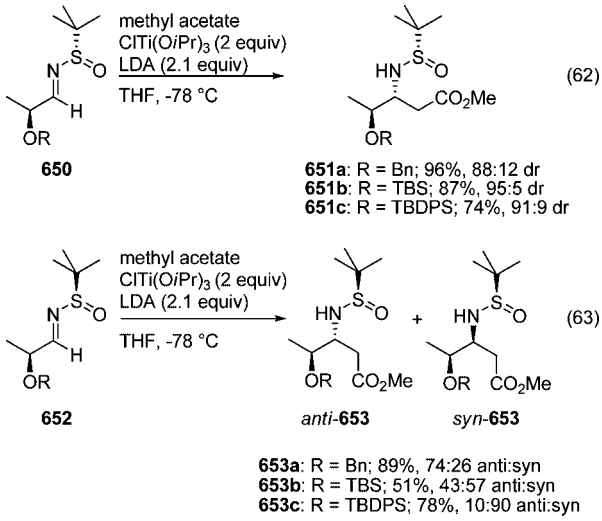
Scheme 160. Synthesis of 647 and 648 for Determination of Configuration at C43 of Bottromycin A$_2$



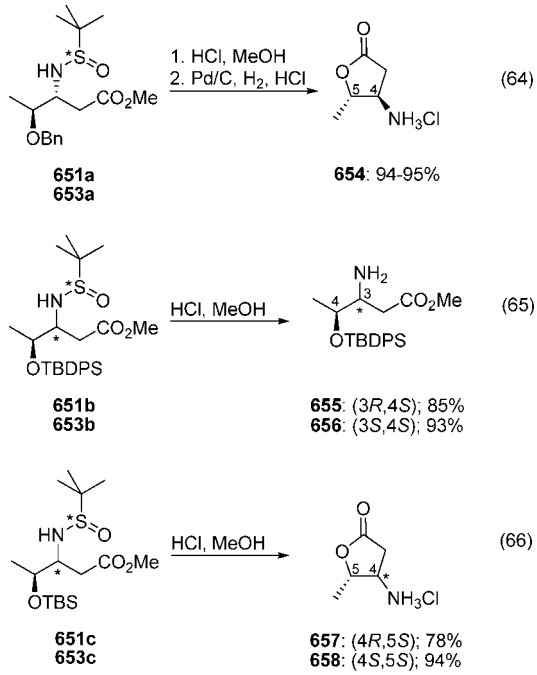
devised. An enolate addition of allyl methyl malonate **640** to *N-tert*-butanesulfinyl imine **638** provided the β-amino ester adduct **641** in quantitative yield. Palladium-catalyzed decarboxylation afforded **643**, and deprotection of the sulfinyl group yielded **645**, which was enantiomerically pure by HPLC analysis. Further manipulation provided the (C43*S*) derivative **647**. The (C43*R*) diastereomer **648** was synthesized following the same route, but starting with the *p*-toluenesulfinyl imine **639** with (*S*) configuration. Comparison by ^{1}H NMR of both **647** and **648** with a sample of natural material confirmed that the C43 stereocenter had an *R* configuration.

10.1.3. 1,2-Additions of Ester Enolates to α-Alkoxy N-tert-Butanesulfinyl Imines

Ellman and Evans further developed the addition of enolates to *N-tert*-butanesulfinyl imines to include α-alkoxy aldimines as effective substrates (eqs 62 and 63).[64] Previous optimization studies had revealed that the highest yields and diastereoselectivities were obtained with titanium enolates, which were prepared by transmetalation of a lithium enolate with ClTi(O*i*Pr)$_3$ at low temperature in THF (see section 10.1.1). Using these conditions, additions to imines **650a**−**c** proceeded in good yields and with high diastereoselectivities (eq 62). For these imine coupling partners, the observed *anti*-stereoselectivity was consistent with previous observations for enolate additions to α-alkoxy aldehydes[245] as well as the addition of titanium enolates to *N-tert*-butanesulfinyl aldimines.[227] However, for the titanium enolate additions to imines **652**, the inherent selectivity imposed by the *tert*-butanesulfinyl group is opposite to the selectivity provided by the α-alkoxy group, as predicted by the Felkin−Ahn and Conforth models, resulting in lowered *anti*-selectivities for **653a** and poor to good *syn*-selectivities for **653b** and **c** (eq 63).



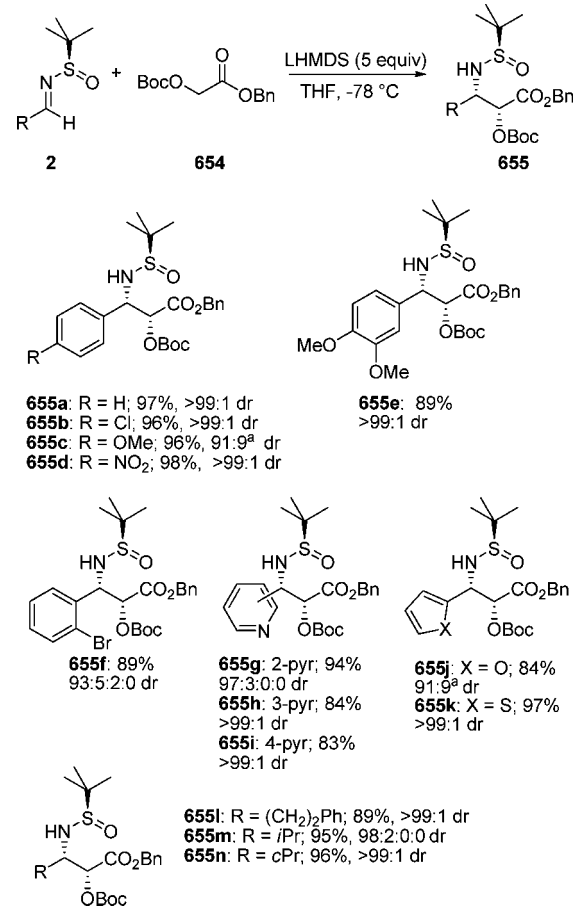
Adducts **651a** and **653a** were further converted to lactone **654** in 94−95% yield by acidic removal of the sulfinyl group followed by hydrogenolysis (eq 64). Concomitant removal of the sulfinyl and TBDPS groups of **651b** and **653b** could not be achieved, but selective cleavage of the sulfinyl group was demonstrated under acidic conditions (eq 65). However, removal of both protecting groups in addition products **651c** and **651c** was achieved, resulting in a direct synthesis of lactones **657** and **658** in 78% and 94% yields, respectively (eq 66). Later, this methodology was extended to the addition of *O*-protected α-hydroxyacetates to α-alkoxy *N-tert*-butanesulfinyl imines (see section 10.1.4).[246]



10.1.4. 1,2-Additions of α-Heteroatom Ester Enolates to N-tert-Butanesulfinyl Imines

The first example of the addition of an α-alkoxy enolate to an *N-tert*-butanesulfinyl aldimine was reported by Qin and co-workers in their studies on the synthesis of *N*-protected isoserine esters **655** (Scheme 161)[247] as side chain analogues for the anticancer drug paclitaxel (Figure 8). Optimization of the reaction conditions revealed that the highest yields and diastereoselectivites for the desired adducts **655** were

Scheme 161. Diastereoselective Additions of 654 to *N-tert*-Butanesulfinyl Imines



[a] The other isomers were isolated as an inseparable mixture contaminated with byproducts.

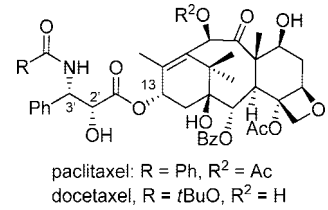
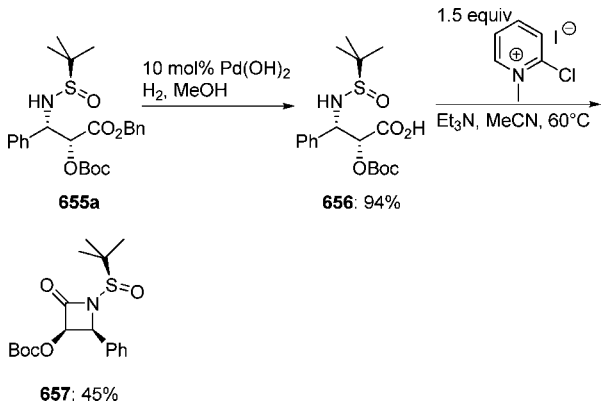


Figure 8. Structures of Paclitaxel and Docetaxel.

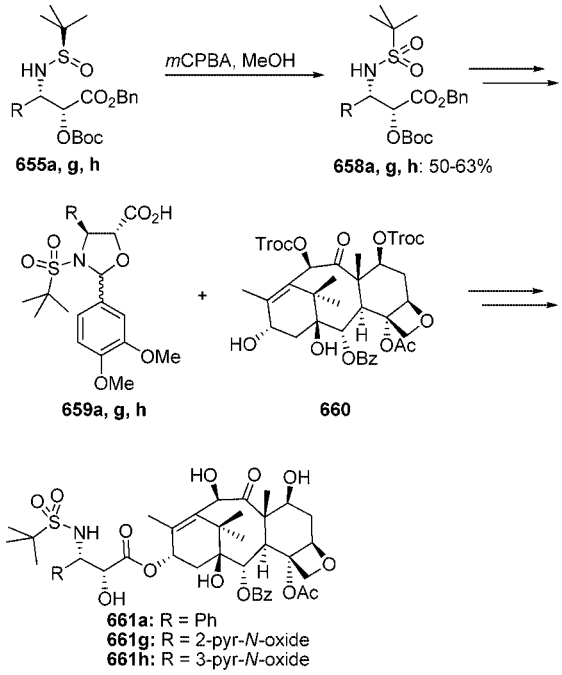
obtained when the reaction was conducted at −78 °C in THF with *tert*-butyloxycarbonyl (Boc) protected α-hydroxy acetate **654** as the nucleophile and LHMDS as the base. Additions to aromatic and heteroaromatic *N-tert*-butanesulfinyl imines bearing a variety of electronically diverse substituents provided **655a**−**k** in very high yields (83−98%) and with excellent diastereoselectivities. Several alkyl imines were also employed, providing the desired adducts **655l**−**n** in excellent yields and diastereoselectivities. While **655c** and **j** were obtained as inseparable mixtures of isomers, compounds **655d**, **f**, and **m** could be isolated in diastereomerically pure form by silica gel chromatography. The absolute configuration of **655a** was determined by X-ray structural analysis.

Subsequent synthetic transformations were performed on compound **655a** to provide *N*,*O*-protected isoseric acid **656** and β-lactam **657**, which have both been used in semisyntheses of paclitaxel (Scheme 162). The free carboxylic acid **656** was generated in 94% yield after hydrogenolysis.

Scheme 162. Protecting Group Manipulations of 655a



Scheme 163. Synthesis of *N-tert*-Butanesulfonyl Analogues of Docetaxel



Treatment of **656** with Et_3N and 2-chloro-1-methylpyridinium iodide provided the desired β-lactam **657** in 45% yield.

Several adducts that were synthesized by this methodology were further converted into *N-tert*-butanesulfonyl derivatives of docetaxel by Qin, Qu, and co-workers (Scheme 163).[248] Paclitaxel and docetaxel, a semisynthetic analogue of paclitaxel, have both been approved by the FDA for the treatment of cancer (Figure 8). Compounds **655a**, **g**, and **h** were oxidized with *m*CPBA to the corresponding sulfonamides **658** in 50−63% yield with concomitant oxidation of the pyridyl group to the pyridyl *N*-oxide in the case of **658g** and **658h**. Subsequent synthetic transformations provided oxazolidines **659** as 3:1 mixtures of diastereomers. Coupling of the carboxylic acids with **660** followed by protecting group manipulations provided the desired analogues **661**. These derivatives were tested in vitro for their cytotoxicity against a number of human cancer cell lines, revealing that **661g** and **h** each showed the same level of potency as paclitaxel and docetaxel, while **661a** was less cytotoxic.

The addition of an α-alkoxy enolate to *N-tert*-butanesulfinyl α-alkoxy imines was applied by Aitken and co-workers in their synthesis of the polyhydroxylated β-amino acid

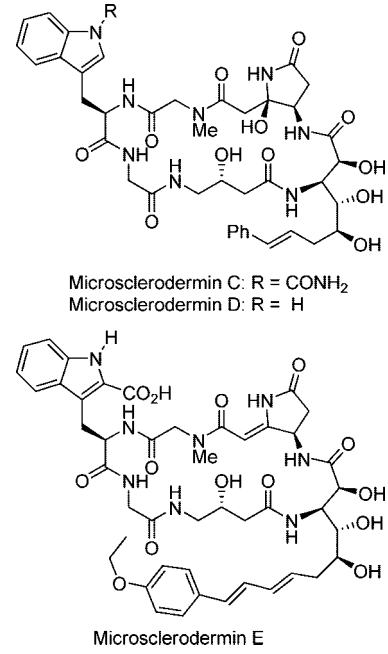


Figure 9. Microsclerodermins C, D, and E.

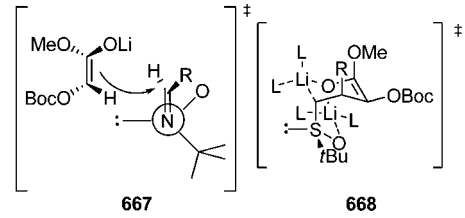
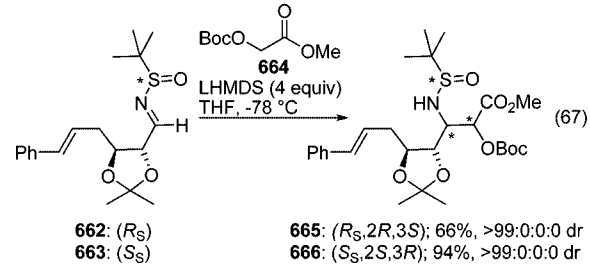
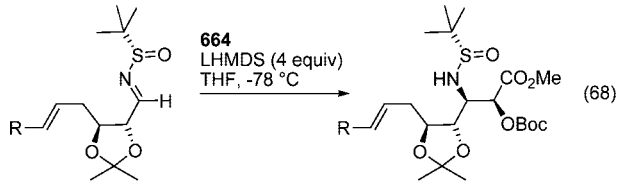


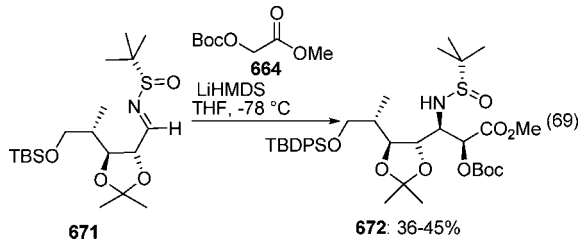
Figure 10. Proposed transition states.

subunits in microsclerodermins C, D, and E (Figure 9).[246] Evaluation of a number of *O*-protected α-hydroxyacetates revealed that use of the enolate derived from **664** provided the highest yields and diastereoselectivities for the synthesis of the β-amino acid present in microsclerodermins C and D (eq 67). Under these conditions, **665** and **666** were synthesized in 66% and 94% as single diastereomers, respectively. X-ray structural analysis of both **665** and **666** determined that **666** possessed the desired (2*S*,3*R*) configuration. The stereochemical outcome of this reaction was controlled exclusively by the sulfinyl group, and both an open transition state **667** and a closed transition state **668** were suggested as possible explanations for the observed stereocontrol (Figure 10). The β-amino acid fragment for microsclerodermin E was synthesized in a similar fashion (eq 68).



The methodology developed by Aitken and co-workers was later applied by Williams and Burnett in their synthesis of the polyhydroxylated β-amino acid fragments of microsclerodermins F−I, providing **672** in 36−45% yield (eq 69).[249]

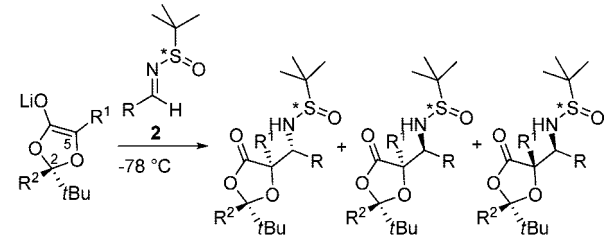




The addition of enantiomerically pure cyclic enolates **673**−**675** to *N*-*tert*-butanesulfinyl aryl or alkyl aldimines **2** for the synthesis of α-hydroxy-β-aminoalkanoic acids was demonstrated by Guerrini, Varchi, and co-workers (Table 20).[250] Enolates **673**, **674**, and **675** were chosen to probe the reactivity and the stereochemical effects of different steric constraints at the C2 and C5 positions. A number of imines, derived from both (*R*)- and (*S*)-*tert*-butanesulfinamide, were first evaluated as coupling partners with enolate **673** (entries 1−8). Regardless of the stereochemistry of the sulfinyl group, the major product for this reaction was diastereomer **676** (entries 1−8, Table 20), arising from an exo approach of the aldimine to the dioxalone enolate (see transition state **680**, Figure 11). However, isomer **677**, arising from transition state **681**, was more prevalent in products derived from (R_S)-imines **2** than for the reactions with the analogous (S_S)-imines **2** (compare entries 1, 3, 5, and 7 to entries 1, 4, 6, and 8). When enolate **674** was employed, the phenyl substituent at the C5 position played the dominant role in the diastereoselectivity of the reaction. Racemic and enantiomerically pure imines all provided diastereomer **677** exclusively (entries 9−11). The benzyl substituent at the C5 position and the hydrogen substituent at the C2 position of enolate **675** resulted in a more varied product distribution (entries 12−17). Here the exo approach of the aldimine to the enolate was more disfavored than when enolate **673** was employed, resulting in a decrease in diastereomer **676**. Once again, (S_S)-aldimines favored the formation of diastereomer **676** more than the enantiomeric (R_S)-aldimines, but an increased amount of **678** was observed. With this enolate coupling partner, the (R_S)-aldimines mainly formed diastereomer **677**. In general, the desired products were obtained in good yields. In most cases, each stereoisomer was separated by column chromatography.

The orthogonality of the acetal and sulfinyl protecting groups was demonstrated in further synthetic transformations. The sulfinyl groups for each isolated product **676**−**678** (a−q) were selectively removed under acidic conditions to afford the corresponding amines **684** in 72−92% yield without epimerization. In the presence of LHMDS, base-induced cyclization occurred to provide the β-lactams **685** in 71−90% yield, with minor epimerization in some cases (eq 70). Alternatively, the acetal group was removed by base-induced methanolysis of select 1′-*N*-sulfinylamino-dioxalones to provide the corresponding *N*-*tert*-butanesulfinyl α-hydroxy-β-amino methyl esters **686** in 75−90% yields (for example, eq 71).

Table 20. Addition of Chiral Cyclic Enolates to *N*-*tert*-Butanesulfinyl Aldimines



entry	enolate	S_S or R_S	R	major product	combined yield (%)	676/677/678
1	**673**	R_S	2-thienyl	**676a**	79	55:45:0
2	**673**	S_S	2-thienyl	**676b**	82	80:5:15
3	**673**	R_S	*i*Bu	**676c**	84	83:17:0
4	**673**	S_S	*i*Bu	**676d**	80	93:7:0
5	**673**	R_S	Bn	**676e**	78	63:37:0
6	**673**	S_S	Bn	**676f**	75	79:0:21
7	**673**	R_S	*i*Pr	**676g**	88	89:9:2
8	**673**	S_S	*i*Pr	**676h**	93	>98:0:0
9	**674**	rac	*i*Bu	**677i**	86	0:100:0
10	**674**	rac	Bn	**677j**	75	0:100:0
11	**674**	S_S	*i*Pr	**677k**	80	0:100:0
12	**675**	R_S	*i*Bu	**677l**	77	24:72:4
13	**675**	S_S	*i*Bu	**678m**	79	46:0:54
14	**675**	R_S	Bn	**677n**	58	45:50:5
15	**675**	S_S	Bn	**676o**	60	73:0:27
16	**675**	R_S	*i*Pr	**676p**	61	57:43:0
17	**675**	S_S	*i*Pr	**676q**	70	89:11:0

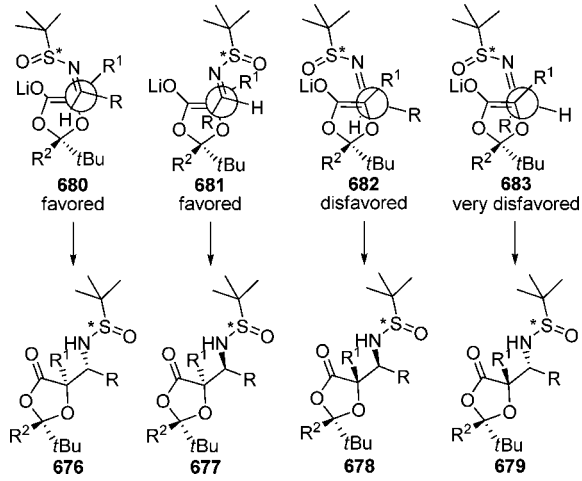
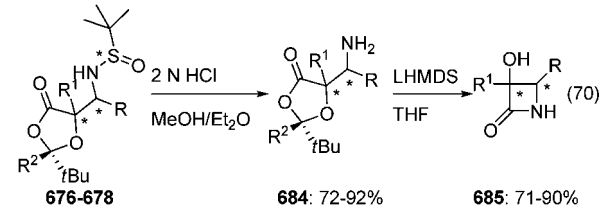
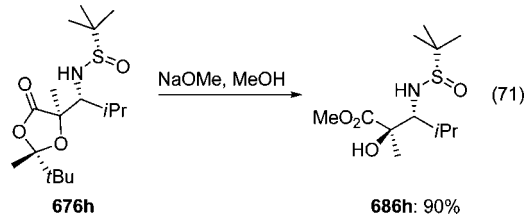


Figure 11. Proposed transition states.

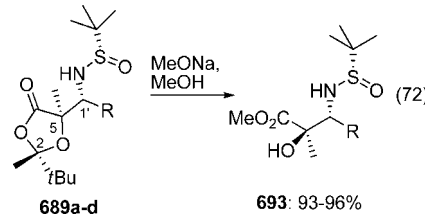


In their studies on the syntheses of conformationally constrained chiral α-hydroxy-$\beta^{2,2,3}$-amino acids, Battaglia and co-workers reported the addition of enantiomerically pure enolates **673** or **674** to *N*-*tert*-butanesulfinyl aldimines **2**. The



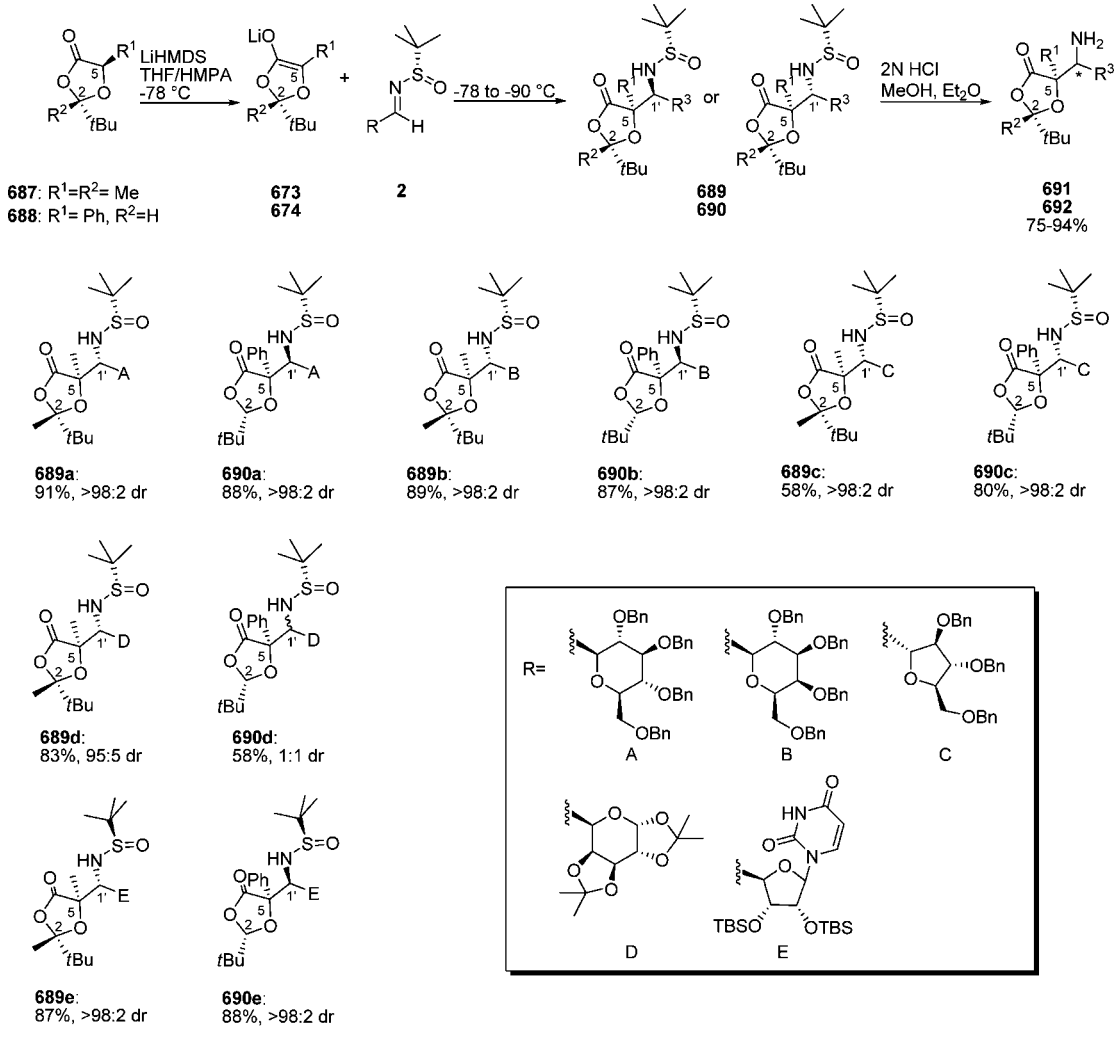
products of this reaction, *N-tert*-butanesulfinyl substituted C-(1′)-aminoglycosyl-1,3-dioxolan-4-one adducts **689** or **690**, serve as *N,O*-orthogonally protected α-hydroxy-$\beta^{2,2,3}$-amino acids analogues (Scheme 164).[251] *N-tert*-Butanesulfinyl imines **2**, derived from carbohydrate scaffolds A−E, were chosen to incorporate the pharmacokinetic and transport properties of sugars with the structural features of α-hydroxy-β-amino acids. In initial studies, it was determined that the imines derived from (*S*)-*tert*-butanesulfinamide yielded the desired products with the highest diastereoselectivity. Treatment of **687** or **688** with lithium bishexamethyldisilazide (LHMDS) at low temperature in a THF/HMPA solvent mixture provided the corresponding chiral enolates **673** and **674**. Slow addition of the enolate to the appropriate carbohydrate-based *N-tert*-butanesulfinyl imines **2** minimized imine oligomerization and other side reactions to provide **689a−e** and **690a−e** in 58−91% yield. When enolate **673** was employed, the configuration at the newly formed 1′ stereocenter was consistently *R*, while, for reactions with **674**, the stereochemical outcome varied depending on the sugar substituent. The absolute configurations of select products were established by nuclear Overhauser effect experiments. Selective cleavage of the sulfinyl group under acidic conditions was demonstrated for all of the compounds to generate the 1′-aminodioxolanones **691** and **692** in 75−94% yield.

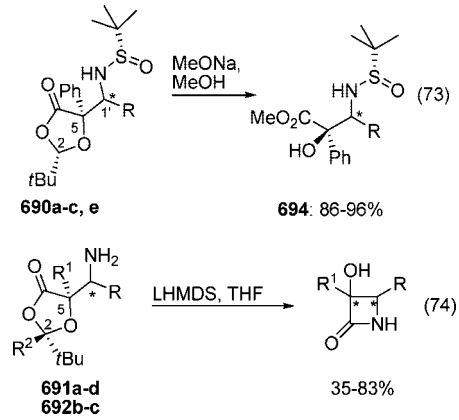
Selective removal of the acetal group was also demonstrated by treatment of select products **689** and **690** with sodium methoxide/methanol (eqs 72 and 73). The corresponding methyl isoserinates **693** and **694** were obtained in 86−96% yields. Furthermore, the deprotected 1′-aminodioxolanones **691a−d** and **692b−c** were converted to the corresponding β-lactams in 35−83% yields (eq 74).



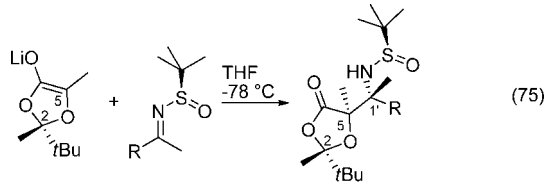
The methodology was then further expanded to include additions of enantiomerically pure enolates to *N-tert*-butanesulfinyl ketimines **65** for the first synthesis of enantiomerically enriched tetrasubstituted β-amino acids with two adjacent quaternary stereogenic centers (eqs 75 and 76).[252]

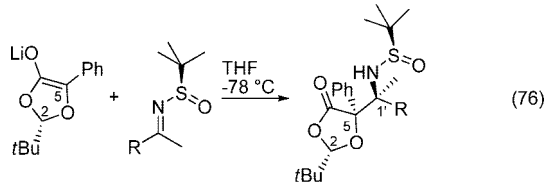
Scheme 164. Addition of Enolates 673 and 674 to Carbohydrate-Derived *N-tert*-Butanesulfinyl Imines



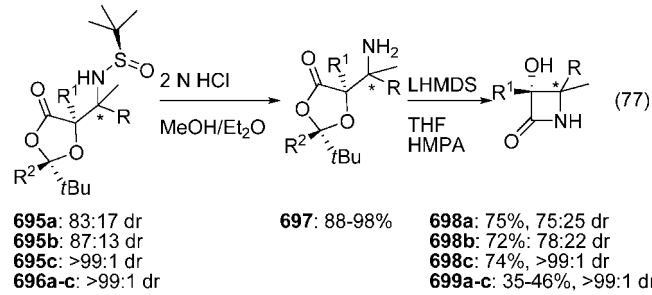


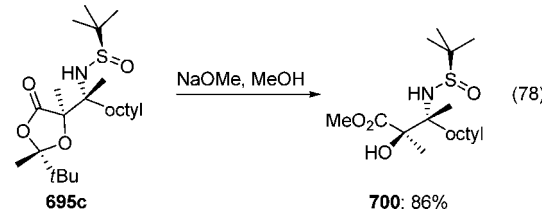
Again, the lithium enolates **673** and **674** were studied to probe the effects of sterically distinct substituents at the C2 and C5 sites on the diastereoselectivity of the reaction. Only ketimines **65** derived from (*R*)-*tert*-butanesulfinamide were utilized as coupling partners because preliminary experiments had revealed that they provided the desired products with higher diastereoselectivites. When enolate **673** was utilized, products **695a**−**c** were obtained in 70−76% yield and with 83:17 to 91:9 diastereomeric ratios (eq 75). A change in diastereoselectivity was observed when enolate **674** was employed and products **696a**−**c** were synthesized in moderate yields (52−55%), but with excellent diastereoselectivities (92:8 to 95:5 dr, eq 76). Additionally, separation of the diastereomers was achieved by column chromatography for **695c** and **696a**−**c**.





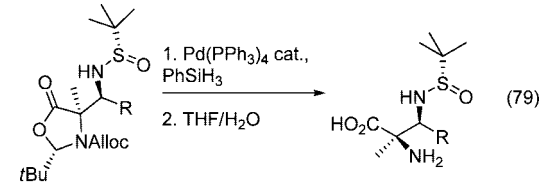
Selective removal of the sulfinyl protecting group was demonstrated to provide the free 1′-aminodioxolanones **697** in very high yields without any degradation in diastereomeric purity (eq 77). Treatment of the free amines with LHMDS promoted cyclization to the β-lactams **698a**−**c** in good yields and to **699a**−**c** in moderate yields (eq 77). After this transformation, **698a** and **698b** were formed along with their corresponding 1′ epimers, but column chromatography provided the diastereomerically pure products. The absolute configurations at the 1′ positions of the 1′-amino dioxolanes **695** and **696** were established by ^{1}H NMR NOE experiments on the corresponding β-lactam derivatives **698** and **699**. Base-induced methanolysis selectively cleaved the acetal protecting group of **695c** to provide the methyl ester **700** in 86% yield (eq 78).





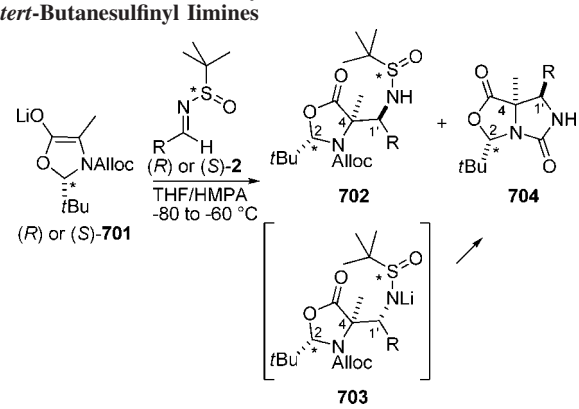
The use of chiral *N*-acyloxazolidinone enolates **701** in additions to *N*-*tert*-butanesulfinyl imines **2** was examined by Varchi, Guerrini, and co-workers (Table 21).[253] The enolates **701** were prepared using LHMDS in THF/HMPA at −78 to −90 °C. Slow addition of the *N*-*tert*-butanesulfinyl imine to the enolate was required to minimize imine self-condensation under the basic reaction conditions. Following this protocol, open adducts **702** and bicyclic adducts **704** (proposed to arise from cyclization of the diastereomeric open adducts **703**) were isolated. The observed stereochemistry at the C4 position of adducts **702** and **704** was always consistent with approach from the less hindered face of the enolate (opposite the *t*Bu group). Both the chirality of the sulfinyl group and the chirality of the enolate affect the product outcome (entries 1−6). This trend was also observed for reactions with imines bearing a sterically demanding sugar substituent (entries 7−11; for **A** and **E** see Scheme 164). The absolute configurations of the products were established by NOE experiments and chemical correlation methods.

Acidic cleavage of the sulfinyl group was demonstrated for several adducts. Alternatively, selective deprotection of the Alloc group was accomplished by transfer hydrogenation under neutral conditions with tetrakis(triphenylphosphine)palladium(0) catalyst and $PhSiH_3$. The free N−H cyclic compounds were converted to the *N*-*tert*-butanesulfinyl protected *syn*-amino acids **705** in 98% yield after standing in THF/H_2O (eq 79).



Hu and co-workers reported a multicomponent reaction in which *N*-*tert*-butanesulfinyl imine **706** is used to trap an oxonium ylide, yielding β-amino-α-hydroxy acid derivatives **708** with high optical purity.[254] Generation of a rhodium carbenoid from diazo compound **702** followed by reaction with an alcohol produced the oxonium ylide in situ, which subsequently reacts with the imine (Scheme 165). It was noted that electron-withdrawing substituents on the aryl ring were necessary to increase the electrophilicity of the *N*-*tert*-butanesulfinyl imine, allowing for more efficient trapping

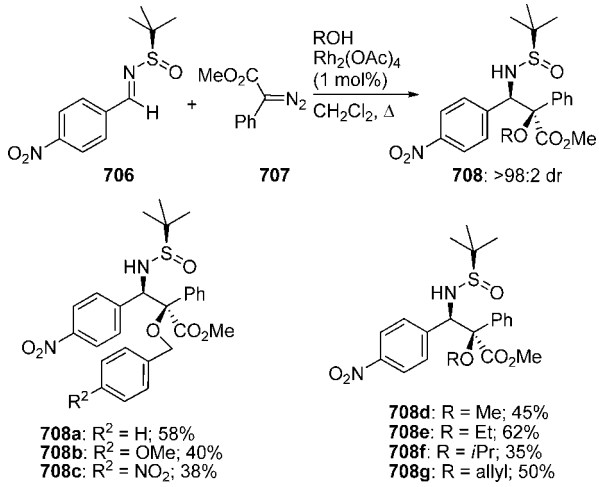
Table 21. Addition of *N*-Acyloxazolidinone Enolates 701 to *N-tert*-Butanesulfinyl Iimines



entry	(*R*)- or (*S*)-**701**	(*R*)- or (*S*)-**2**	R	combined yield (%)	**702/704**
1	*S*	*R*	Ph	80	<2:>98
2	*S*	*S*	Ph	80	1:1
3	*S*	*R*	2-thienyl	83	<2:>98
4	*S*	*R*	*i*Bu	trace **704**	
5	*S*	*S*	*i*Bu	89	88:12
6	*S*	*S*	*i*Pr	82	>98:2
7	*S*	*S*	A	59	>98:2
8	*R*	*S*	A	<15[a]	
9	*S*	*R*	A	63	>98:2
10	*R*	*R*	A	79	5:95
11	*S*	*S*	E	89	>98:2

[a] Inseparable mixture of addition products obtained.

Scheme 165. Additions of Oxonium Ylides to *N-tert*-Butanesulfinyl Imines



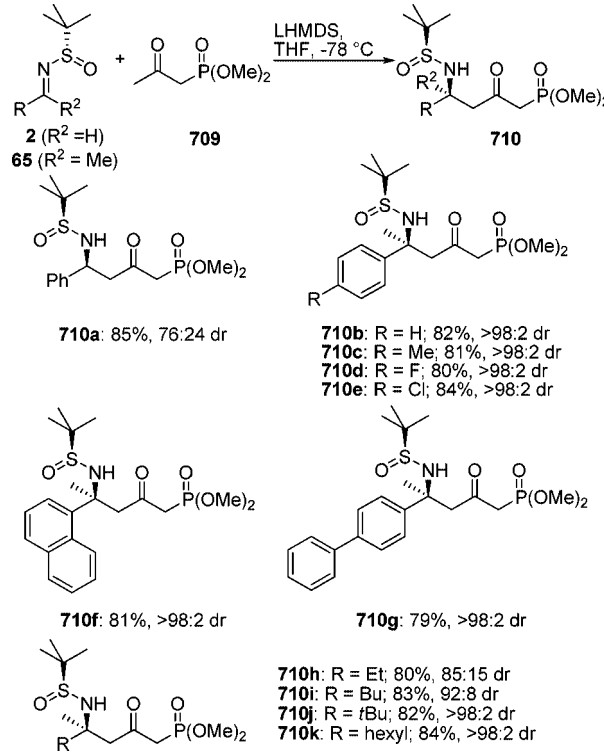
of the oxonium ylide. Yields for **708a**−**g** were moderate due to formation of a competitive O−H insertion product, but in all examples the diastereoselectivity was very high (>98:2). The absolute configuration was determined by X-ray analysis of **708a**. Cleavage of the sulfinyl group under acidic conditions without racemization was also demonstrated.

10.2. Synthesis of Other β-Amino Acid Derivatives

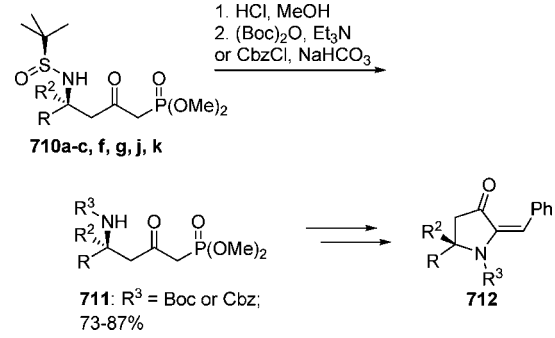
10.2.1. Synthesis of β-Amino Ketones

The first example of an addition of a ketone enolate to an *N-tert*-butanesulfinyl imine was reported by Yuan and Chen for the synthesis of chiral 4-amino-2-oxophosphonates (Scheme 166).[255] Treatment of **709** with lithium hexamethyldisilazide (LHMDS) generated the dianion that then added

Scheme 166. Synthesis of 4-(*N-tert*-Butanesulfinylamino)-2-oxoalkylphosphonates 710



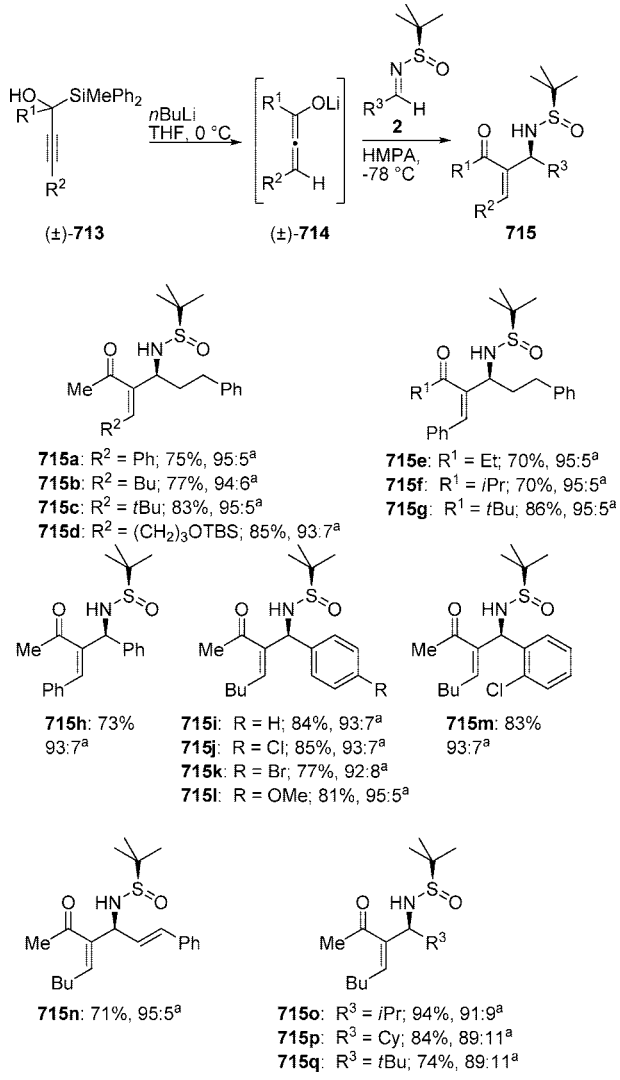
Scheme 167. Conversion of 710 to Pyrrolidines 712



to enantiomerically pure *N-tert*-butanesulfinyl aldimines **2** or ketimines **65**. While the addition to the *N-tert*-butanesulfinyl imine derived from benzaldehyde provided **710a** in high yield (85%), only moderate diastereoselectivity was achieved. The addition of **709** to *N-tert*-butanesulfinyl ketimines proceeded in good yields (79−84%) and generally with very high diastereoselectivities (**710b**−**g**, **j**, and **k**). The lower diastereoselectivity observed for adducts **710h** and **710i** was attributed to the presence of both *Z*- and *E*-isomers of the ketimine precursors. Removal of the sulfinyl groups for select substrates was achieved under acidic conditions, and the resulting amines were reprotected as the carbamates **711**, which were further converted to a number of 2-benzylidenepyrrolidinones **712** (Scheme 167).

Recently, Scheidt and co-workers published an example of additions of α-acylvinyl anion equivalents to *N-tert*-butanesulfinyl imines (Scheme 168).[256] Lithium allenolates (±)-**714** were generated in situ by treatment of (±)-**713** with *n*BuLi in THF at −78 °C before addition of the *N-tert*-butanesulfinyl imine **2**. HMPA was identified as a necessary additive to achieve high diastereoselectivity. Under the optimized conditions, a series of α-hydroxypropargylsilanes (±)-**713** were investigated as substrates. A variety of

Scheme 168. Addition of α-Acylvinyl Anions to *N-tert*-Butanesulfinyl Imines



[a] Ratios provided as major/sum of the minor isomers.

substituents could be incorporated at the R^1 and R^2 positions, providing adducts **715a**−**d** and **715e**−**g**, respectively, in high yields and diastereoselectivities. A variety of *N-tert*-butanesulfinyl imines **2** were also successfully employed, affording aryl (**715h**−**m**), α,β-unsaturated (**715n**), and branched alkyl (**715o**−**q**) adducts in high yields and with good diastereoselectivities.

The absolute stereochemistry of addition product **715h** was determined by X-ray structural analysis. Mechanistic studies were conducted to evaluate the possibility of a kinetic resolution of the racemic allene under the reaction conditions. To probe this hypothesis, excess lithium allenolate (±)-**714** (R^1 = Me, R^2 = Ph) was employed under the standard reaction conditions. Analysis of the remaining silyloxyallene after consumption of the limiting imine reagent revealed some optical enrichment (32% ee), indicating a preferential reaction between one enantiomer of the allene and the *N-tert*-butanesulfinyl imine. To rationalize this result and the stereoselectivity observed in the reaction, the authors proposed two open transition states, **716** and **717**, which form the coupled product **715** at different rates (Figure 12). Addition of the nucleophile to the imine from the face opposite to the *tert*-butyl group explains the high diastereoselectivity, and the regioselectivity favoring the Z-alkene

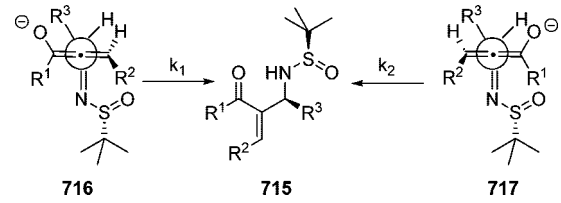
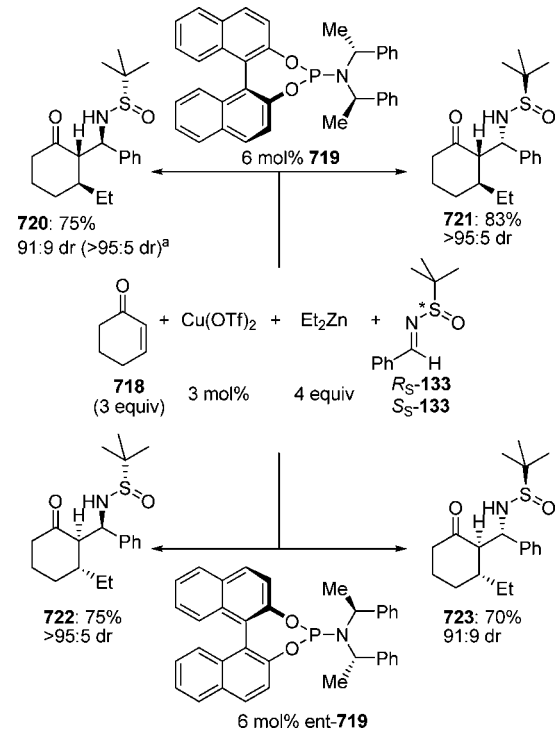


Figure 12. Proposed transition states **716** and **717**.

Scheme 169. Tandem Conjugate Addition−Mannich Reaction



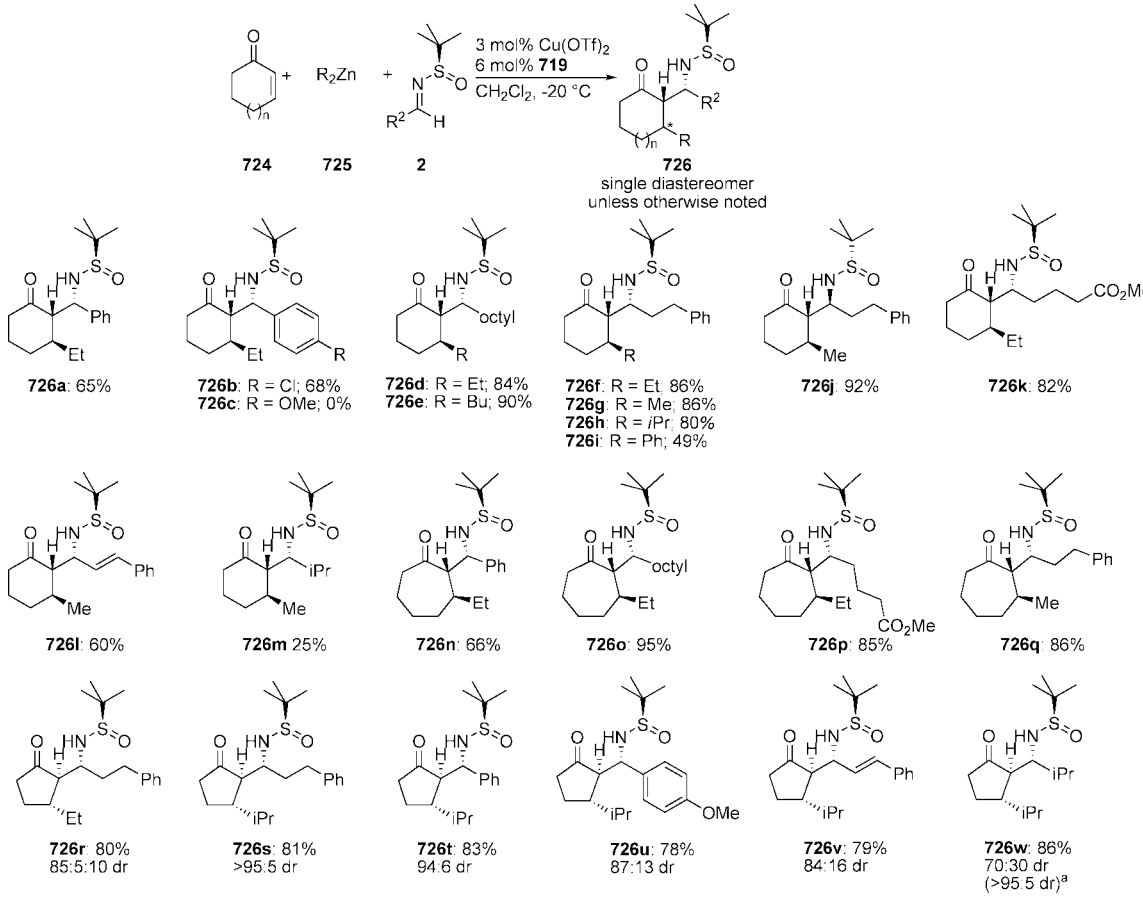
[a] Five equivalents of Et_2Zn were utilized.

results from the approach of the imine opposite to the R^2 substituent. The different rates of allene addition are then dictated by the interactions with the R^1 substituent.

The asymmetric synthesis of β-amino ketones via tandem enantioselective conjugate addition and a Mannich reaction with *N-tert*-butanesulfinyl imines was first evaluated by Gonzalez-Gomez, Foubelo, and Yus in 2008[257] and was later expanded in a full report (Scheme 169).[258] Optimization of the reaction conditions revealed that good conversion to the desired product was achieved in the presence of 3 mol % $Cu(OTf)_2$, 4 equiv of diethylzinc, and 3 equiv of enone **718**. The chiral phosphoramidite ligand **719**, developed by Feringa,[259] was chosen due to its previous success in asymmetric copper-catalyzed conjugate addition of dialkyl zinc reagents to cyclic enones (>98% ee). Under these conditions, **721** was generated from imine R_S-**133** in 83% yield as a single diastereomer. Likewise, **722** was produced in 75% yield as a single diastereomer from the reaction between imine S_S-**133** and *ent*-**719**. A slightly lower diastereoselectivity was observed for the reaction between the pairs **719**/S_S-**133** and *ent*-**719**/R_S-**133**, but this was overcome by increasing the amount of Et_2Zn to 5 equiv in the case of **720**.

The scope of the reaction was evaluated using several *N-tert*-butanesulfinyl imines **2**, dialkyl zinc reagents **725**, and cyclic enones **724** (Scheme 170). Addition of diethyl zinc to electron-neutral and electron-deficient aryl imines **2**

Scheme 170. Reaction Scope for the Addition of Enones to *N-tert*-Butanesulfinyl Imines



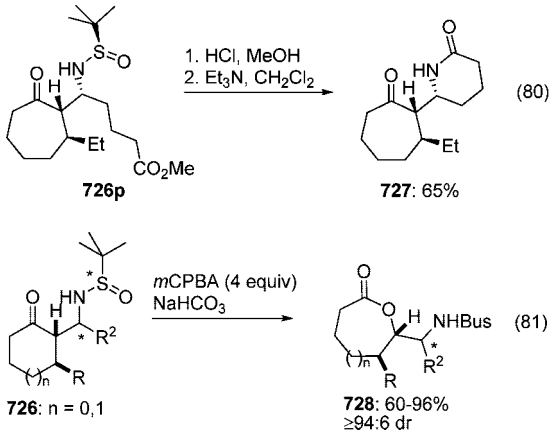
[a] After purification by column chromatography.

provided **726a** and **726b** in good yields as single diastereomers, but no product was observed when an electron-rich aryl substituent was employed (**726c**). Aliphatic unbranched *N-tert*-butanesulfinyl imines **2** were more reactive than the aromatic precursors. For these substrates, several dialkyzinc reagents were employed to provide **726d**−**h** in 80−90% yield. When diphenyl zinc was used, diastereomerically pure **726i** was isolated after column chromatography in 49% yield. However, the authors noted that the minor diastereomer resulting from poor enantioselectivity in the conjugate addition step was also present in the crude mixture. Additionally, by increasing the amount of diethyl zinc from 3 to 4 equiv, **726j**, derived from the *S*-enantiomer of the *N-tert*-butanesulfinyl imine, was generated in high yield and with excellent diastereoselectivity. The mild reaction conditions also enabled the preparation of the functionalized adduct **726k** in 82% yield. An α,β-unsaturated imine and an α-branched alkyl imine were also explored, and the expected products **726l** and **m** were generated, albeit in lower yields. Cycloheptenones were also compatible as the enone component, providing **726n**−**q** in good yields and diastereoselectivities.

The scope of the methodology was extended to include the more challenging cyclopentenone as the enone reactant.[258] Optimization of the reaction conditions included a screen of several chiral ligands that had been developed for this Michael acceptor, but **719** provided the best results. Premixing all of the components before addition of the dialkylzinc also increased the diastereoselectivity. Under these conditions, **726r** was isolated in 80% yield and with a 85:5:10 diastereomeric ratio. Notably, the opposite configuration was obtained at the β stereocenter when cycopentenone versus cyclohexenone was used. Increased diastereoselectivity was observed for **726s**, obtained by reaction with the more bulky iPr$_2$Zn reagent. A number of *N-tert*-butanesulfinyl imines **2** were evaluated with cyclopentenone and iPr$_2$Zn. While unbranched alkyl and electron-neutral aryl imines proceeded with high diastereoselectivity (**726s**−**t**), electron-rich aryl, α,β-unsaturated, and branched alkyl imines provided adducts **726u**−**w** with lower stereoselectivity. Electron-rich aromatic imines and α-branched alkyl imines were both compatible with this transformation, providing **726u** and **w** in high yields, where poor or no reactivity was observed for the analogous reaction with cyclohexenone. Although **726w** was formed with the lowest diastereoselectivity (70:30 dr), the diastereomers could be separated by column chromatography.

Cycloheptenone **726p** was converted to piperidone **727** in two steps, and the absolute configuration of this product was determined by X-ray structural analysis (eq 80). This stereochemical outcome was rationalized by invoking a six-membered cyclic transition state (see transition state **572**, Scheme 146). Concomitant *m*CPBA-mediated oxidation of the *tert*-butanesulfinyl group and Baeyer−Villiger oxidation of a number of β-amino ketones was also demonstrated (eq 81). Alternatively, stereoselective reduction of β-amino ketone **726f** was also explored (see section 13.2).

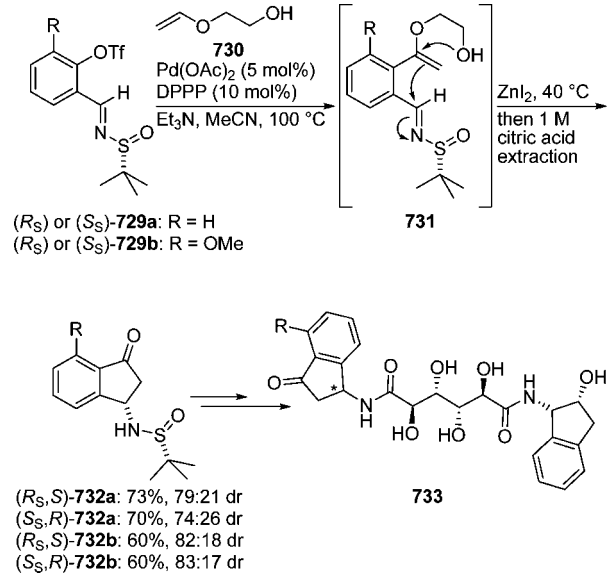
In their studies on the development of HIV-1-protease inhibitors, Larhed and co-workers developed a novel method for the synthesis of 3-aminoindan-1-ones from either the (R_S)- or (S_S)-*N-tert*-butanesulfinyl imines **729a** and **b** (Scheme 171).[260] The annulation reaction was performed in a one-



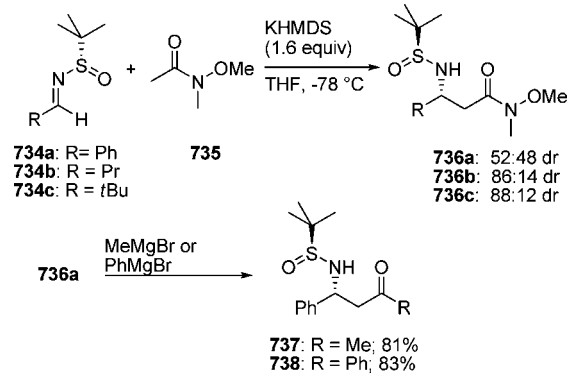
pot, two-step sequence commencing with an α-arylation of **730** via a Heck reaction providing intermediate **731**. Treatment with ZnI_2 then resulted in efficient cyclization. Extraction with citric acid to cleave the resulting acetal group yielded the desired compounds **732** in moderate yields (60−73%) and diastereoselectivities (74:26 to 83:17). These compounds were converted to HIV-1 protease inhibitors **733**.

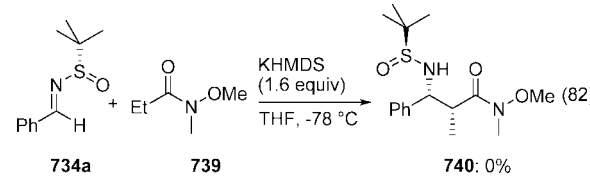
In an effort to develop an expedient synthesis of β-amino aldehydes and ketones, Davis and co-workers explored the addition of enolates derived from the Weinreb amide **735** to *N*-sulfinyl aldimines (Scheme 172).[261] While their study focused on the use of *p*-toluenesulfinamide as the chiral amine reagent, the effect of the sulfinyl substituent was probed with several *N*-*tert*-butanesulfinyl imines **734a**−**c**. The additions of the amide enolate of **735** to imines **734** were carried out in the presence of KHMDS in THF at low temperature (−78 °C) to form the *N*-*tert*-butanesulfinyl β-amino amides **736a**−**c** with lower diastereoselectivity than their analogous *N*-*p*-toluenesulfinyl derivatives. In the presence of excess methyl or phenyl magnesium bromide, adduct **736a** was converted to the β-amino ketones **737** and **738** in 81% and 83% yield, respectively.[262] Davis and Song also extended this methodology to the synthesis of *syn*-α-substituted β-amino ketones via the addition of the enolate of **739** to a series of *N*-sulfinyl aldimines (eq 82).[263] While good yields and diastereoselectivities were observed for *p*-toluenesulfinyl, *N*-2,4,6-mesitylsulfinyl, and *N*-2,4,6-triisopropylphenylsulfinyl aldimines, when the enolate derived from **739** was mixed with imine **734a**, only unreacted starting material was obtained. The authors hypothesize that the larger size of the *tert*-butanesulfinyl group inhibits the addition of the bulkier amide enolate.

Scheme 171. Synthesis of 3-Aminoindan-1-ones 732



Scheme 172. Addition of Weinreb Amide Enolates to *N*-*tert*-Butanesulfinyl Imines



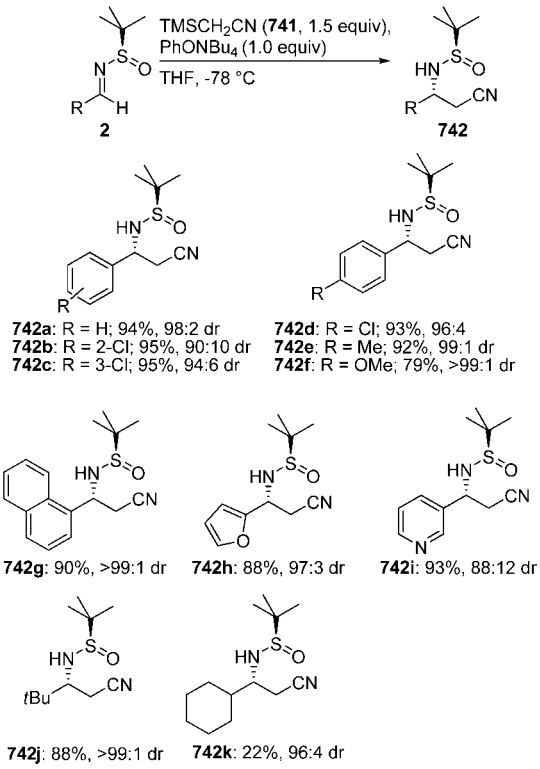


10.2.2. Synthesis of β-Amino Nitriles

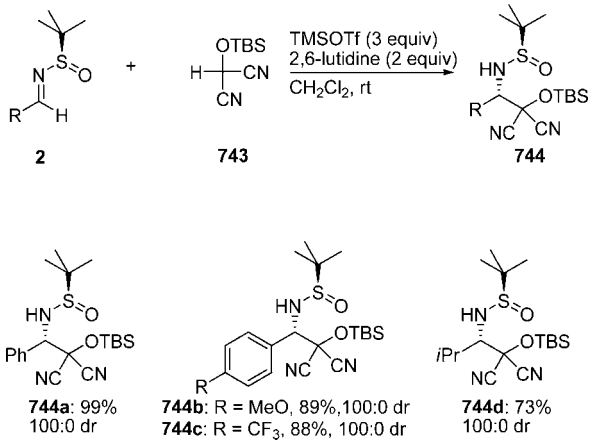
The synthesis of β-amino nitriles by the direct stereoselective addition of a cyanomethyl group to *N*-*tert*-butanesulfinyl aldimines was accomplished by Mukaiyama and Michida.[264] For this transformation, $TMSCH_2CN$, activated by a Lewis base, was employed as the nucleophile, and the reaction conditions were optimized with *N*-*tert*-butanesulfinyl benaldimine (**2**, R = Ph). A screen of Lewis bases was conducted, and the highest yield and diastereomeric ratio of **742a** was obtained when 1 equiv of tetrabutylammonium phenoxide ($PhONBu_4$) was utilized in THF at −78 °C (Scheme 173). Electronically diverse *N*-*tert*-butanesulfinyl aromatic aldimines with substitution at the *ortho*-, *meta*-, or *para*-position were readily converted to the corresponding cyanomethylated adducts in good yield and diastereoselectivity (**742a**−**g**), and heteroaromatic compounds could also be synthesized (**742h** and **i**). Addition to an aliphatic imine lacking α-protons provided **742j** in 88% yield and >99:1 dr while a low yield was obtained when imine **2** (R = Cy) was employed, presumably due to α-deprotonation under the reaction conditions (**742k**, 22% yield). Purification by crystallization then afforded the diastereomerically pure cyanomethylated products. The (R_S, *R*) configuration was determined by an X-ray crystal structure of **742a**, and the configurations of **742b**−**k** were assigned by analogy.

A masked acyl cyanide reagent **743**[265] has also been developed and added to *N*-*tert*-butanesulfinyl aldimines.[266] Addition of **743** to imines **2** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid and 2,6-lutidine as the base provided adducts **744a**−**d** in high yields and with excellent diastereoselectivity (Scheme 174). Deprotection of the TBS group in **744a** followed by *in situ* amide bond formation with butylamine afforded **745** in 92% yield as a single diastereomer (Scheme 175). The sulfinyl group was removed followed by conversion to the *N*-tosyl product.

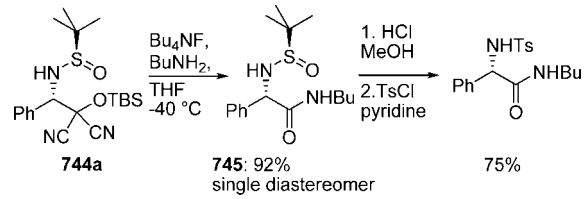
Scheme 173. Addition of a Cyanomethyl Silane to *N-tert*-Butanesulfinyl Imines



Scheme 174. Addition of a Masked Acyl Cyanide to *N-tert*-Butanesulfinyl Imines



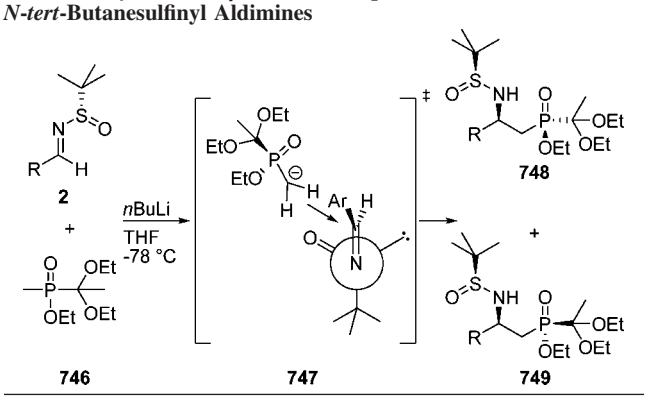
Scheme 175. Subsequent Synthetic Transformations of 744a



10.2.3. Synthesis of β-Amino Phosphinates

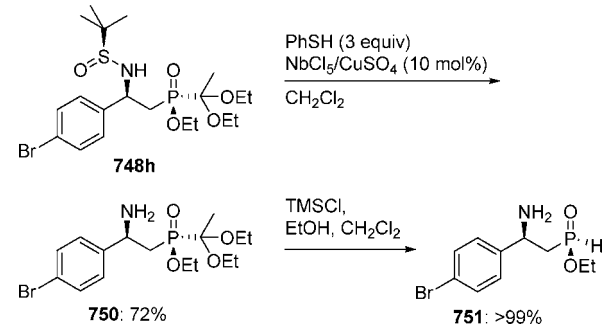
Yuan and Zhang developed a method for the synthesis of β-amino phosphinates, a β-amino acid isostere, from *N-tert*-butanesulfinyl aldimines and ethyl (1,1-diethoxyethyl)methylphosphinate **746** (Table 22).[267] Deprotonation of **746** with *n*BuLi followed by addition to *N-tert*-butanesulfinyl aldimines **2** proceeded smoothly at −78 °C to afford a mixture of phosphorus stereoisomers **748** and **749**, which were separable by column chromatography. A crystal structure of each isomer was obtained revealing that **748** (with S_P stereochemistry) and **749** (with R_P stereochemistry) both displayed *R* stereochemistry at the newly formed α-carbon. The stereochemistry of the adducts was rationalized by the open transition state **747**. A variety of aryl, heteroaryl, and alkyl aldimines were subjected to the reaction conditions, providing mixtures of **748** and **749** in good yields and with complete stereocontrol at the newly formed β-carbon stereocenter (entries 1−13). However, the authors noted that these reaction conditions were not applicable to ketimine substrates and provided only trace amounts of the desired adducts for these substrates.

Table 22. Synthesis of β-Amino Phosphinates from *N-tert*-Butanesulfinyl Aldimines



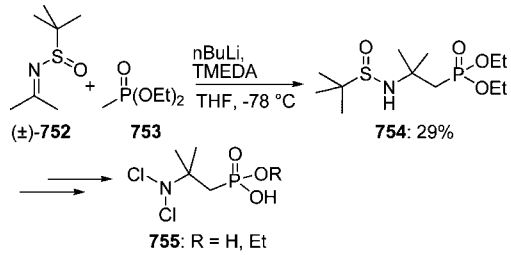
entry	R	748	yield (%) of 748	749	yield (%) of 749
1	Ph	**748a**	42	**749a**	43
2	4-Me-Ph	**748b**	47	**749b**	43
3	4-MeO-Ph	**748c**	49	**749c**	50
4	4-Me_2N-Ph	**748d**	49	**749d**	44
5	4-CH_3S-Ph	**748e**	46	**749e**	44
6	4-F-Ph	**748f**	47	**749f**	47
7	4-Cl-Ph	**748g**	47	**749g**	48
8	4-Br-Ph	**748h**	47	**749h**	44
9	2,4-Cl-Ph	**748i**	48	**749i**	48
10	2-thienyl	**748j**	48	**749j**	50
11	2-naphthyl	**748k**	41	**749k**	49
12	biphenyl	**748l**	45	**749l**	41
13	tridecanyl	**748m**	48	**749m**	48

Scheme 176. Deprotection of 748h

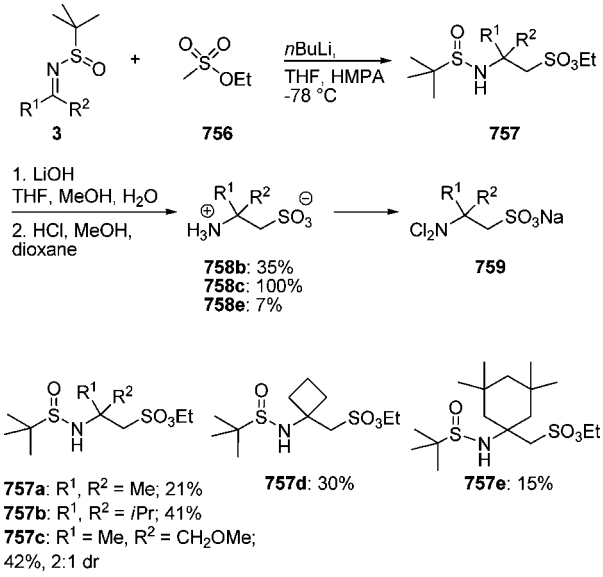


A deprotection strategy to access the desired β-amino phosphinates was also developed (Scheme 176). The acid lability of **748h** prevented concomitant deprotection of the sulfinyl group and hydrolysis of the ethyl phosphinate group under aqueous conditions and hampered the selective removal of the sulfinyl group under acidic conditions (HCl in MeOH/dioxane). In addition, all attempts to cleave the sulfinyl group after removal of the diethoxyethyl group from the phosphorus resulted in decomposition. An alternative protocol for the removal of the sulfinyl group was achieved by thiophenolysis

Scheme 177. Synthesis of Chloramine 755 from *N-tert*-Butanesulfinyl Ketimine 752



Scheme 178. Synthesis of β-Amino Sulfonates



in the presence of 10 mol % $NbCl_5$ and 10 mol % $CuSO_4$ to provide **750** in 72% yield. Removal of the diethoxyethyl group was then implemented, providing **751** in >99% yield. This sequence was also conducted with **749h** with comparable results.

Recently, Jain and co-workers coupled (diethoxyphosphoryl)methyllithium, generated *in situ* from the reaction between *n*BuLi and diethyl methylphosphonate (**753**), with racemic *N-tert*-butanesulfinyl ketimine **752** (Scheme 177).[11] While the resulting adduct **754** was produced in modest yield, this is the only example of phosphonate anion addition to an *N-tert*-butanesulfinyl ketimine. Hydrolysis and chlorination of **754** provided the desired dichloramines **755**, which were evaluated as antimicrobial agents against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*.

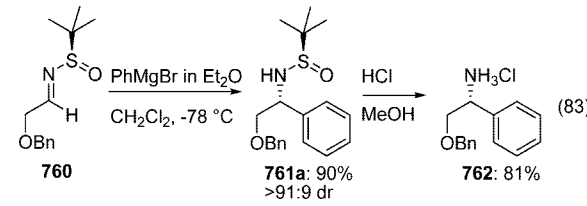
10.2.4. Synthesis of β-Amino Sulfonates

Shiau, Jain, and co-workers at NovaBay Pharmaceuticals developed a method to prepare β-amino sulfonate esters **757** from *N-tert*-butanesulfinyl ketimines (Scheme 178).[9] In this study, the β-amino sulfonate skeleton was synthesized by coupling *N-tert*-butanesulfinyl ketimines **3** with ethoxysulfonylmethyl anion generated from **756** and base. Several bases and cosolvents were screened in an effort to optimize the reaction, but even under the best conditions evaluated (*n*BuLi, THF, HMPA, −78 °C), yields remained modest for compounds **757a**−**e** (15−42%). These adducts were converted to the corresponding β-amino sulfonates **758** after hydrolysis and removal of the sulfinyl protecting group. *N*-Chlorination provided a number of *N*,*N*-dichlorotaurines **759**, which were evaluated for their aqueous stability in order to assess their suitability as antimicrobial agents.

11. Synthesis of 1,2-Amino Alcohols

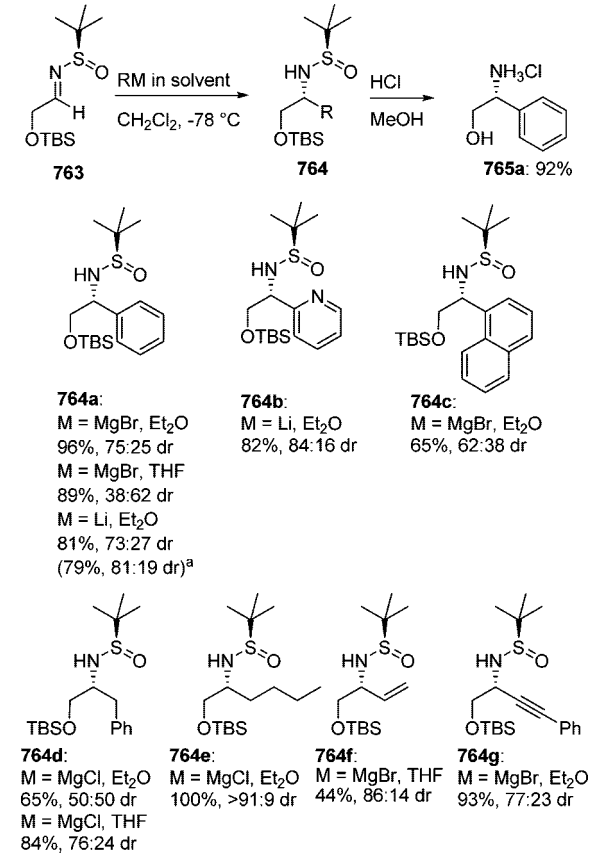
11.1. 1,2-Addition to α-Alkoxy Imines

Barrow and co-workers at Merck published the first report on addition of organometallic reagents to α-alkoxy *N-tert*-butanesulfinyl aldimines for the synthesis of 1,2-amino alcohols.[62] Both α-benzyloxy imine **760** (eq 83) and α-silyloxy imine **763** (Scheme 179) were investigated as substrates. Additions of phenyl organometallic reagents (both Grignard and organolithium) to α-benzyloxy imine **760** in a variety of solvents revealed that the highest stereoselectivity (>91:9) was observed for the addition of PhMgBr (in Et_2O) to the imine in dichloromethane as a reaction solvent. Lower selectivity was observed when PhMgBr in THF was used. Acidic deprotection of the sulfinyl group was demonstrated, providing benzyl protected amino alcohol **762** in high yield.



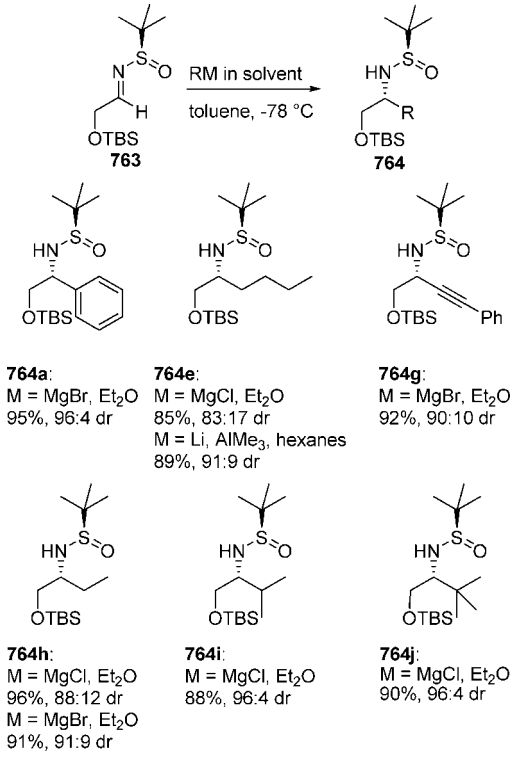
Organometallic reagent additions to α-silyloxy imine **763** were also investigated, with the best stereoselectivity obtained when an Et_2O solution of PhMgBr was employed with

Scheme 179. Addition of Organometallic Reagents to α-Silyloxy *N-tert*-Butanesulfinyl Aldimines



[a] Reaction conducted in hexanes instead of CH_2Cl_2.

Scheme 180. Addition of Organometallic Reagents to α-Silyloxy *N-tert*-Butanesulfinyl Aldimines



CH_2Cl_2 as the reaction solvent (75:25 dr, Scheme 179). A solution of PhLi in cyclohexane/Et_2O also provided moderate stereoselectivity when hexanes were used as the reaction solvent (81:19 dr). Examples of aryl, heteroaryl, benzyl, alkyl, vinyl, and alkynyl additions to this imine were provided. Surprisingly, while addition of an Et_2O solution of BnMgCl provided product **764d** as a 1:1 diastereomer mixture, switching to a THF solution of BnMgCl resulted in a modest improvement in stereoselectivity (76:24). This is in contrast to the solvent effects observed in the PhMgBr additions to provide **764a**. Simultaneous deprotection of both the silyl and sulfinyl groups under acidic conditions was demonstrated for **764a**, providing the desired free amino alcohol **765a** in high yield.

The configuration of the newly formed stereocenter is opposite to that observed for Grignard addition to α-unfunctionalized imines, which are proposed to proceed via chelated transition state **128** (Scheme 33, section 4.1). Based on the observed solvent and substituent effects (noncoordinating solvents generally provided higher stereoselectivity than coordinating ones, and higher selectivity is obtained with the more coordinating benzyloxy group than the bulkier silyloxy group), Barrow and co-workers proposed chelated transition state **767** (Figure 13), which invokes rapid imine isomerization to the less stable Z-isomer, with coordination of the α-alkoxy substituent in the axial position to the metal. An alternative possible explanation is that the role of the α-alkoxy substituent is to disrupt formation of the chelated transition state by providing an alternate site for competitive coordination of the metal. Two possible transition state pictures are open transition state **768**, which is similar to that proposed by Davis for addition to α-imino esters[69] (see section 9.1) and is also proposed for most organolithium additions to α-unfunctionalized imines (see section 4.1.2), or, alternatively, coordination of both the imine nitrogen and the α-alkoxy substituent to the metal, as depicted in transition

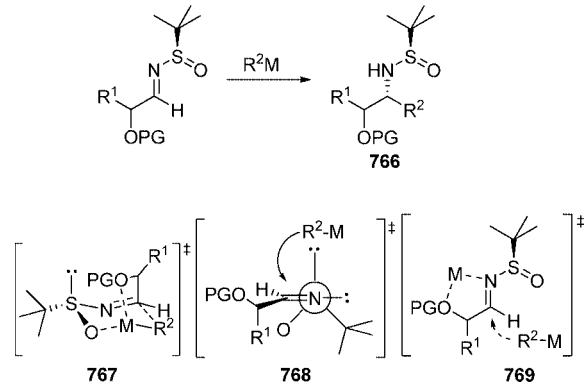
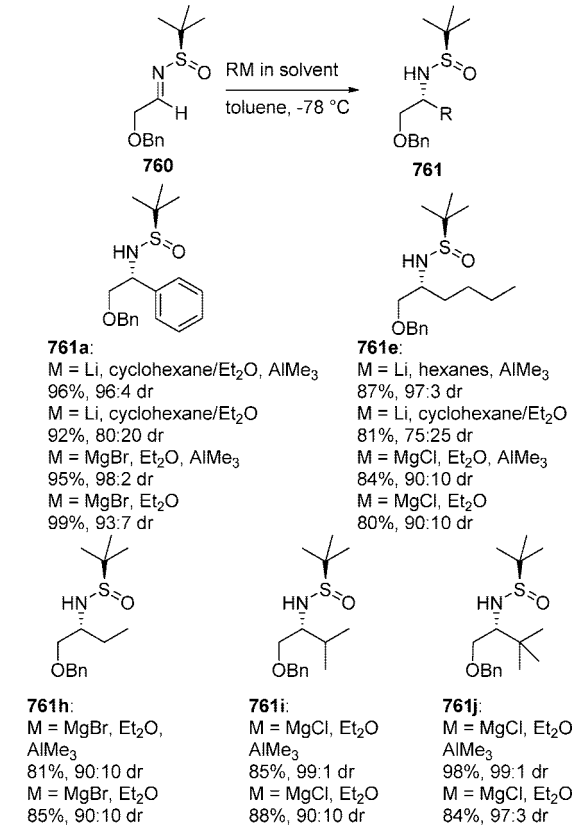


Figure 13. Possible transition states for the addition to α-alkoxy imines.

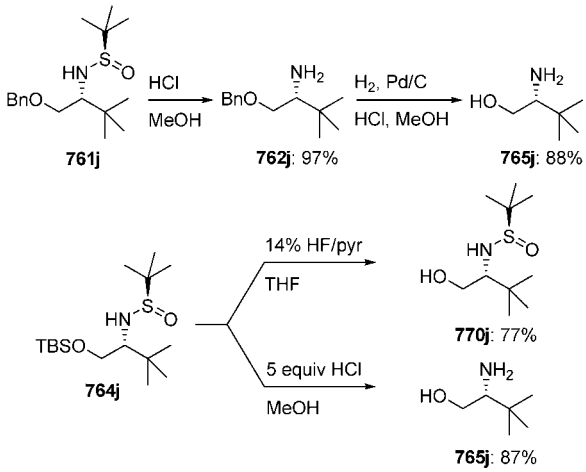
Scheme 181. Addition of Organometallic Reagents to α-Benzyloxy *N-tert*-Butanesulfinyl Aldimines



state **769**. It is difficult to distinguish between these possibilities, because they all lead to the same configuration of product.

Shortly after the report by Barrow and co-workers, Ellman and co-workers disclosed their own work on organometallic additions to the same imines **763** (Scheme 180) and **760** (Scheme 181).[63] Solvent and additive screening led them to select toluene as the optimal solvent for these addition reactions, providing the desired adducts in high yield and stereoselectivity (toluene had not been investigated by Barrow and co-workers.) Additions to α-silyloxy imine **763** proceeded smoothly, allowing isolation of each adduct **764a**, **e**, and **g**−**j** in high yield (85−95%) and with high diastereoselectivity (91:9 to 96:4 dr). A small difference in yield and stereoselectivity was observed between the use of EtMgBr and EtMgCl. While $AlMe_3$ was tried as an additive in each case, a significant improvement was only noted in the addition of BuLi to provide **764e**. The additions to

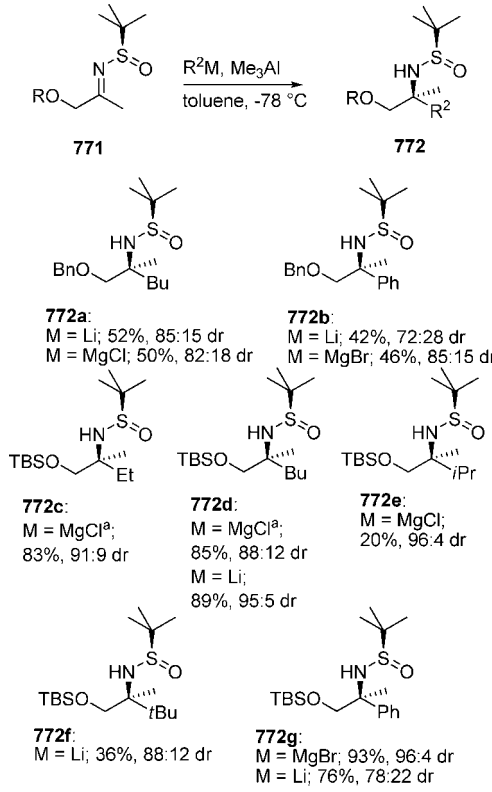
Scheme 182. Deprotection of 1,2-Amino Alcohols



benzyloxy imine **760** (Scheme 181) also proceeded smoothly, providing the desired adducts in most cases with slightly higher stereoselectivity than the additions to the silyl derivative, in agreement with the results from Barrow and co-workers. These reactions were performed in both the presence and absence of $AlMe_3$, which was found to have very little effect on many of the Grignard reactions but provided notable enhancement of diastereoselectivity in the organolithium additions. Protecting group manipulation of the adducts was also addressed (Scheme 182). Benzyloxy derivative **761j** was treated with HCl in MeOH to provide **762j** in 97% yield. Hydrogenolysis of the benzyl group then afforded free amino alcohol **765j** in 88% yield. Selective deprotection of silyloxy derivative **764j** to provide *N*-*tert*-butanesulfinyl amino alcohol **770j** was accomplished by treatment with HF/pyridine, while efficient removal of both the sulfinyl and silyl groups was accomplished by treatment with HCl in MeOH.

Ellman and co-workers also reported the direct synthesis of β,β-disubstituted β-amino alcohols via addition of organometallic reagents to α-benzyloxy or α-silyloxy *N*-*tert*-butanesulfinyl ketimines.[63] Using the reaction conditions previously developed for the addition of organolithium reagents to *N*-*tert*-butanesulfinyl ketimines (R^2Li, $AlMe_3$, toluene, −78 °C), additions of organolithium or Grignard reagents to an α-benzyloxy *N*-*tert*-butanesulfinyl ketimine **771** (R = Bn) provided disubstituted products **772a** and **772b** in moderate yields and with moderate diastereoselectivities (Scheme 183). Additions to α-silyloxy *N*-*tert*-butanesulfinyl ketimine **771** (R = TBS) were also explored. For the additions of unbranched alkyl Grignard reagents, $AlMe_3$ was unnecessary (**772c** and **d**), but for the more sterically hindered or aryl Grignard reagents, superior results were obtained with this Lewis acid additive. When more sterically hindered nucleophiles were utilized (R^2 = *i*Pr, *t*Bu), lower yields of the desired products (**772e** and **f**) were obtained due to competitive α-deprotonation of the ketimine precursor and subsequent self-condensation. Competitive methyl transfer from $AlMe_3$ to **771** was also a side reaction. While the addition of phenylmagnesium bromide to α-silyloxy *N*-*tert*-butanesulfinyl ketimine **771** proceeded smoothly, affording **772g** in 93% yield and with 96:4 dr, a significant drop in yield and diastereoselectivity was observed when phenyllithium was utilized. This drop in stereoselectivity was tentatively attributed to the presence of Et_2O in the commercially available solution of PhLi, which was absent in the solutions of *n*BuLi and *t*BuLi. The absolute configurations

Scheme 183. Additions of Organometallic Reagents to α-Alkoxy *N*-*tert*-Butanesulfinyl Ketimines



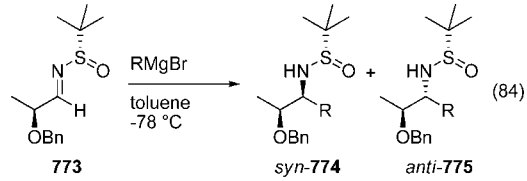
[a] No $AlMe_3$ was added.

of the products **772b**, **c**, and **g** were determined by chemical correlation experiments. Despite the presence of an α-chelating group, the stereochemistry was consistent with the sense of induction observed for additions of organometallic reagents to alkyl and aryl *N*-*tert*-butanesulfinyl ketimines (Scheme 78, section 5.1).

Evans and Ellman extended the scope of Grignard reagent addition to *N*-*tert*-butanesulfinyl α-alkoxy aldimines to include α-chiral aldimines.[64] Both diastereomers of each imine (with benzyl, TBS, and TBDPS alcohol protecting groups) were used to probe the effects of relative stereochemistry at the *N*-sulfinyl group and the α-stereocenter. The synthesis of each imine (via $Ti(OiPr)_4$-mediated condensation) and the subsequent reactions with Grignard reagents were all carried out without epimerization of the α-stereocenter, as determined by chiral HPLC analysis. Deprotections of the addition products to provide the *syn*- or *anti*-1,2-amino alcohols were carried out under similar conditions to those described previously for the addition products of *N*-*tert*-butanesulfinyl-α-alkoxyacetaldimines[63] (*vide supra*), and assignment of product stereochemistry was performed using either chemical correlation or NOE analysis of oxazolidinone derivatives of the free amino alcohols.

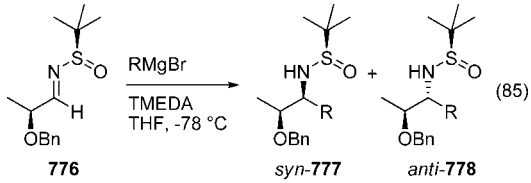
Additions of PhMgBr and EtMgBr to α-benzyloxy imine **773** in toluene proceeded smoothly, providing high yields and diastereoselectivities of the *syn*-1,2-amino alcohol adducts **774** (eq 84). This addition reaction represents a matched case between the inherent stereocontrol of the *N*-sulfinyl group (*vide supra*) and the Cram chelate model for additions to α-alkoxyaldehydes. In contrast, in the corresponding mismatched case for addition to α-benzyloxy imine **776**, only moderate stereoselectivity (23:77 to 14:86 *syn*/*anti*) was observed when the reaction was carried out in

toluene. However, the use of TMEDA as an additive in THF as a solvent, conditions that would be expected to disrupt a chelate-controlled transition state, allowed highly diastereoselective addition to form *anti*-1,2-amino alcohol adducts **778**, in which the stereochemical outcome is controlled by the *N*-sulfinyl stereochemistry (eq 85).



(84)

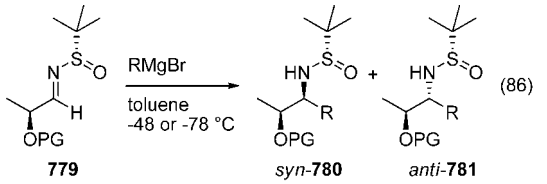
774a: R = Ph; 94%, 99:1 dr
774b: R = Et; 75%, 91:9 dr



(85)

778a: R = Ph; 80%, 5:95 dr
778b: R = Et; 86%, 2:98 dr

Addition of PhMgBr to the α-OTBDPS imine **779** proceeded with high *anti*-selectivity in either CH_2Cl_2 or toluene as the reaction solvent, while addition of EtMgBr to the same imine proceeded with moderate *anti*-selectivity in the same solvents (eq 86). The *anti*-stereochemistry observed in these addition reactions is consistent with both the Felkin−Ahn and Cornforth models for additions to α-alkoxy-aldehydes and is opposite to the selectivity that would be expected based on the *N*-sulfinyl stereochemistry. Meanwhile, addition of PhMgBr to the less bulky α-OTBS imine **779** proceeded with low stereoselectivity (**781c**), and addition of EtMgBr proceeded with *syn*-selectivity (**780d**).

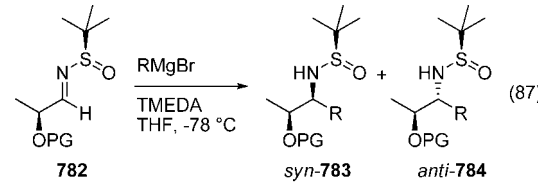


(86)

781a: PG = TBDPS, R = Ph; 86%, 7:93 dr
781b: PG = TBDPS, R = Et; 90%, 17:83 dr
781c: PG = TBS, R = Ph; 89%, 40:60 dr
780d: PG = TBS, R = Et; 94%, 92:8 dr

Additions of both PhMgBr and EtMgBr to *N*-*tert*-butanesulfinyl α-silyloxy imines **782** were carried out in THF with TMEDA as an additive to provide high *anti*-selectivity (12:88 to 2:98 *syn*/*anti*) for adducts **784** (eq 87). The *anti*-selectivity corresponds to a matched case between the *N*-sulfinyl stereocontrol and the Felkin−Ahn or Cornforth models. The beneficial effect of TMEDA suggests that, in the absence of additives, competitive chelation to the silyl ether lowers the diastereoselectivity.

Harried and co-workers investigated addition of organometallic reagents to *N*-*tert*-butanesulfinyl bis(silyloxy)imine **785**, providing *N*-sulfinyl amine products **786** (Scheme 184).[268] The directing effects of the *N*-sulfinyl group and the chiral α-silyloxy group are matched for this addition, to provide product **786a** with 85:15 dr favoring the *anti*-diastereomer. In contrast, when the corresponding *N*-*tert*-



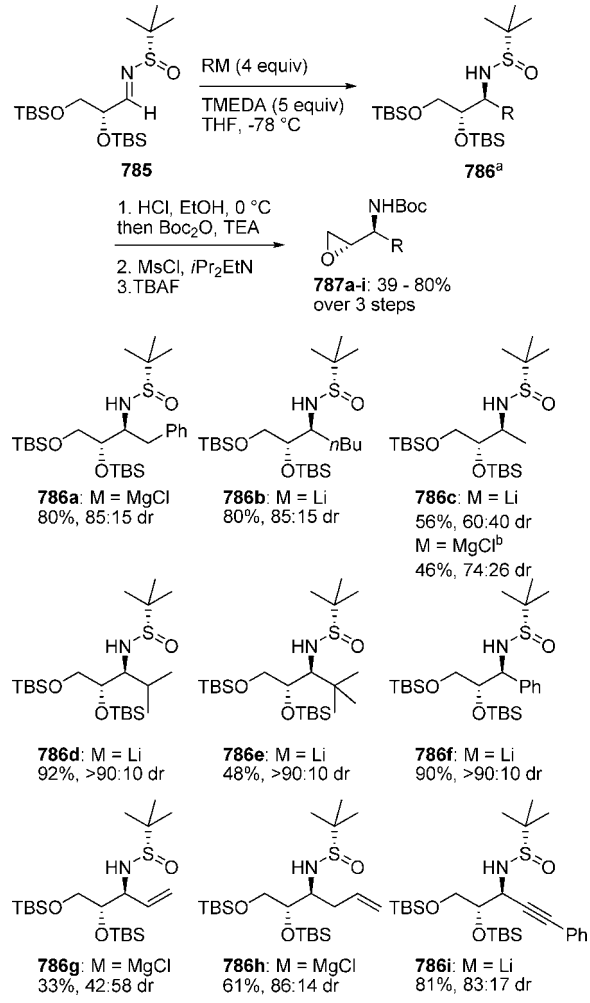
(87)

784a: PG = TBDPS, R = Ph; 72%, 12:88 dr
784b: PG = TBDPS, R = Et; 93%, 2:98 dr
784c: PG = TBS, R = Ph; 78%, 2:98 dr
784d: PG = TBS, R = Et; 81%, 2:98 dr

butanesulfinyl aldimine epimer derived from (*R*)-*tert*-butanesulfinamide was used, a 78:22 mixture of diastereomers (*anti*/*syn*) was obtained. Further transformations provided access to *anti*-*N*-Boc-3-amino-1,2-epoxides **787**, which are commonly used intermediates for the synthesis of inhibitors of aspartic acid proteases such as HIV protease as well as for BACE inhibitors. This route toward the amino epoxides circumvented several shortcomings of the previously used amino-acid based routes toward these intermediates, allowing late stage introduction of structural diversity and preventing epimerization at stereocenters α to a carbonyl group.

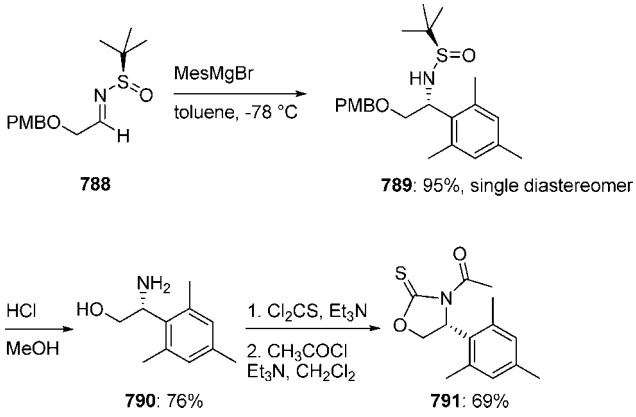
Several synthetic applications of additions to α-alkoxy aldimines have been reported. Crimmins and Shamzad reported the addition of mesitylmagnesium bromide to α-alkoxy imine **788**, which gave a single diastereomer of

Scheme 184. Synthesis of *anti*-*N*-Boc-3-Amino-1,2-epoxides

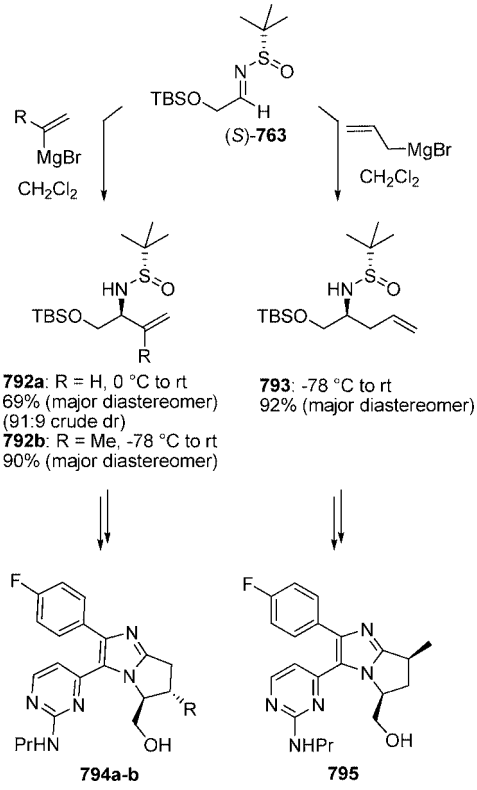


[a] Isolated yield of pure *anti*-diastereomer, dr (*anti*/*syn*) determined by mass balance of separated diastereomers after silica gel chromatography. [b] Reaction conducted at −45 °C.

Scheme 185. Aryl Grignard Addition to an α-Benzyloxy *N-tert*-Butanesulfinyl Aldimine



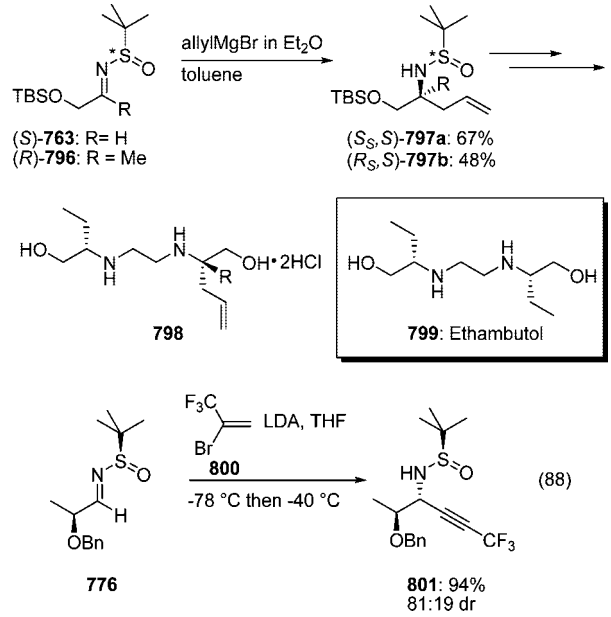
Scheme 186. Grignard Additions to an α-Silyloxy-*N-tert*-butanesulfinyl Aldimine



product **789** in high yield (Scheme 185).[269] This adduct was further elaborated to provide *N*-acetyloxazolidinethione **791**, which was used for stereoselective acetate aldol reactions.[270] In another example, Bergman, Ellman, and co-workers utilized the stereoselective addition of allyl and vinyl additions to α-silyloxy imine (*S*)-**763** in the synthesis of bisarylimidazoles **794** and **795**, which are inhibitors of c-jun *N*-terminal kinase 3 (Scheme 186).[271] Lee and Yendapally also carried out allylations of α-silyloxy *N-tert*-butanesulfinyl aldimine **763** and ketimine **796** in their synthesis of analogues of ethambutol (**799**), a drug used for the treatment of tuberculosis (Scheme 187).[272]

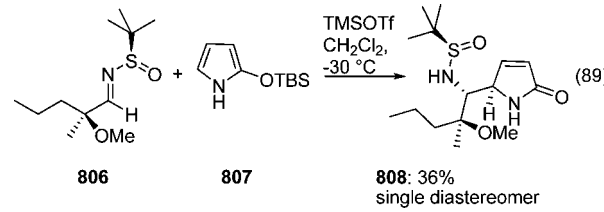
Recently, Konno and co-workers demonstrated a synthesis of a γ-trifluoromethyl substituted *N-tert*-butanesulfinyl propargylamine **801** (eq 88).[273] *N-tert*-Butanesulfinyl imine **776** was treated with 2-bromo-3,3,3-trifluoropropene (**800**) and LDA at low temperature, providing **801** in 94% yield as a 81:19 mixture of diastereomers.

Scheme 187. Synthesis of Ethambutol Analogues



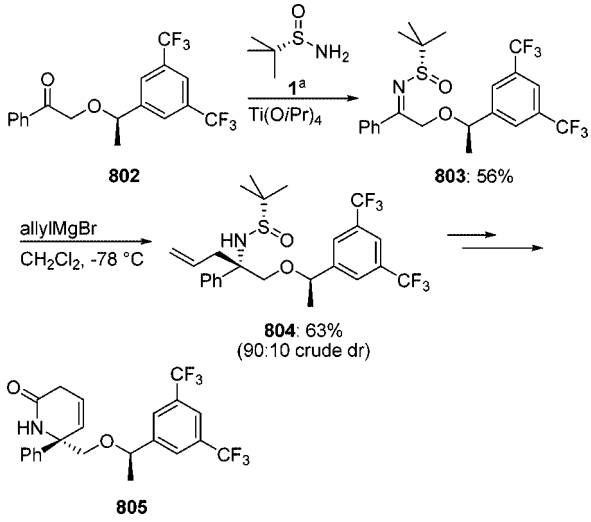
Xiao and co-workers at Schering-Plough developed an asymmetric synthesis of a neurokinin (NK_1) receptor antagonist utilizing *tert*-butanesulfinamide chemistry to set a piperidine quaternary center (Scheme 188).[274] The authors noted that synthesis of the requisite *N-tert*-butanesulfinyl ketimine **803** was challenging, requiring modification of the standard imine formation reaction conditions (neat $Ti(OiPr)_4$ instead of $Ti(OEt)_4$/EtOH) to circumvent the low reactivity of the sterically hindered ketone **802**. Allylation of ketimine **803** using allylmagnesium bromide in CH_2Cl_2 at low temperature (−78 °C) provided **804** with 90:10 diastereoselectivity. The reaction was performed on a multigram scale, and diastereomerically pure material was obtained after column chromatography. The stereochemistry of the product was confirmed by correlation of product **805** with previously synthesized material.

In their preliminary studies on the preparation of an influenza neuraminidase inhibitor, DeGoey and co-workers at Abbott Laboratories explored the condensation of α-alkoxy *N-tert*-butanesulfinyl imine **806** with silyloxypyrrole **807** to afford the key intermediate, pyrrolinone **808**, in their synthetic sequence (eq 89).[275] Although the product was obtained with complete stereocontrol, the yield of **808** was low (36%) under the reaction conditions surveyed.



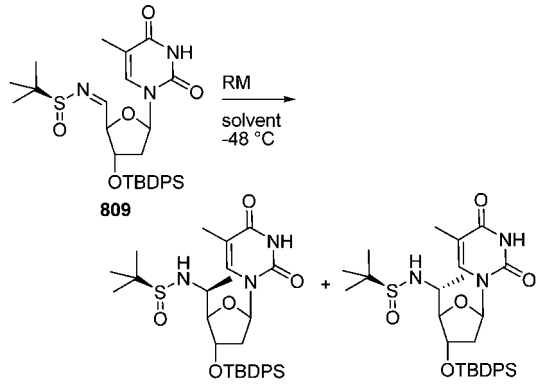
Jung and co-workers from Syngenta reported the addition of organometallic reagents to *N-tert*-butanesulfinyl aldimine **809** for the synthesis of 5′-amino-5′-methyl-2′,5′-dideoxynucleosides **810** and **811** as inputs for RNA and DNA analogues for therapeutic and diagnostic applications (Scheme 189).[276] Adducts **810** and **811** were chromatographically separable, allowing isolation of each despite the moderate diastereoselectivity for the reaction. In contrast, addition to the imine diastereomer derived from (*R*)-*tert*-butanesulfina-

Scheme 188. Preparation of NK_1 Receptor Antagonist 805



[a] The sulfinyl stereocenter is consistently depicted with the (*S*) configuration, but the manuscript states that (*R*) sulfinamide (**1**) was used.

Scheme 189. Synthesis of 5′-Amino-5′-methyl-2′,5′-dideoxynucleosides

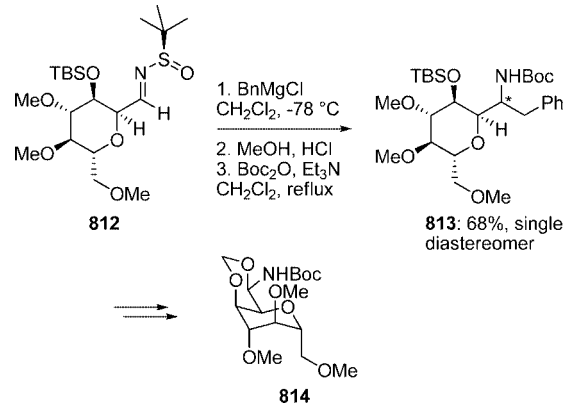


	810	811
MeMgBr, Et_2O -48 °C to rt	76%	15%
MeLi, THF, -48 °C	30%	65%

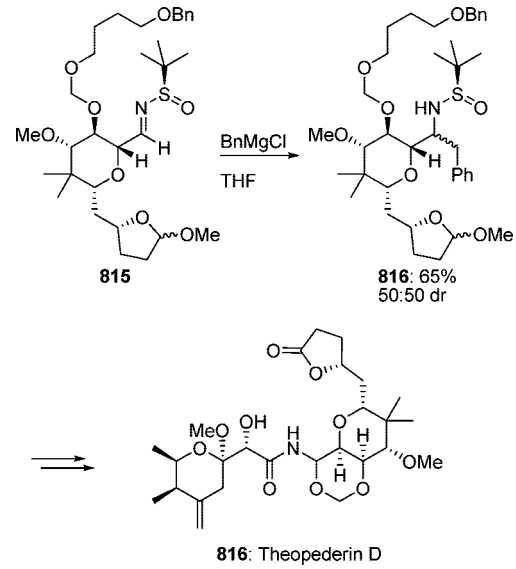
mide resulted in inseparable mixtures of products. The highest yield of **810** was obtained upon addition of MeMgBr in Et_2O, while the highest yield of **811** was obtained from the addition of MeLi in THF.

The first addition of an organometallic reagent to a sugar-derived *N-tert*-butanesulfinyl aldimine was disclosed by Rech and Floreancig in their work toward the synthesis of amido trioxadecalins.[277] Addition of BnMgCl to imine **812**, followed by sulfinyl cleavage and Boc protection of the resulting amine, proceeded in high yield (68% over three steps, Scheme 190). While complete diastereoselectivity was observed in this transformation, the stereochemistry of the product was not determined because a subsequent oxidative cyclization (via an sp^2-hybridized acyliminium ion) results in a loss of that stereochemical information. Floreancig and co-workers utilized a related addition reaction in the total synthesis of theopederin D (Scheme 191).[278] While the addition of BnMgCl to imine **815** proceeded without diastereoselectivity (the opposite sulfinyl epimer provided comparable results), the resulting stereocenter was again inconsequential because it was transformed into an acyliminium ion in a subsequent oxidative cyclization reaction.

Scheme 190. Grignard Addition in the Synthesis of Amido Trioxadecalins

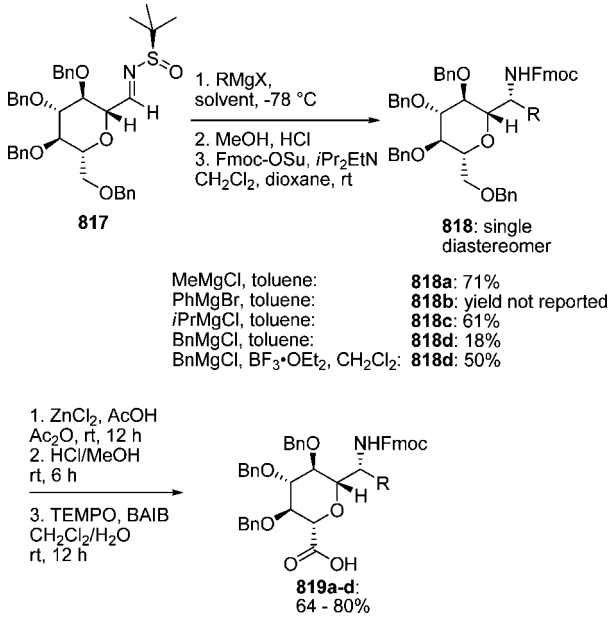


Scheme 191. Synthesis of Theopederin D

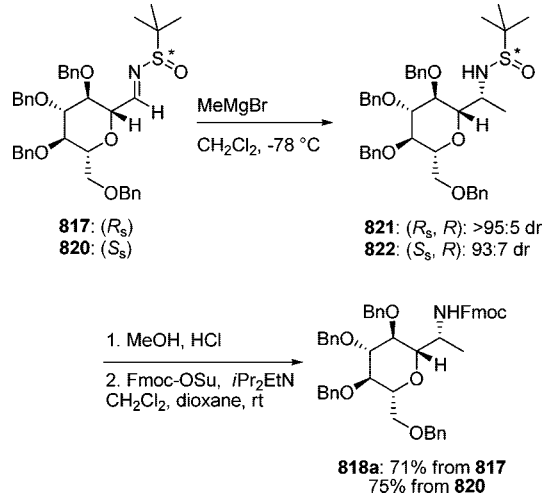


Overhand and co-workers described the highly diastereoselective addition of several Grignard reagents to sugar-derived *N-tert*-butanesulfinyl aldimines **817** followed by protecting group manipulation to provide Fmoc-protected amines **818** in good overall yields (50−71% over three steps, Scheme 192).[279] Subsequent selective debenzylation and oxidation of the primary alcohol provided sugar amino acids (SAAs) **819**. While the addition reaction was efficient in toluene for most substrates, benzyl addition under these conditions led to significant decomposition. In this case, use of CH_2Cl_2 as the reaction solvent in the presence of $BF_3 \cdot OEt_2$ allowed isolation of the desired product in reasonable yield. These SAAs are of interest for use as dipeptide isosteres, and the use of methyl derivative **819a** under standard peptide coupling conditions was demonstrated. In an attempt to access the epimers of these SAAs, addition to the analogous imine **820** derived from (*S*)-*tert*-butanesulfinamide was attempted.[280] However, upon sulfinyl deprotection, the same major diastereomer of **818a** was obtained, albeit with slightly lower stereoselectivity (Scheme 193). This reveals that the stereoselectivity in this addition is dominated by the sugar and not by the sulfinyl group.

Scheme 192. Synthesis of Sugar Amino Acids (SAAs)



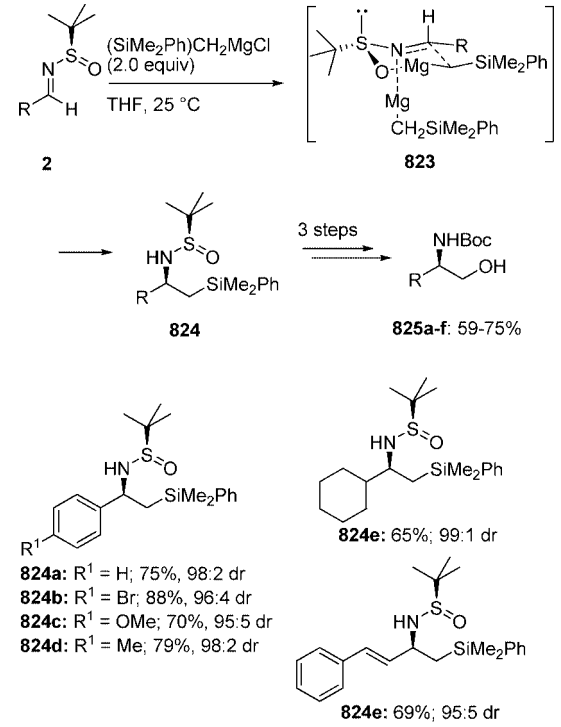
Scheme 193. Stereochemistry of Addition Reaction[280]



11.2. 1,2-Addition of α-Substituted Organometallic Reagents to *N-tert*-Butanesulfinyl Imines

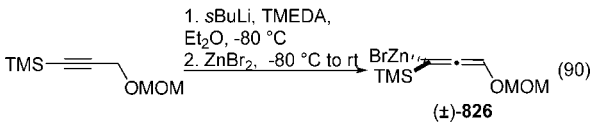
Kim and co-workers investigated the addition of a silyl-functionalized Grignard reagent to *N-tert*-butanesulfinyl aldimines **2** (Scheme 194).[281] The desired products **824** were obtained with superior yield and stereoselectivity when THF was used as a reaction solvent (compared to Et_2O, CH_2Cl_2, and toluene). Careful control of reaction stoichiometry was found to be essential, with no product formation in the presence of only 1 equiv of the Grignard reagent and with lowered stereoselectivity in the presence of more than 2 equiv of Grignard reagent. Chelated transition state **823** is proposed, in which the second equivalent of the Grignard reagent is necessary to activate the imine for attack by the Grignard reagent, which is a relatively weak nucleophile due to the α-anion stabilizing effect of silicon. The utility of the α-silyl amines **824** was demonstrated by replacement of the sulfinyl group with a carbamate protecting group, followed by Tamao−Fleming oxidation of the silyl group to 1,2-amino alcohols **825a**−**f** in good yield. Because the hydroxyl group is derived from the nucleophilic fragment, this approach is complementary to Grignard addition to α-alkoxy imines.

Scheme 194. Addition of α-Silylmethylmagnesium Chloride to *N-tert*-Butanesulfinyl Imines



Ferreira and Chemla explored the addition of 3-alkoxy allenylzinc species (±)-**826**, prepared according to eq 90, to *N-tert*-butanesulfinyl imines. This transformation provided an efficient route to chiral acetylenic *anti*-1,2-amino alcohols **829** via a kinetic resolution (Scheme 195).[282] Several parameters were evaluated to identify the optimal reaction conditions. The higher reactivity of (±)-**826**, as compared to its 3-chloro derivative (see section 17.3), resulted in a rapid reaction at lower reaction temperatures (−80 °C). Addition of an excess of (±)-**826** and a catalytic amount of TMEDA provided the desired products **828** in the highest yields and >95:5 diastereomeric ratios. For adducts **828a**, **e**, and **f**, derived from unbranched aliphatic *N-tert*-butanesulfinyl aldimines **2**, a slow addition of the imine to the reaction mixture was required to achieve high levels of stereoselectivity (>20:1 *anti*/*syn*). However, for the less reactive secondary or unsaturated *N-tert*-butanesulfinyl aldimines, slow addition was not necessary. Based on these observations, the authors hypothesize that the racemization of allenylzinc (±)-**826** is comparable to its rate of reaction with the primary *N-tert*-butanesulfinyl aldimines but fast relative to its reaction with less reactive *N-tert*-butanesulfinyl imines. With the hindered aldimine **2** (R = *t*Bu), none of the desired product **828d** was observed at −80 °C, and higher temperatures resulted in poor stereoselectivites and a complex mixture of isomers. An *N-tert*-butanesulfinyl ketimine also afforded adduct **828i** with high diastereoselectivity but in moderate yield due to competitive byproduct formation under the reaction conditions. The stereochemistry of **828h** was established by X-ray crystal structural analysis. The observed *anti*-stereoselectivity was rationalized by transition state **827**, where the zinc is solely coordinated to the nitrogen of the *tert*-butanesulfinyl group and addition of the nucleophile occurs from the less hindered *Si*-face of the imine.

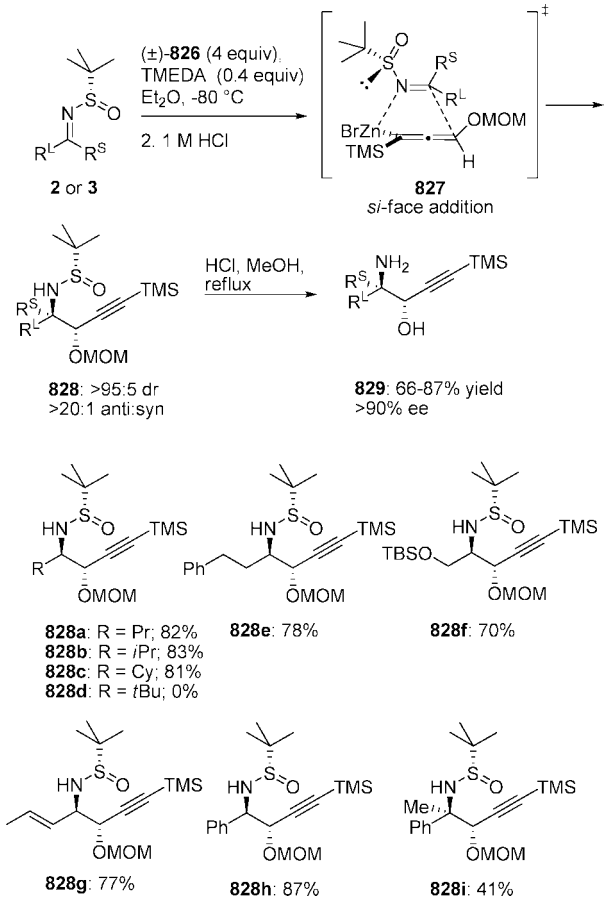
Concomitant removal of the sulfinyl group and methoxymethyl (MOM) ether moiety of the acetylenic 1,2 amino ethers **828** under acidic conditions afforded the corresponding



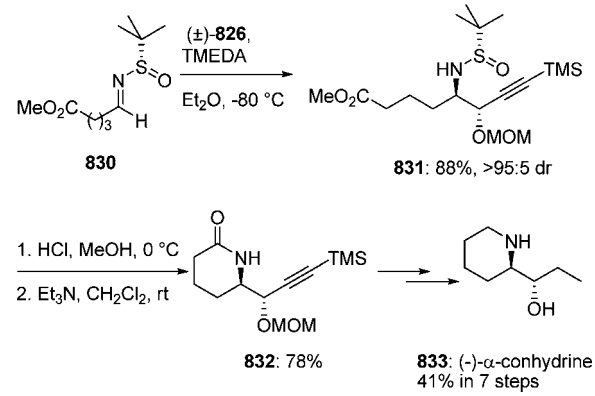
anti-1,2-amino alcohols **829** in good isolated yields (66−87%) without any detectable racemization (Scheme 195).[283] When adduct **828f** was subjected to these reaction conditions, removal of the primary alcohol silyl protecting group was also observed. Of note, these *anti*-1,2-amino alcohols are enantiomeric to those obtained by the ring-opening of acetylenic *N*-*tert*-butanesulfinyl aziridines (see section 11.3). Additionally, this methodology is compatible with a wider substrate scope than the analogous synthesis of *anti*-1,2-amino alcohols via the aziridine ring-opening protocol (see section 11.3). Selective deprotection of the sulfinyl group was achieved by treatment of **828f** with methanolic HCl at low temperatures, but selective removal of the MOM ether was not achieved.

This methodology was further applied to the synthesis of (−)-α-conhydrine, an alkaloid isolated from the seeds and leaves of the poisonous plant *Conium maculatum* L (Scheme 196).[284] The reaction between *N*-*tert*-butanesulfinyl imine **830** and the *in situ* formed (±)-**826** provided compound **831** in 88% yield as a single isomer, as determined by ^{1}H NMR. An X-ray crystal structure of a more advanced intermediate confirmed the *anti*-relationship of the two new stereogenic centers. Quantitative deprotection of the sulfinyl group of **831** was achieved at 0 °C under acidic conditions, and base-promoted cyclization gave lactam **832** in 78% yield. Subsequent transformations generated (−)-α-conhydrine (**833**) in a total of seven steps and a 41% overall yield.

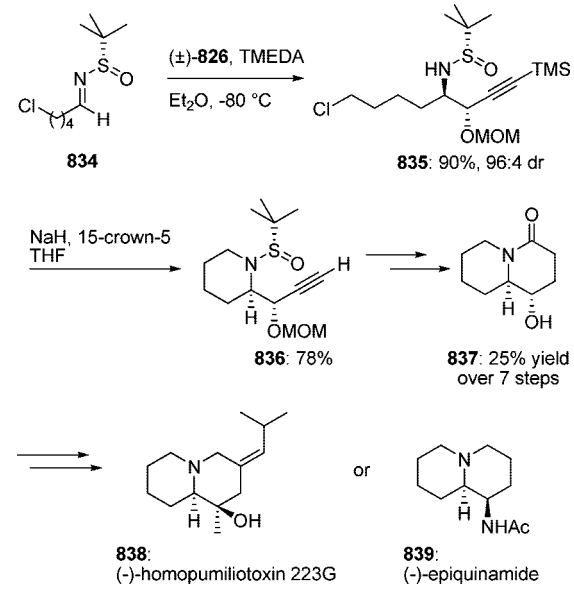
Scheme 195. Synthesis of *N*-*tert*-Butanesulfinyl α-Alkyl Methoxymethyl Ethers



Scheme 196. Synthesis of (−)-α-Conhydrine



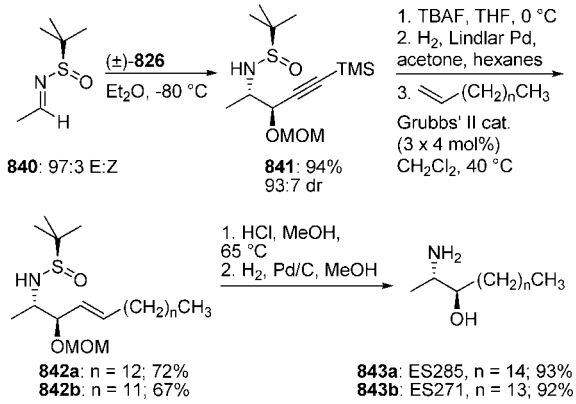
Scheme 197. Formal Synthesis of (−)-Homopumiliotoxin 223G and (−)-Epiquinamide



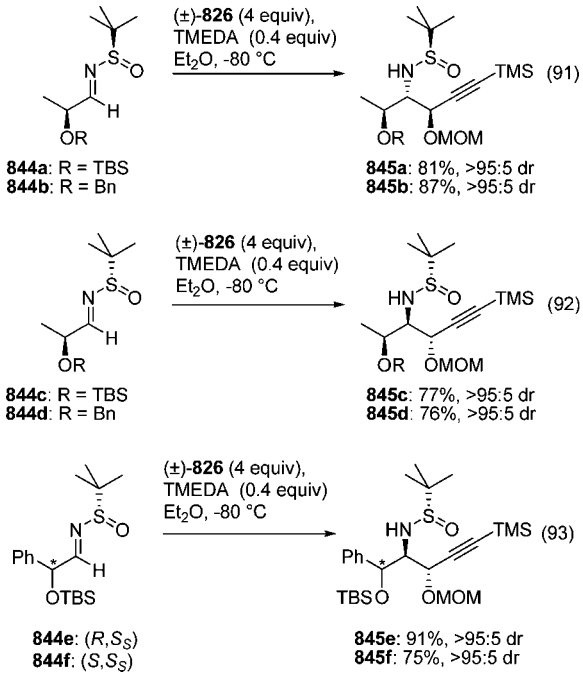
The formal syntheses of the alkaloids (−)-homopumiliotoxin 223G and (−)-epiquinamide via the common intermediate **837** were also demonstrated by Chemla and co-workers (Scheme 197).[285] The addition of racemic allenylzinc species (±)-**826** to *N*-*tert*-butanesulfinyl imine **834** yielded the desired product **835** in 90% yield and with a 96:4 diastereomeric ratio. Removal of the silyl group from the acetylenic position and cyclization by *N*-alkylation were achieved in the presence of NaH to give **836** in 78% yield after purification to remove the minor isomer. Further synthetic transformations provided **837** in a 25% overall yield, completing the formal syntheses of **838** and **839**.

Chemla, Ferreria, and co-workers also reported the syntheses of spisulosines ES285 and ES271, two bioactive molecules that display anticancer activity, from *N*-*tert*-butanesulfinyl imine **840** and allenylzinc reagent (±)-**826** (Scheme 198).[286] The coupling reaction proceeded in 94% yield, generating the common intermediate **841** as a 93:7 mixture of diastereomers. Removal of the silyl group, hydrogenation of the terminal alkyne to the alkene in the presence of Lindlar catalyst, and subsequent olefin cross-metathesis using a portionwise addition of 12 mol% Grubbs' II catalyst afforded **842a** and **b** in good yields. Sulfinyl deprotection and hydrogenation of the internal alkene completed the syntheses of spisulosines ES285 and ES271 from **840** in six steps and 62% and 58% overall yields, respectively.

Scheme 198. Synthesis of Spisulosines ES285 and ES271

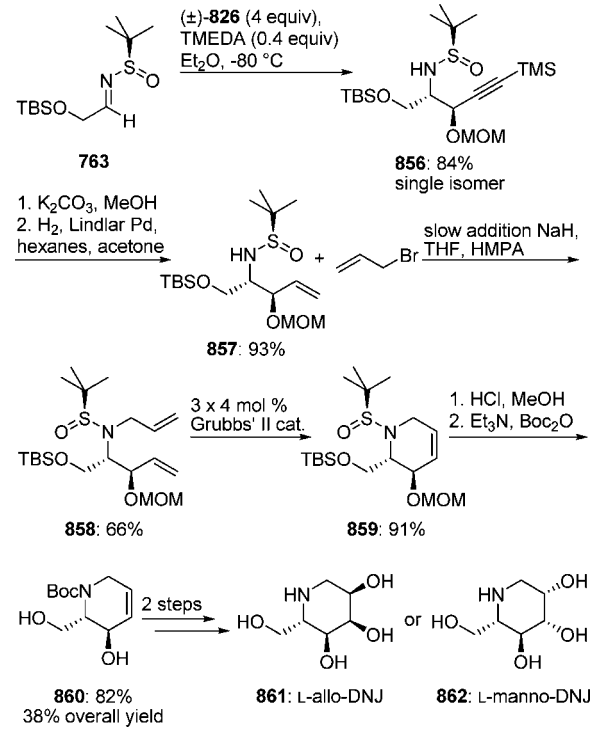


Recently, Chemla, Ferreira, and co-workers have expanded their method to include the synthesis of 2-amino-1,3-diol stereotriads via the addition of (±)-**826** to *N*-*tert*-butanesulfinyl α-alkoxy imines **844a**−**f** (eqs 91−93).[287] Following the previously reported reaction conditions, the silyl- and benzyl-protected *N*-*tert*-butanesulfinyl amines **845a**−**b** were generated in an 81% and 87% yield, respectively, with >95:5 dr (eq 91). The relative and absolute configurations were determined by derivatization and established that **845a**−**b** displayed an *anti*,*anti*-relationship, corresponding to the addition of the nucleophile to the *Re*-face of the imine. The analogous reaction with the diastereomeric imines **844c**−**d** provided **845c**−**d** with excellent stereoselectivity in 76−77% yield (eq 92). These compounds displayed a *syn*,*anti*-relationship, indicative of addition to the *Si*-face of the imine. The influence of the substituent at the α-alkoxy stereocenter was also probed, and uniformly high diastereoselectivities were observed (**845e**−**f**, eq 93). In all cases, the stereochemical outcome was governed solely by the configuration of the *tert*-butanesulfinyl group.

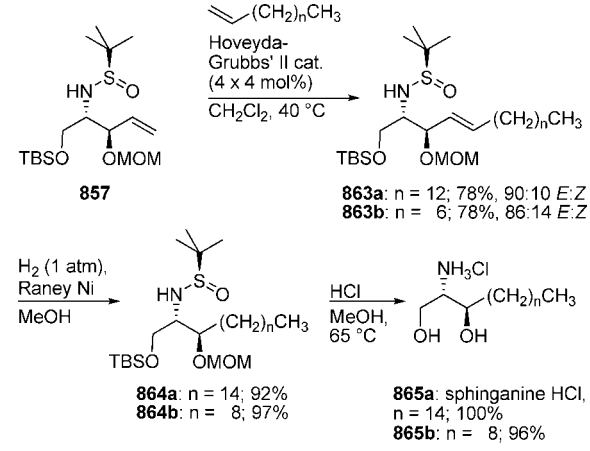


Ferreira, Chemla, and co-workers utilized this methodology to prepare a common intermediate **860** to both L-1-deoxyallonojirimycin (**861**) and L-1-deoxymannojirimycin (**862**) (Scheme 199).[288] The synthesis began with the addition

Scheme 199. Synthesis of 860, a Common Intermediate for of L-allo-DNJ and L-manno-DNJ



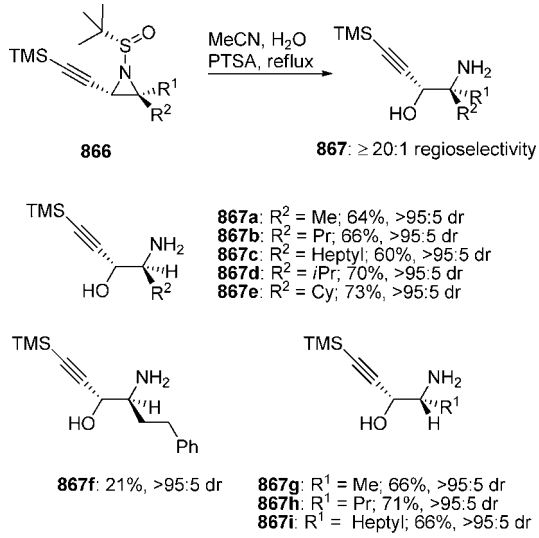
Scheme 200. Synthesis of Sphingoid-Type Bases 865



of (±)-**826** to α-silyloxy *N*-*tert*-butanesulfinyl imine **763**. The desired product **856** was isolated as a single isomer in high yield and was further converted to **857** after desilylation and Lindlar hydrogenation of the alkyne. Slow addition of NaH to a mixture of **857** and allyl bromide provided **858** in 66% yield. Ring closing metathesis to give the 3,6-dihydro-2*H*-pyridine sulfinamide **859** proceeded in good yield when 12 mol % of Grubbs II catalyst was added in three portions over 60 h. Cleavage of the sulfinyl, silyl, and MOM groups under acidic conditions followed by Boc protection provided the target compound **860** in 38% overall yield from *N*-*tert*-butanesulfinyl imine **763**.

Intermediate **857** was also used in the synthesis of sphinganine (**865a**) as well as the first synthesis of the hydrolysis product (**865b**) of clavaminol H, which has been shown to display selective cytotoxicity in gastric carcinoma (Scheme 200).[286] Adduct **857** was subjected to olefin cross-metathesis conditions, providing **863a** and **b** in good yields as predominantly the *E* isomers when 16 mol % of the Hoveyda-Grubbs' II catalyst was added in four aliquots over

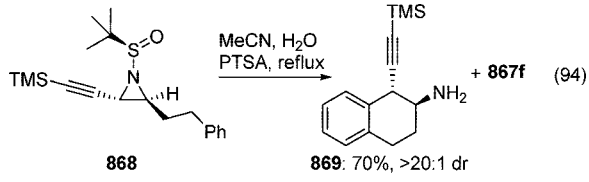
Scheme 201. Regio- and Stereoselective Ring-Opening of *N-tert*-Butanesulfinyl Aziridines



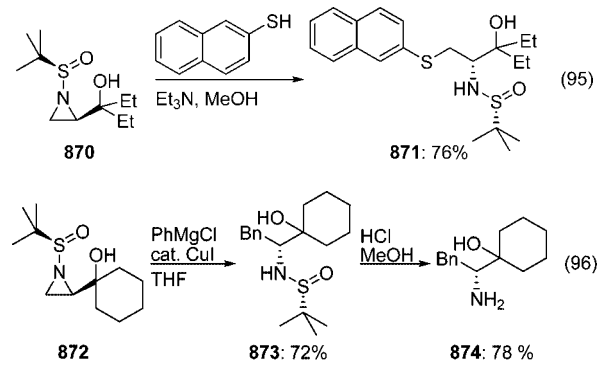
60 h. Hydrogenation of each alkene was achieved in the presence of Raney nickel, and subsequent global deprotection of the sulfinyl, silyl, and ether functionalities then provided **865a** and **b**.

11.3. Ring-Opening of *N*-Sulfinyl Aziridines

Ferreira and co-workers have developed efficient methods for the preparation of *trans*- and *cis*-*N*-*tert*-butanesulfinyl aziridines **866** (see section 17.3) and have further demonstrated that these compounds are useful intermediates for the preparation of enantiomerically pure acetylenic 1,2-amino alcohols **867** (Scheme 201).[289] Application of the reaction conditions developed by Concellon and co-workers[290] for the ring-opening of nonactivated aziridines (1 equiv of *p*-toluenesulfonic acid (PTSA), reflux in 7:1 MeCN/H_2O) resulted in concomitant aziridine ring-opening and removal of the sulfinyl group, providing the acetylenic 1,2-amino alcohols **867** with high regio- and diastereoselectivity. Indeed, products **867a**−**i** were formed with >95:5 diastereomeric ratios, as determined by ^{1}H NMR and <5% of the corresponding regioisomers. Isolated yields for the products ranged from 60 to 73%, except for **867f**, which was obtained in 21% yield. In this case, **867f** was the minor product, and compound **869**, generated from the intramolecular 6-endocyclization of the aryl moiety, was isolated as the major product in 70% yield as a single diastereomer (eq 94). The authors also noted that acetylenic α-amino alcohols derived from *trans*-aziridines with alkenyl or aryl substituents could not be obtained, and only unidentified byproducts were observed under the optimal reaction conditions. Derivatization of **867f** to an oxazolidinone and analysis by ^{1}H NMR confirmed the regioselective ring-opening of **866** by water at the more electrophilic propargylic carbon. NOE experiments on the oxazolidinone derivatives of **867b** and **867h** confirmed the stereochemistry of the acetylenic 1,2-amino alcohols.



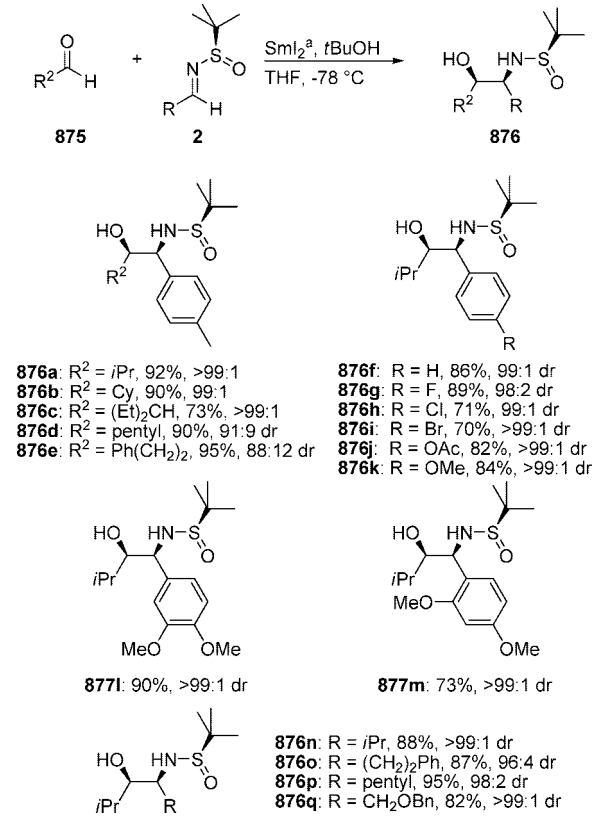
The synthesis of 1,2-amino alcohols via nucleophilic ring-opening of α-hydroxy aziridines was demonstrated by Hodgson and co-workers (eqs 95 and 96; for the synthesis of these aziridines, see section 17.6).[291]



11.4. Reductive Coupling of Imines with Aldehydes and Ketones

The SmI_2 induced pinacol-type reductive coupling of *N*-*tert*-butanesulfinyl aldimines with aldehydes has proven to be a very powerful method for the convergent synthesis of β-amino alcohols (Scheme 202).[292] Addition of a solution of *N*-*tert*-butanesulfinyl aldimine **2** (R = 4-Me-Ph) and aliphatic aldehydes **875** in *t*BuOH to a precooled solution of SmI_2 in THF at −78 °C provided **876a**−**e** in high yields (73−95%) and with high diastereomeric ratios, ranging from 88:12 to >99:1. The lowest diastereoselectivites were observed when linear aliphatic aldehydes were employed (**876d** and **e**). Electronically diverse *para*-substituted benzaldimines

Scheme 202. Reductive Cross-Coupling of Aldehydes with *N*-*tert*-Butanesulfinyl Imines in the Presence of SmI_2[292]



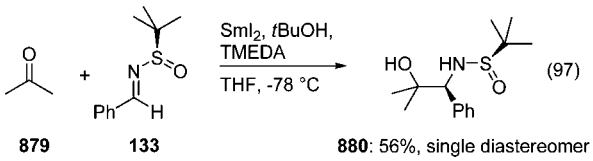
[a] Slow addition of a solution of **875**, **2**, and *t*BuOH to SmI_2.

2 were also suitable coupling partners, providing **876f−k**, but lower yields were observed for the aromatic imine substrates with bromo- or chloro-substituents, due to the formation of some homocoupled product (**876h** and **i**). *Meta*- and *ortho*-substituted benzaldimines were also evaluated, with products **876l** and **m** obtained with >99:1 dr and in 90% and 73% yields, respectively. In addition, aliphatic *N*-*tert*-butanesulfinyl aldimines **2** were examined for the reductive coupling reaction with isobutyraldehyde, and the corresponding products were isolated in high yields and diastereomeric ratios (**876n−q**). In contrast, little to no desired cross-coupling product was obtained for the reaction between benzaldehyde or *p*-tolualdehyde and imine **2** (R = 4-Me-Ph). Instead, a significant amount of pinacol formation from homocoupling of the aryl aldehyde was observed. The free β-amino alcohols were generated from adducts **876a−q** by acidic cleavage of the sulfinyl group. The absolute configuration of the coupled products was based upon an X-ray crystal structure of **876i**.

Soon after the initial report by Xu, Lin, and co-workers, Bentley and co-workers reported almost identical conditions for the reductive coupling of *N*-*tert*-butanesulfinyl aldimines with aldehydes, where the primary difference was a slow addition of SmI_2 to the reaction mixture (Scheme 203).[293] A series of linear, β-branched, α-branched, and functionalized aldehydes were surveyed with imine **2** (R = Ph). Yields were generally high (69−91%), and the diastereoselectivities for **876r−w** ranged from 86:14 to 90:10. When the highly sterically hindered aldehyde **875** (R = *t*Bu) was employed, the highest diastereoselectivity was observed (>96:4), but at the cost of a low yield (**876w**). The effect of electronically different substituents on the aryl moieties of some *N*-*tert*-butanesulfinyl imines was also probed (**876x−z**). The reductive coupling between an aliphatic *N*-*tert*-butanesulfinyl imine and isobutyraldehyde was also reported, and in this case **876n** was isolated in 51% yield and with 89:11 dr.

Bentley and co-workers also reported a three-step synthesis of (−)-cytoxazone, a cytokine modulator that has been shown to inhibit the Th2 cell's signaling pathway,[294] from the SmI_2 mediated reductive coupling product, amino alcohol *ent*-**876z** (Scheme 204).[293] Removal of the sulfinyl group and transformation to the oxazolidinone provided **877** in 85% yield. Deprotection of the primary alcohol then yielded (−)-cytoxazone in 86% yield.

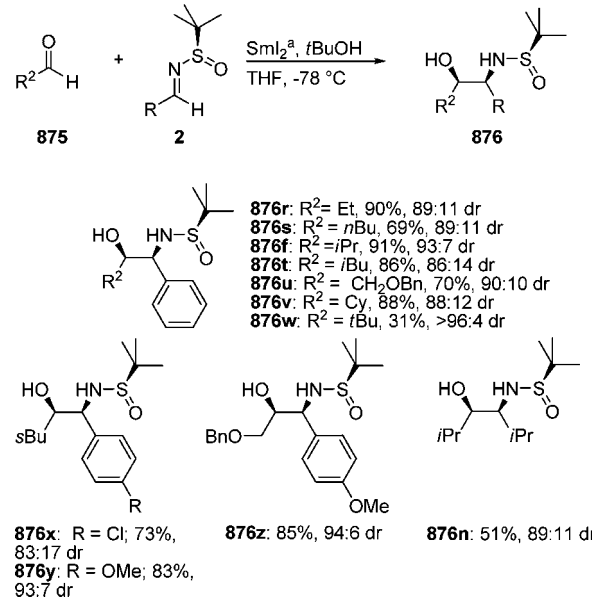
The first example of a SmI_2 induced reductive coupling of an *N*-*tert*-butanesulfinyl aldimine with a ketone was also provided (eq 97).[293] For this substrate combination, an improvement in yield was observed when TMEDA was used as an additive, and **880** was obtained in moderate yield as a single diastereomer.



879 **133** **880**: 56%, single diastereomer

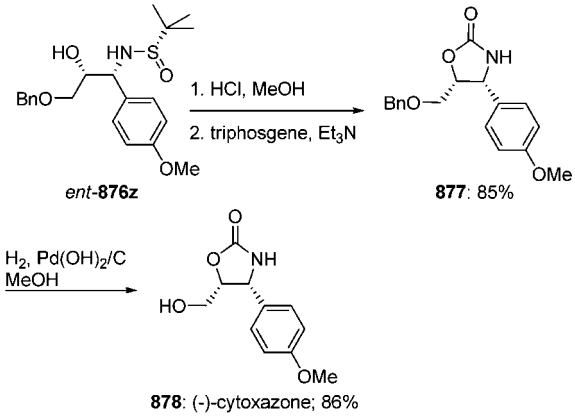
An intramolecular reductive coupling of *N*-*tert*-butanesulfinyl imines with ketones was reported by Wang and Wang (Scheme 205).[295] Initial attempts to promote an intermolecular SmI_2-mediated reductive coupling between an *N*-*tert*-butanesulfinyl ketimine and acetophenone were unsuccessful. However, upon employing the reaction conditions optimized for the reductive coupling of aldehydes and

Scheme 203. Reductive Cross-Coupling of Aldehydes with *N*-*tert*-Butanesulfinyl Imines in the Presence of SmI_2[293]



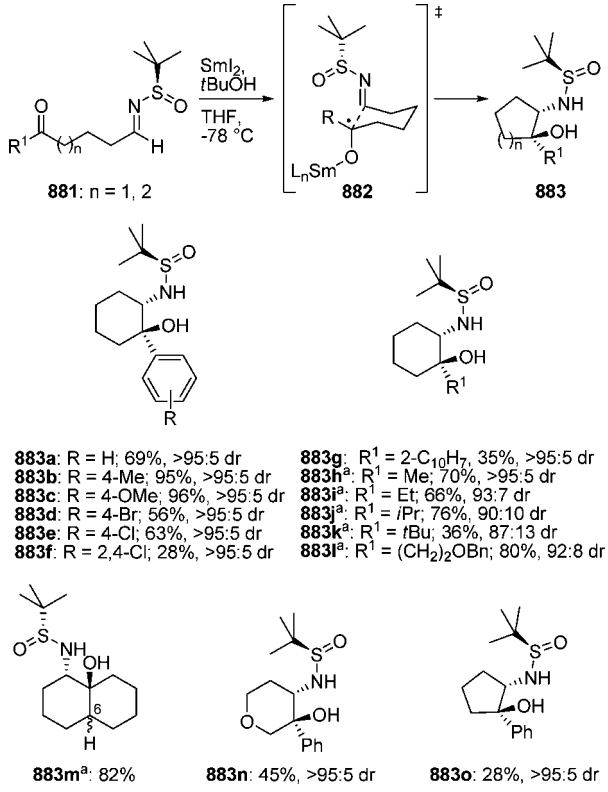
[a] Slow addition of SmI_2 to a solution of **875**, **2**, and *t*BuOH.

Scheme 204. Synthesis of (−)-Cytoxazone

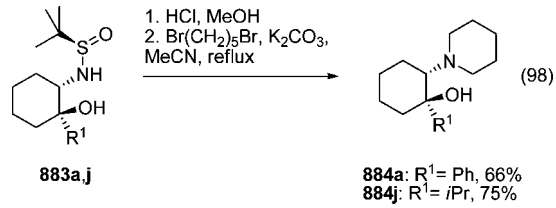


N-*tert*-butanesulfinyl imines (2 equiv of SmI_2 and 3 equiv of *t*BuOH) to substrate **881** (R^1 = Ph, n = 2), cyclization product **883a** was obtained in 69% yield with >95:5 dr. A number of electron-rich and poor aryl substituted ketones were employed in the reaction, providing **883b−g** in moderate to good yields and with excellent diastereoselectivities. When alkyl substituted ketones were examined, the authors noted that the addition of 4 equiv of *t*BuOH and 16 equiv of HMPA was necessary to obtain optimal results. Under these conditions, **883h−l** were generated in 36−80% yield and 87:13 to >95:5 dr. The fused bicyclic product **883m** was obtained in 84% yield with a dr of 70:30 at C6. Because the diastereomeric ratio at the stereocenter α to the ketone starting material was 1:1, the authors hypothesize that equilibration prior to cyclization occurred. The heterocyclic product **883n** was produced in moderate yield (45%) and excellent diastereoselectivity. Formation of the five-membered ring in **883o** was also successful, albeit in lowered yields, but the authors noted that attempts to generate the seven-membered ring failed. The absolute configurations of **883a** and **j** were determined by X-ray structural analysis rationalized by transition state **882**. Conversion of **883a** and **j** to the known chiral catalyst **884a**[296] and the novel derivative **884j**, respectively, was also demonstrated (eq 98).

Scheme 205. SmI_2-Promoted Intramolecular Reductive Coupling between Ketones and *N-tert*-Butanesulfinyl Imines



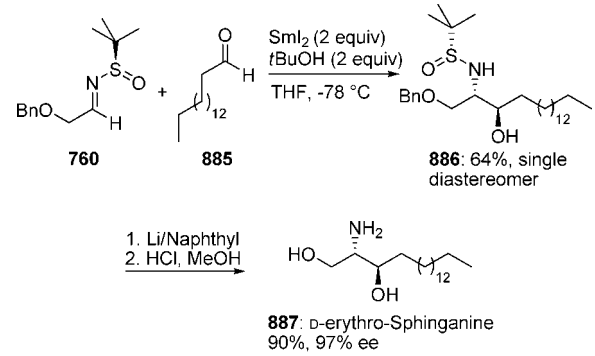
[a] Sixteen equiv of HMPA was used as an additive.



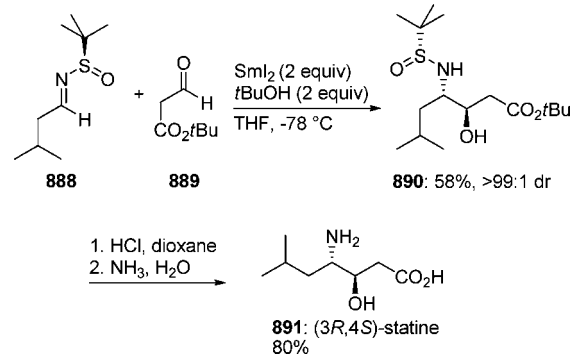
The utility and efficiency of the SmI_2 mediated reductive coupling of *N-tert*-butanesulfinyl imines with aldehydes for the direct synthesis of β-amino alcohols has been amply demonstrated in the preparation of a number of biologically active molecules. In their initial report, Xu, Lin, and co-workers completed the syntheses of D-*erythro*-sphinganine and (3*R*,4*S*)-statine.[292] The cross-coupling of palmitaldehyde **885** and *N-tert*-butanesulfinyl imine **760** provided *N-tert*-butanesulfinyl β-amino alcohol **886** in 64% yield as a single diastereomer (Scheme 206). Removal of the benzyl and sulfinyl groups provided **887** in 90% yield to complete a highly expedient synthesis of D-*erythro*-sphinganine. Xu, Lin, and co-workers further reported a very efficient synthesis of (3*R*,4*S*)-statine via the reductive coupling of aldehyde **889** with imine **888** to afford 1,2-amino alcohol **890** in 58% yield and with >99:1 dr (Scheme 207). Concomitant cleavage of the *N*-sulfinyl group and the *tert*-butyl ester by acid treatment then provided enantiomerically pure statine (**891**) in high yield.

More recently, Wang, Xu, Lin, and co-workers have applied this methodology to the synthesis of (+)-CP-99,994 and (+)-L-733,060, two potent and selective human neurokinin-1 substance P receptor antagonists (Scheme 208).[297] For the synthesis of (+)-CP-99,994, reductive coupling of 4-pivaloxybutanal **892** with *N-tert*-butanesulfinyl imine **133** afforded adduct **893** in 78% yield and with >90:

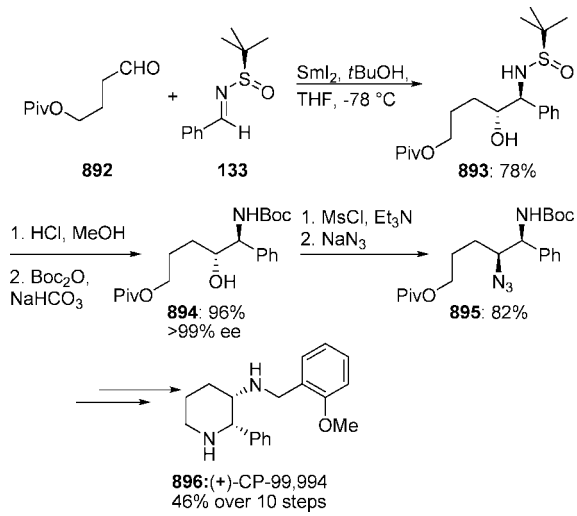
Scheme 206. Synthesis of D-*erythro*-Sphinganine



Scheme 207. Synthesis of (3*R*,4*S*)-Statine



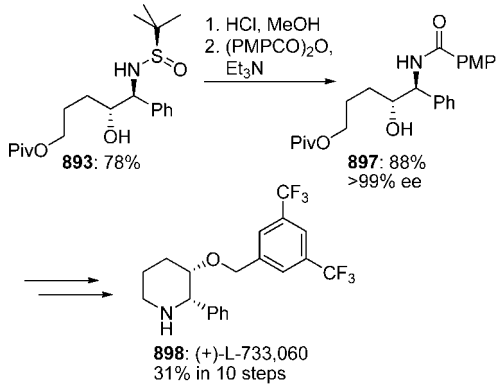
Scheme 208. Synthesis of (+)-CP-99,994



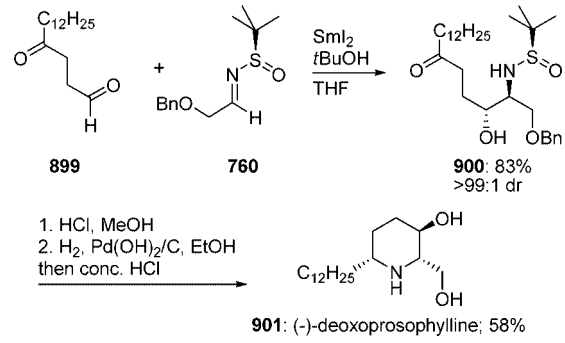
10 diastereomeric ratio, as determined by ^{1}H NMR analysis of the crude material. The minor diastereomer was removed by either recrystallization or chromatography, and subsequent cleavage of the sulfinyl group followed by Boc protection of the resulting amine provided **894** in 96% yield and with >99% ee. Mesylation and subsequent azide displacement afforded **895** in 82% yield. Further synthetic manipulations led to the completion of the synthesis of (+)-CP-99,994 in an overall yield of 46% over ten steps.

The total synthesis of (+)-L-733,060 was also accomplished starting from chiral building block **893** (Scheme 209). Removal of the sulfinyl group and selective *N*-acylation with 4-methoxybenzoic anhydride provided PMP-amide **897** in 88% yield and >99% ee. Further synthetic transformations then provided (+)-L-733,060 in an overall yield of 31% over ten steps from commercial materials.

Scheme 209. Total Synthesis of (+)-L-733,060



Scheme 210. Synthesis of (−)-Deoxoprosophylline

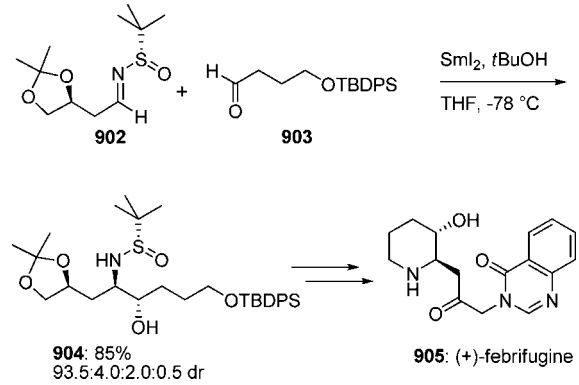


A novel route to (−)-deoxoprosophylline was reported by Lin, Wei, and co-workers, utilizing a reductive coupling of *N*-*tert*-butanesulfinyl imine **760** with aldehdye **899** (Scheme 210).[298] Aldehyde **899**, synthesized in three steps from γ-butyrolactone,[299] coupled efficiently with **760** to afford the hydroxymethyl β-amino alcohol **900** in 83% yield and with >99:1 dr. Cleavage of the sulfinyl group followed by liberation of the amine from the amine hydrochloride salt yielded the cyclic imine, which was hydrogenated to provide (−)-deoxoprosophylline (**901**) in 58% yield over the two steps.

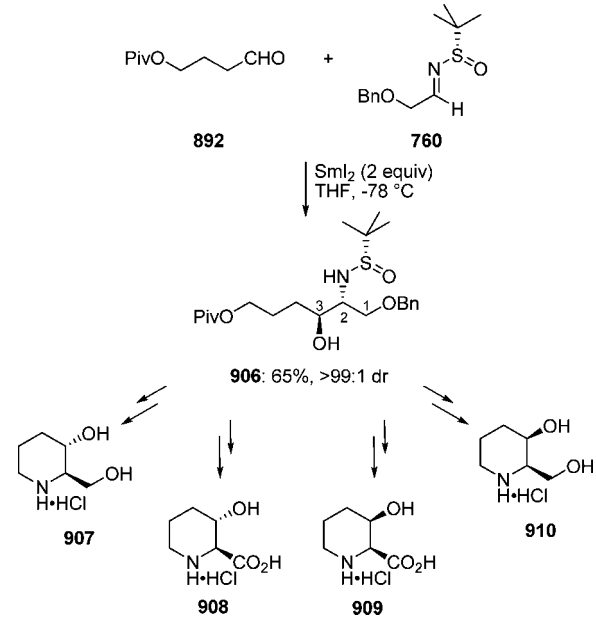
Xu, Lin, and co-workers also recently utilized their reductive coupling methodology in the asymmetric synthesis of (+)-febrifungine, an alkaloid that has antimalarial properties.[300] Optimization of the coupling reaction between *N*-*tert*-butanesulfinyl imine **902** and aldehyde **903** revealed that using freshly prepared solutions of reactants and maintaining a low temperature for several hours after addition of the reagents was necessary to provide high diastereoselectivity, and according to this protocol **904** was obtained in 85% yield and with 93.5:4.0:2.0:0.5 dr (Scheme 211). The *tert*-butanesulfinyl group was oxidized to form the *tert*-butanesulfonyl protecting group, which was cleaved in the last step of the synthesis (after cyclization and further functionalization) to provide (+)-febrifungine (**905**).

Wang and Liu reported the reductive coupling of aldehyde **892** with *N*-*tert*-butanesulfinyl aldimine **760**, forming intermediate **906** in good yield (65%) and with excellent diastereoselectivity (>99:1). This intermediate was then applied to the diastereodivergent synthesis of both *trans*- and *cis*-3-hydroxy-L-pipecolic acids **908** and **909** (Scheme 212).[301] The total synthesis of **909** was completed in ten linear steps and 30% yield. The synthesis of **908**, which required inversion of stereochemistry at C3, was achieved in 12 steps and 27% yield. The reduced analogues, alcohols **907** and **910**, were also prepared.

Scheme 211. Synthesis of (+)-Febrifungine



Scheme 212. Stereodivergent Asymmetric Synthesis of 3-Hydroxy-L-pipecolic Acids and Alcohols

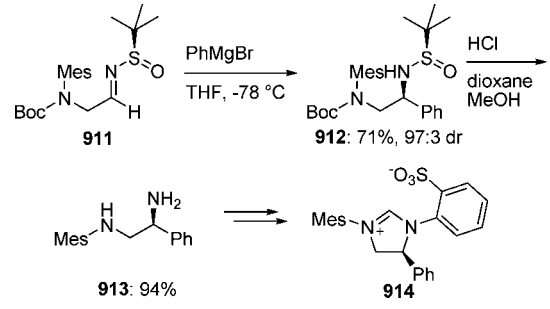


12. Synthesis of 1,2-Diamines

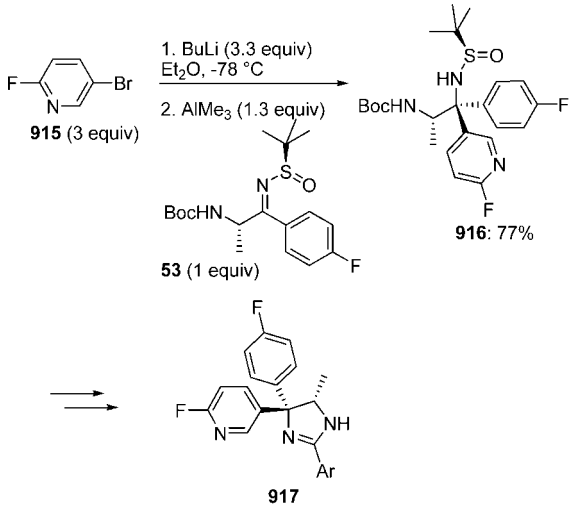
12.1. Additions to α-Amino Imines

Hoveyda and co-workers reported the stereoselective (97:3 dr) addition of PhMgBr to α-amino imine **911** to provide chiral protected diamine **912** in 71% yield (Scheme 213).[302] Deprotection afforded **913**, which was ultimately converted to an *N*-heterocyclic carbene (NHC) ligand **914** for copper-catalyzed enantioselective allylic alkylation reactions. The configuration of the newly formed stereocenter is consistent with those found in Grignard additions to α-unfunctionalized aldimines via a chelated transition state, in contrast to that

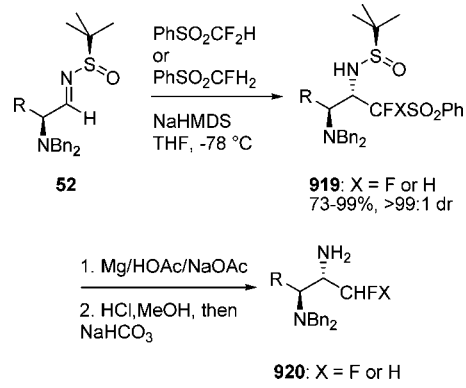
Scheme 213. Synthesis of a 1,2-Diamine by Addition to an α-Amino Aldimine



Scheme 214. Synthesis of a 1,2-Diamine by Addition to an α-Amino Ketimine



Scheme 215. Mono- and Difluoromethylation of α-Amino Imines



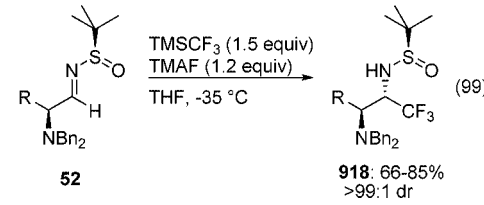
observed for addition to α-alkoxy imines. It is possible the bulky amino substituents (both mesityl and Boc) prevent the pendant amine from having any coordinating role in the transition state.

Ando and co-workers reported the synthesis of diamine **916** via the addition of a heteroaryl lithium reagent to α-amino *N-tert*-butanesulfinyl ketimine **53** (Scheme 214).[66] This chiral diamine was used as an intermediate in the synthesis of a series of imidazolines **917** for SAR studies on the inhibition of the neuropeptide Y Y5 receptor.

Syntheses of several mono-, di-, and trifluoromethyl substituted 1,2-diamines have been reported (for details, see sections 15.1.1 and 15.2). In particular, the synthesis of α-amino *N-tert*-butanesulfinyl trifluoromethyl amines **918** was accomplished via the addition of $TMSCF_3$ to α-amino aldimines **52** (eq 99).[65] Hu and co-workers disclosed a highly diastereoselective method for the synthesis of α-amino *N-tert*-butanesulfinyl difluoromethyl and monofluoromethyl amines via the addition of mono- and difluoromethylsulfone anions to α-amino imines **52**, followed by reductive desulfonylation and sulfinyl deprotection to provide products **920** (Scheme 215).[303]

12.2. Additions to 1,2-Bisimines

Deng and co-workers described the addition of organometallic reagents to C_2-symmetric bisimine **921** (Scheme 216).[304] After extensive optimization of solvent, metal, and additives, the addition of organolithium reagents in THF with

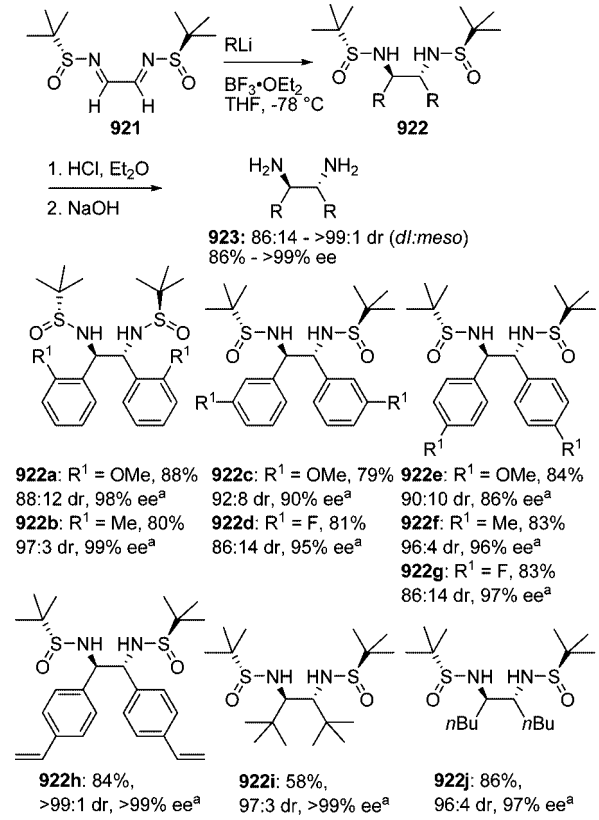


$BF_3 \cdot OEt_2$ as an additive was found to provide the desired bis-*N,N-tert*-butanesulfinyl 1,2-diamines in moderate to high isolated yield and with high stereoselectivity, ranging from 86:14 to >99:1 *dl/meso* diastereoselectivity and 86 to >99% ee of the major stereoisomer after deprotection. In several cases, the isolation of products **922** as single stereoisomers was accomplished by chromatographic or crystallographic removal of the minor diastereomers. The stereochemistry of the major product, based upon the crystal structures of both **922b**[304] and **922i**,[305] is consistent with two sequential additions, each via an open transition state. This is similar (both with respect to reaction conditions and product stereochemistry) to the results obtained by Davis and co-workers[69] in organometallic reagent additions to α-imino esters (see section 9.1) and is opposite (with respect to the sulfinyl stereocenters) from the stereochemistry obtained by Xu and Lin in the reductive coupling of *N-tert*-butanesulfinyl aldimines (see section 12.3).[306]

12.3. Reductive Coupling of Imines

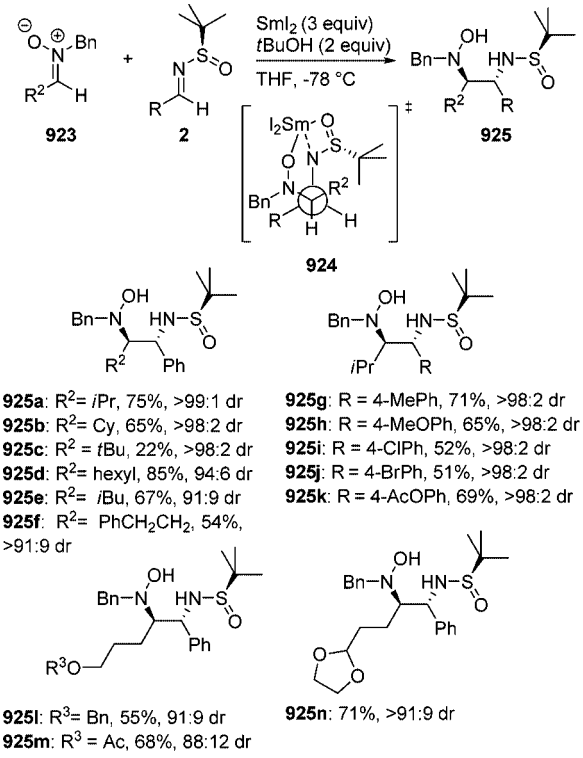
The first example of a SmI_2 mediated reductive coupling between an *N-tert*-butanesulfinyl imine and another electrophilic coupling partner was reported by Xu and co-workers

Scheme 216. Synthesis of C_2-Symmetric 1,2-Diamines by Addition to a Bisimine



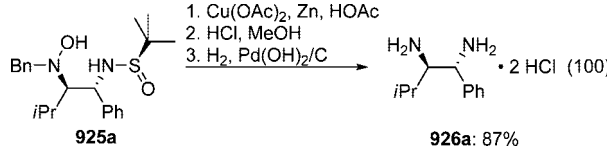
[a] The stereoselectivity of the reaction (dr and %ee) refers to the 1,2-diamine product **923** after cleavage of the sulfinyl groups.

Scheme 217. SmI_2-Induced Reductive Coupling of Nitrones with *N-tert*-Butanesulfinyl Aldimines

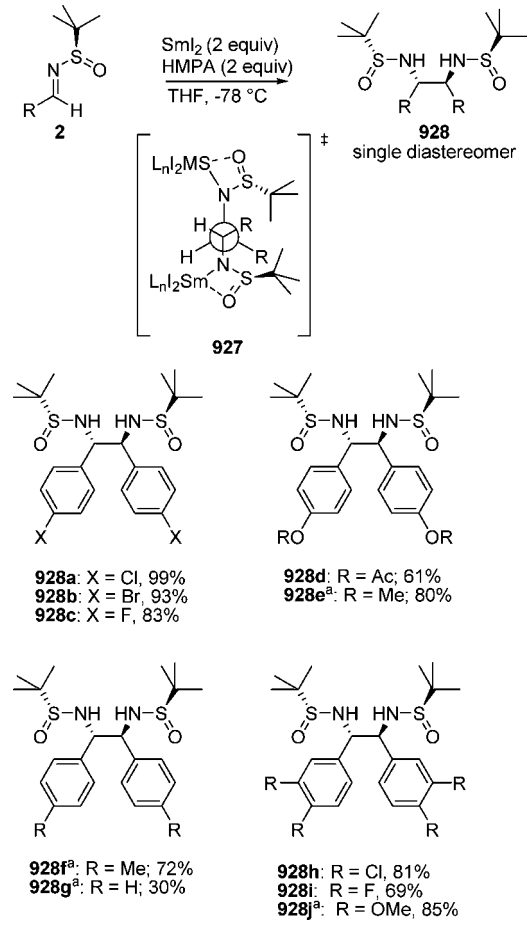


in their asymmetric synthesis of vicinal diamines (Scheme 217).[307] For the coupling partner, Xu and co-workers focused on nitrones **923** because they had been previously shown to undergo coupling with aldehydes[308] and α,β-unsaturated esters[309] in the presence of SmI_2. An optimization study of the reaction between imine **2** (R = Ph) and nitrone **923** (R^2 = *i*Pr) revealed that the highest yield for **925a** was obtained when 3 equiv of SmI_2, 2 equiv of *t*BuOH, and a slight excess of nitrone were utilized. The (*R*,*R*) configuration of the coupled adduct **925a** was determined by X-ray structural analysis. The authors hypothesize that the stereoselectivity of the reaction can be rationalized by the chelation controlled transition state **924**. The scope of the reaction was probed with a number of structurally diverse nitrones **923**, revealing that the outcome of the reaction was influenced by sterics. A panel of electronically diverse *N-tert*-butanesulfinyl aryl aldimines **2** was also coupled with nitrone **923** (R = *i*Pr). Substrates bearing electron-donating or -withdrawing substituents at the *para* position were effective in this reaction, providing adducts **925g**−**k** in moderate yields (51−71%). Several oxygen-tethered aliphatic nitrones were also employed in the reductive coupling transformation to provide **925l**−**n** in moderate yields (55−71%) and with good diastereoselectivities (88:12 to >91:9 dr). However, the authors noted that no reaction occurred if both the imine and nitrone inputs were aromatic (R = R^2 = Ph) or aliphatic (R = R^2 = *i*Pr). A three-step procedure for the conversion of **925a** to the free diamine product was also demonstrated (eq 100). Deoxygenation of the hydroxylamine group was accomplished using Zn/$Cu(OAc)_2$[310] followed by removal of the sulfinyl and benzyl groups to provide **926a** in an 87% overall yield.

Following their initial report, Xu and co-workers demonstrated that C_2-symmetric vicinal diamines could also be synthesized via a SmI_2 promoted homocoupling of *N-tert*-butanesulfinyl aldimines (Scheme 218).[306] In their investigation of the reductive cross-coupling of *N-tert*-butanesulfinyl aldimines with nitrones (*vide supra*), they had observed a trace amount of the homocoupled product in the presence of 2 equiv of SmI_2. When these conditions were employed with *N-tert*-butanesulfinyl imine **2** (R = 4-Cl-Ph), the homocoupled product was obtained in 81% yield as a 58:42 mixture of diastereomers. A screen of additives revealed that the addition of 2 equiv of HMPA was essential for the exclusive formation of **928a**, which was produced as a single diastereomer in almost quantitative yield (Scheme 218). The absolute stereochemistry for **928a** was established by X-ray structural analysis, and the authors have explained the observed diastereoselectivity by transition state **927**, which minimizes steric repulsion between the bulky *tert*-butanesulfinyl groups on the nitrogen atoms. A number of electron-poor *para*-substituted aryl imines **2** were evaluated, and adducts **928a**−**d**, **h**, and **i** were obtained in 61−99% isolated yield. When electron-rich aryl imines were employed, the homocoupled products were generated in lower yields, although the yields of these products could be improved by the addition of 6 equiv of HMPA (**928e**, **f**, and **j**). However, a low yield of **928g** (30%) was obtained even when the amount of HMPA was increased.

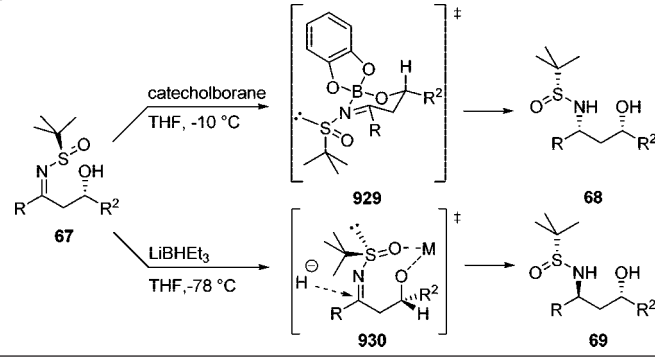


Scheme 218. SmI_2-Induced Reductive Homocoupling of *N-tert*-Butanesulfinyl Aldimines



[a] Six equivalents of HMPA was used.

Table 23. Selective Reductions of β-Hydroxy *N-tert*-Butanesulfinyl Imines



				catecholborane		$LiBHEt_3$	
entry	imine **67**	R	R^2	dr **68**	yield of **68** (%)	dr **69**	yield of **69** (%)
1	**67a**	Ph	Et	95:5	94	>99:1	69
2	**67b**	Ph	*i*Bu	96:4	84	>99:1	85
3	**67c**	Ph	*i*Pr	96:4	88	>99:1	83
4	**67d**	Ph	*t*Bu	96:4	89	>99:1	91
5	**67e**	Ph	Ph	96:4	84	>99:1	73
6	**67f**	*t*Bu	Et	95:5	81	>99:1	96
7	**67g**	*t*Bu	*i*Pr	96:4	91	>99:1	96
8	**67h**	*t*Bu	*t*Bu	95:5	79	>99:1	83
9	**67i**	*t*Bu	Ph	98:2	77	>99:1	95
10	**67j**	*i*Pr	Et	95:5	82	98:2	94
11	**67k**	*i*Pr	*i*Pr	96:4	82	99:1	94
12	**67l**	*i*Pr	*t*Bu	95:5	93	99:1	96
13	**67m**	*i*Pr	Ph	90:10	81	92:8	85
14	**67n**	Et	Et	94:6	76	93:7	78
15	**67o**	Et	*i*Pr	97:3	91	95:5	94
16	**67p**	Et	*t*Bu	92:8	82	97:3	90
17	**67q**	Et	Ph	76:24	69	88:12	80

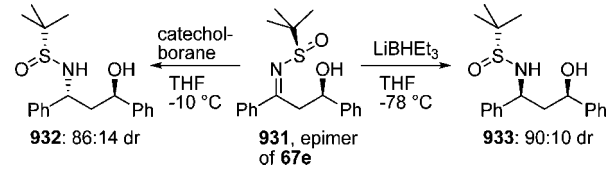
13. Synthesis of 1,3-Amino Alcohols

13.1. Reduction of β-Hydroxy *N-tert*-Butanesulfinyl Imines

The synthesis of either *syn*- or *anti*-1,3-amino alcohols via the reduction of β-hydroxy *N-tert*-butanesulfinyl imines **67** (prepared by addition of an *N-tert*-butanesulfinyl metalloenamine to an aldehyde; see section 3.2.1) was first described by Ellman and co-workers in a 2002 Communication[83] and later expanded upon in a full report (Table 23).[84] This methodology presents a convergent and expedient synthesis to access either isomer of this highly important class of molecules. Several reducing agents were tested with ketimine **67c**. Catecholborane provided amino alcohol **68** with the highest *syn*-selectivity, while $LiBHEt_3$ afforded **69** with complete *anti*-selectivity. A number of aryl and alkyl ketimines (**67a**−**p**) were subjected to both reduction conditions and high yields, and excellent diastereoselectivities were observed for each transformation (entries 1−16). Only the reduction of imine **67q** proceeded with more modest diastereoselectivity (entry 17). The absolute configurations of **68e** and **69f** were determined by X-ray structural analysis. The relative stereochemistries for **68c** and **69c** were further determined by chemical derivatization and NMR spectroscopic methods.

To determine the essential features for achieving high stereoselectivity for these transformations, the catecholborane and $LiBHEt_3$ reduction of the epimer of **67e** was investigated (Scheme 219). The catecholborane reduction of **931** gave **932**, and the $LiBHEt_3$ reduction gave **933**, both in good diastereoselectivities, indicating that the selectivity of the reduction is mainly controlled by the configuration of the

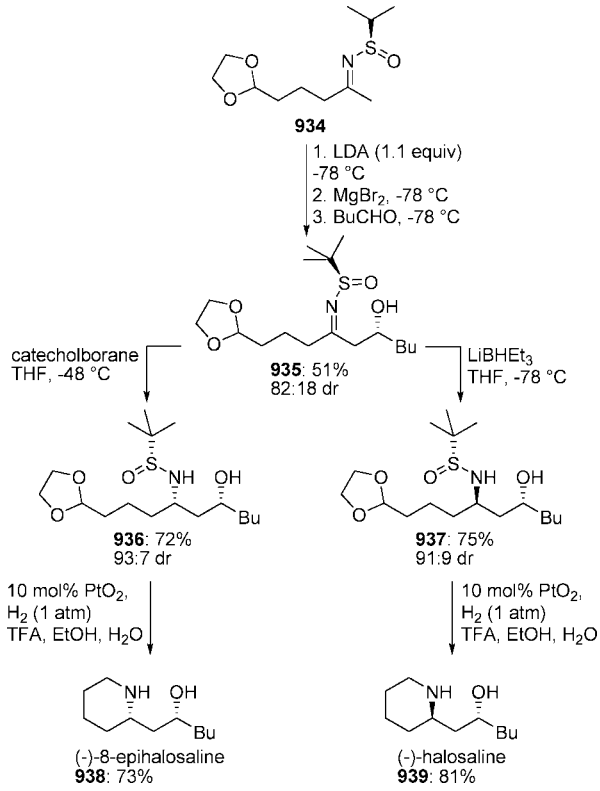
Scheme 219. Selective Reduction of 931, the Epimer of 67e



tert-butanesulfinyl group. To rationalize the switch in diastereoselectivity based on the choice of reductant, the authors presumed that the *E*-geometry of the β-hydroxy *N-tert*-butanesulfinyl imine, as observed in crystal structures of these β-hydroxy imines, would not change during $LiBHEt_3$ reduction. Therefore, transition state **930** was proposed with the hydride delivery occurring from the *si*-face of the imine double bond (Table 23). For the catecholborane reductions, the authors propose six-membered transition state **929**, which requires imine isomerization to the *Z*-geometry, which is in analogy to the stereoselective reductions of β-hydroxy ketones.[311] Indeed, because very little reduction of the *N-tert*-butanesulfinyl ketimine derived from acetophenone was observed in the presence of catecholborone, chelation of the boron to the β-hydroxy *N-tert*-butanesulfinyl imines must play a significant role.

The utility of the *N-tert*-butanesulfinyl metalloenamine methodology and its application to the synthesis of *syn*- or *anti*-1,3-amino alcohols was showcased by the asymmetric syntheses of (−)-halosaline and (−)-8-epihalosaline (Scheme 220).[84] Formation of the metalloenamine from **934** and addition to butyraldehyde gave **935** in 82:18 dr and a 51% isolated yield of the major diastereomer. Reduction of **935** with catecholborane provided the *syn*-isomer **936** as a 93:7 mixture of diastereomers, which was purified to diastereo-

Scheme 220. Total Syntheses of (−)-Halosaline and (−)-8-Epihalosaline

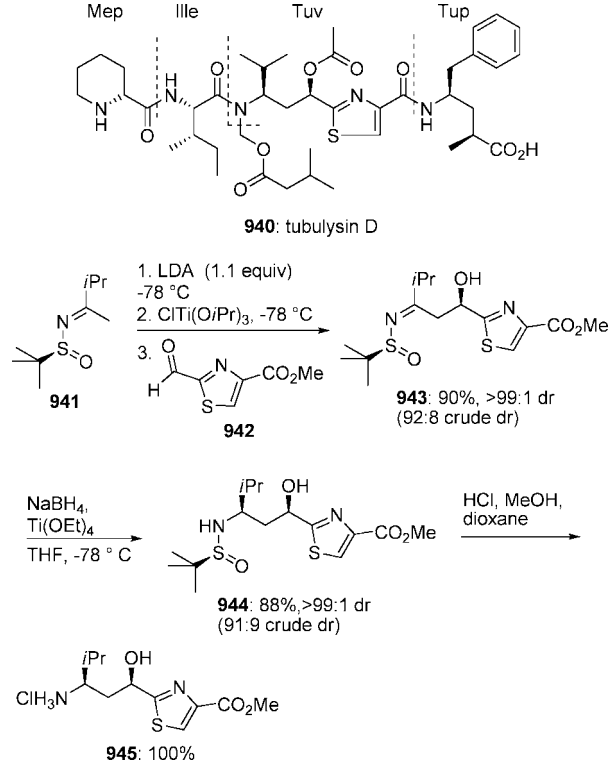


meric purity by column chromatography in 72% yield. The *anti*-isomer **937** was synthesized with high diastereoselectivity by $LiBHEt_3$ reduction of **935**. Again, column chromatography provided diastereomerically pure material in 75% yield. Reductive cyclization with concomitant protecting group cleavage provided **939** or **938** in one step in good yield to complete the syntheses of (−)-halosaline and (−)-8-epihalosaline.

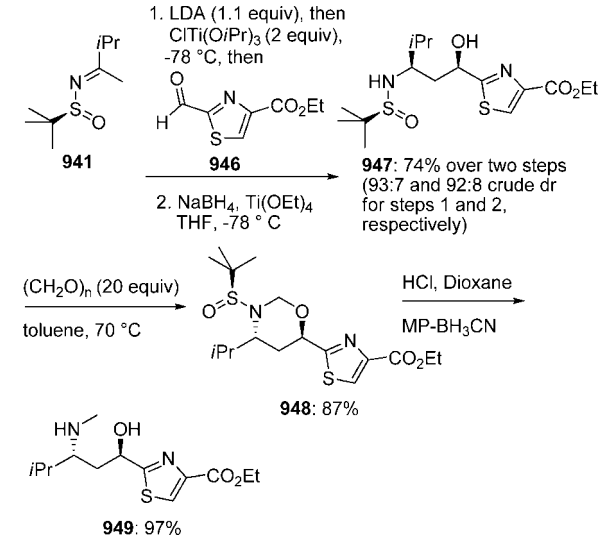
Addition of an *N*-*tert*-butanesulfinyl metalloenamine to an aldehyde and the subsequent reduction of the resulting β-imino alcohol to a 1,3-amino alcohol was employed by Ellman and co-workers in the first total synthesis of the natural product tubulysin D, which is a highly potent inhibitor of tubulin polymerization (Scheme 221; see section 18.2 for an additional example of *tert*-butanesulfinamide chemistry employed in this synthesis).[312] The tubuvaline (Tuv) fragment of tubulysin was synthesized by addition of the metalloenamine derived from **941** to thiazoline aldehyde **942**. This transformation proceeded with high diastereoselectivity (92:8) when $ClTi(OiPr)_3$ was used as the metal additive, and the major diastereomer was isolated in 90% yield after column chromatography. Reduction with $NaBH_4$ at low temperature avoided competitive reduction of the methyl ester and provided the β-amino alcohol **944** as a single diastereomer in 88% yield after column chromatography. Removal of the sulfinyl group provided the amine salt **945** in quantitative yield. Employing the Tuv salt **945**, the total synthesis of tubulysin D was accomplished in 16 steps and 13% overall yield.

Several analogues of tubulysin D were synthesized following this protocol, and notably, replacement of the extremely labile *O*-acyl *N*,*O*-acetal in the Tuv fragment with the considerably more stable *N*-methyl amide did not significantly impact biological activity.[313] Without the acid and base labile *O*-acyl *N*,*O*-acetal group, an efficient

Scheme 221. Synthesis of the Tuv Fragment of Tubulysin D



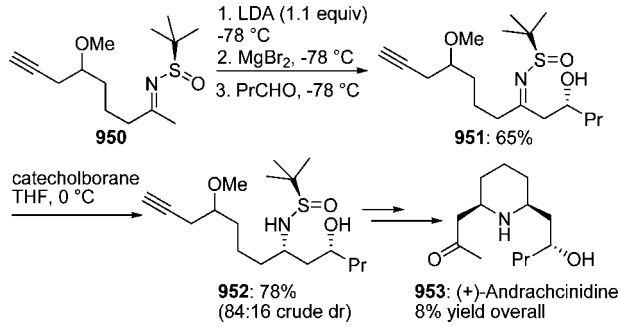
Scheme 222. Synthesis of 949



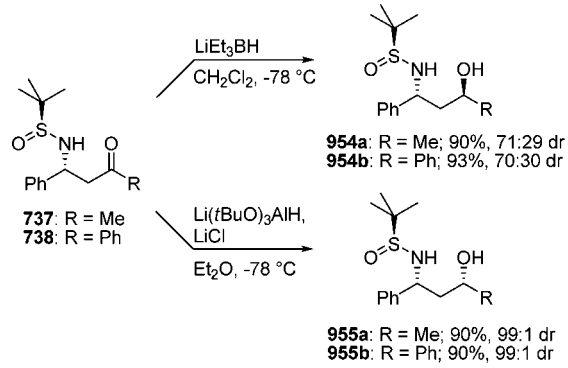
synthesis of the Tuv fragment incorporating the *N*-methyl amine was therefore devised.[314] Following the same route as utilized in the total synthesis of tubulysin D, **947** was isolated in diastereomerically pure form in 74% yield over the two steps (Scheme 222). Condensation of **947** with paraformaldehyde in toluene provided **948** in 87% yield. Reduction of **948** with a support-bound cyanoborohydride ($MP\text{-}BH_3CN$) under acidic conditions yielded **949**, which was incorporated into the desired *N*-methyl analogue of tubulysin D, in 15 linear steps and 40% overall yield.

Floreancig and Jung utilized an *N*-*tert*-butanesulfinyl metalloenamine addition to an aldehyde to prepare the precursor for their key gold-catalyzed cyclization step in the total synthesis of (+)-andrachcinidine (**953**) (Scheme 223).[315] The metalloenamine of **950** was added to *n*-butanal, and the resulting β-hydroxy *N*-*tert*-butanesulfinyl imine **951** was

Scheme 223. Total Synthesis of (+)-Andrachcinidine



Scheme 224. Reduction of 1,3-*N*-*tert*-Butanesulfinyl Amino Ketones



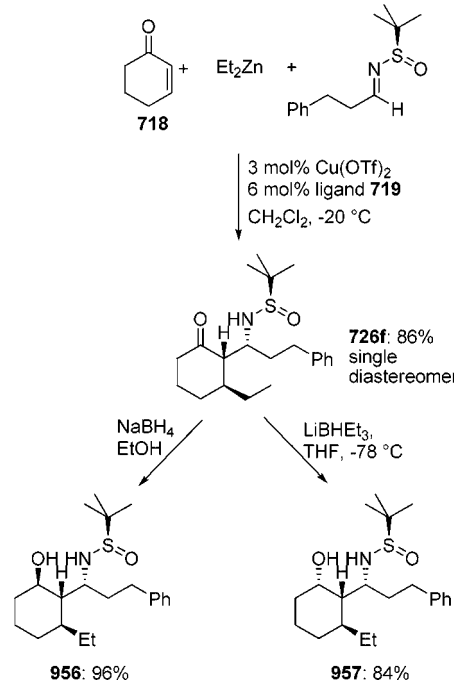
stereoselectively reduced with catecholborane to provide the 1,3-amino alcohol **952** with an 84:16 diastereomeric ratio. Further synthetic transformations provided (+)-andrachcinidine in 8% yield overall.

13.2. Reduction of 1,3-*N*-*tert*-Butanesulfinyl Amino Ketones

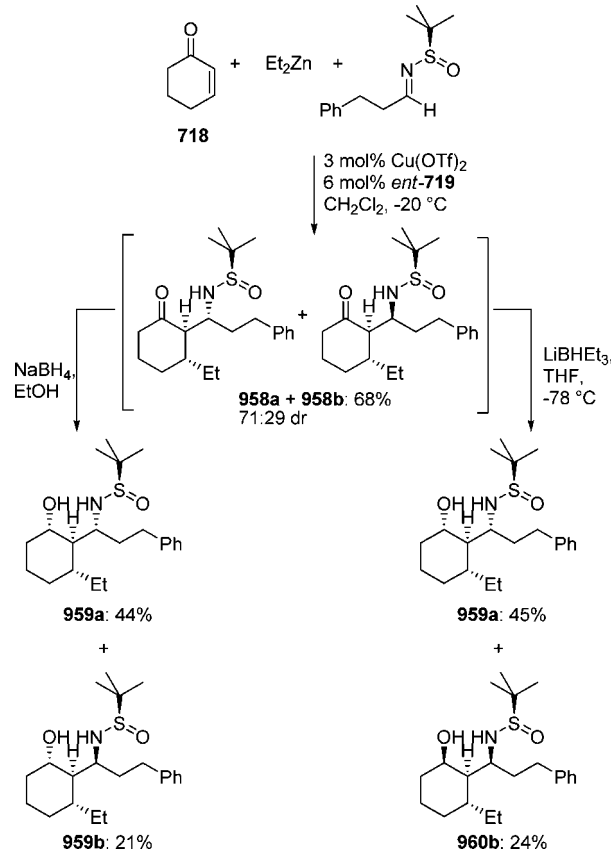
Davis and co-workers developed an alternative route to 1,3-amino alcohols via the reduction of 1,3-*N*-*tert*-butanesulfinyl amino ketones **737** and **738** (Scheme 224; see section 10.2.1 for the synthesis of **737** and **738**).[262] Using the reduction conditions optimized for the analogous synthesis of *anti*-1,3-*N*-*p*-toluenesulfinyl amino alcohols ($LiEt_3BH$, CH_2Cl_2, −78 °C), high yields but moderate diastereoselectivities were observed for the *N*-*tert*-butanesulfinyl amino alcohol products **954a** and **b**. However, excellent yields and diastereoselectivities were obtained for the *syn*-amino alcohol products **955a** and **b** using $Li(tBuO)_3AlH$ as a reductant and LiCl as an additive.

Recently, Gonzalez-Gomez, Foubelo, and Yus demonstrated the stereoselective reduction of the cyclohexanone moiety present in *N*-*tert*-butanesulfinyl β-amino ketones to provide 1,3-amino alcohols.[316] Treatment of compound **726f** (synthesized via a tandem enantioselective conjugate addition followed by a Mannich reaction; for details see section 10.2.1) with $NaBH_4$ provided **956** in almost quantitative yield. Conversely, reduction of **726f** with $LiBHEt_3$ provided the *syn*-amino alcohol **957** in 84% yield (Scheme 225). The absolute configuration of the reduced product **956** was determined by X-ray structural analysis and was consistent with an axial delivery of the hydride from $NaBH_4$. When the enantiomer of ligand **719** was utilized, the β-amino ketones **958a** and **958b** were isolated as an inseparable mixture of diastereomers (Scheme 226). Reduction of the mixture

Scheme 225. Stereoselective Reduction of 726f

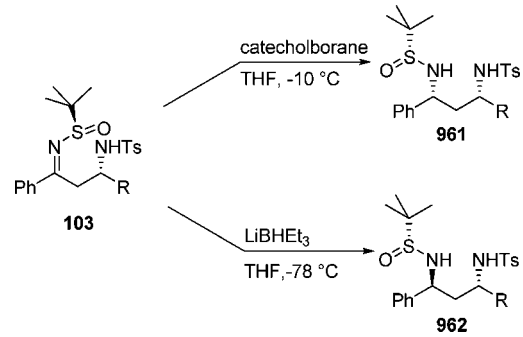


Scheme 226. Stereoselective Reduction of Diastereomer Mixture



with $NaBH_4$ provided **959a** and **959b**, which were isolated as pure compounds after column chromatography. When the mixture of **958a** and **b** was treated with $LiBHEt_3$, *syn*-amino alcohols **959a** and **960b** were obtained after purification.

Table 24. Selective Reductions of β-Amino *N-tert*-Butanesulfinyl Imines



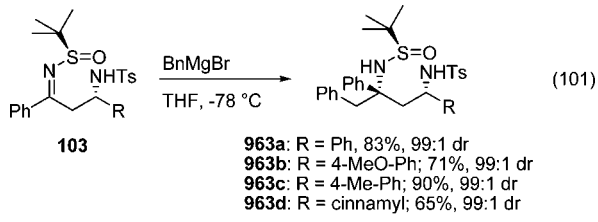
		catecholborane		$LiBHEt_3$	
entry	R	dr **961**	yield of **961** (%)	dr **962**	yield of **962** (%)
1	Ph	>99:1	65	>99:1	81
2	4-Cl-Ph	>99:1	70	>99:1	86
3	2-furyl	>99:1	62	>99:1	90
4	cinnamyl	>99:1	71	>99:1	83

14. Synthesis of 1,3-Diamines

14.1. Transformations of β-Amino *N-tert*-Butanesulfinyl Imines

The stereoselective reduction of β-amino *N-tert*-butanesulfinyl imines **103** (prepared by the addition of an *N-tert*-butanesulfinyl metalloenamine to an imine; see section 3.2.3) to afford either the *syn*- or *anti*-1,3-diamines **961** or **962** was explored by Chen, Wang, and co-workers (Table 24).[90] This method provides a convenient and highly diastereoselective route to prepare this structural motif. Following the reduction protocol developed by Ellman and co-workers for the analogous reductions of β-hydroxy imines (see section 13.1), 1,3-diamines **961** or **962** were generated in the presence of catecholborane or $LiBHEt_3$, respectively. All transformations proceeded in good yields (62−90%) and with excellent diastereoselectivities (>99:1). The absolute configuration of **961** (R = cinnamyl) was determined by X-ray structural analysis and was consistent with the stereochemical model proposed by Ellman and co-workers for the reductions of β-hydroxy *N-tert*-butanesulfinyl imines.

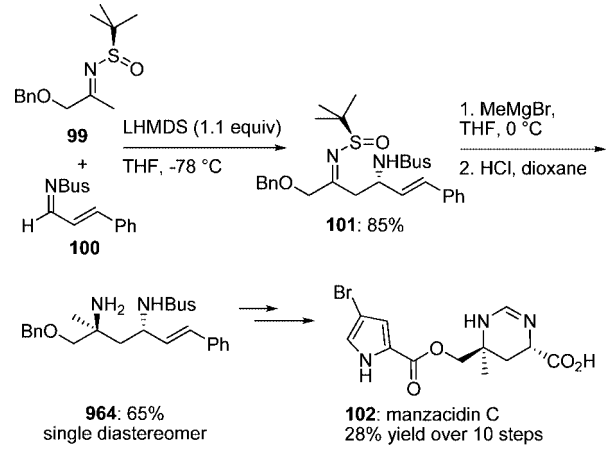
Chen, Wang, and co-workers also demonstrated the addition of benzyl magnesium bromide to β-amino *N-tert*-butanesulfinyl imines **103**. The products **963a**−**d** were obtained in moderate to high yield with excellent diastereoselectivity (eq 101).[90]



(101)

The addition of a Grignard reagent to a β-amino *N-tert*-butanesulfinyl imine, synthesized by addition of an *N-tert*-butanesulfinyl metalloenamine to a sulfonyl imine (see section 3.2.3), was reported by Lanter and co-workers to introduce the 1,3-diamine framework in their elegant asymmetric synthesis of manzacidin C (Scheme 227).[89] Coupling **99** and **100** provided **101** in 85% yield, which was converted

Scheme 227. Total Synthesis of Manzacidin C

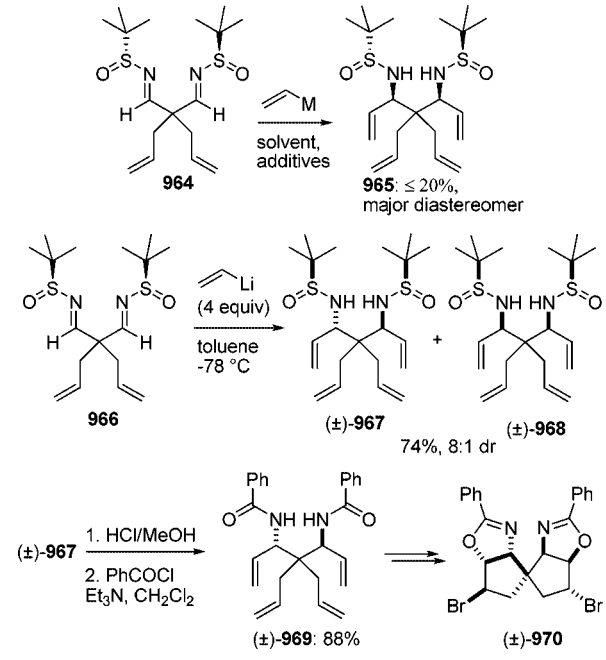


to the tertiary carbinamine **964** as a single diastereomer after treatment with methyl magnesium bromide followed by removal of the sulfinyl protecting group. A number of subsequent synthetic transformations yielded the desired natural product **102** in ten linear steps and 28% overall yield.

14.2. Addition of Organometallic Reagents to Bisimines

Sasai and co-workers utilized additions to bisimines **964** and **966** for the synthesis of 1,3-diamines in their efforts toward the synthesis of spiro bis-oxazoline ligand **970** (Scheme 228).[317] While vinyl Grignard reagent or vinyllithium addition to C_2-symmetric bisimine **964** was originally investigated, the major diastereomer obtained (in less than 20% yield) was the undesired *pseudo-meso* adduct **965**. To obtain this product, two sequential (*in situ*) addition reactions would have to take place from opposite imine faces with respect to the sulfinyl stereochemistry. It is probable that the presence of the coordinating β-amino group after the first addition causes a change in the transition state for the second addition. To circumvent this problem, additions to *meso*-bisimine **966** were next explored. Optimization of reaction

Scheme 228. Organometallic Additions to Bis-*N-tert*-butanesulfinyl Imines



conditions revealed that the use of 4 equiv of vinyl lithium in toluene provided a 74% yield of a chromatographically separable 8:1 mixture of diastereomers, favoring the desired diastereomer (±)-**967**. Acid-mediated cleavage of the sulfinyl groups followed by benzoylation provided the desired C_2 symmetric 1,3-diamide (±)-**969** in 88% yield. Further elaboration provided (±)-**970**, which was resolved by preparative-scale chromatography on a chiral stationary phase. The use of the copper complexes of the enantiomerically pure ligand **970** was demonstrated in both a carbonyl-ene reaction and a Henry reaction.

15. Synthesis of Fluorinated Amine Derivatives

The selective incorporation of fluorine into organic molecules to modulate their biological properties is an important strategy in drug design.[318] Indeed, many of the most widely used pharmaceutical agents contain one or more fluorine atoms. Within this class of compounds, fluorinated amines are important synthetic building blocks in the design of drugs because the strongly electron-withdrawing nature of the fluorine atom attenuates the basicity of proximal amine functionality. Fluorine substitution can also alter metabolism, decrease toxicity, and/or increase the bioavailability of drug candidates.

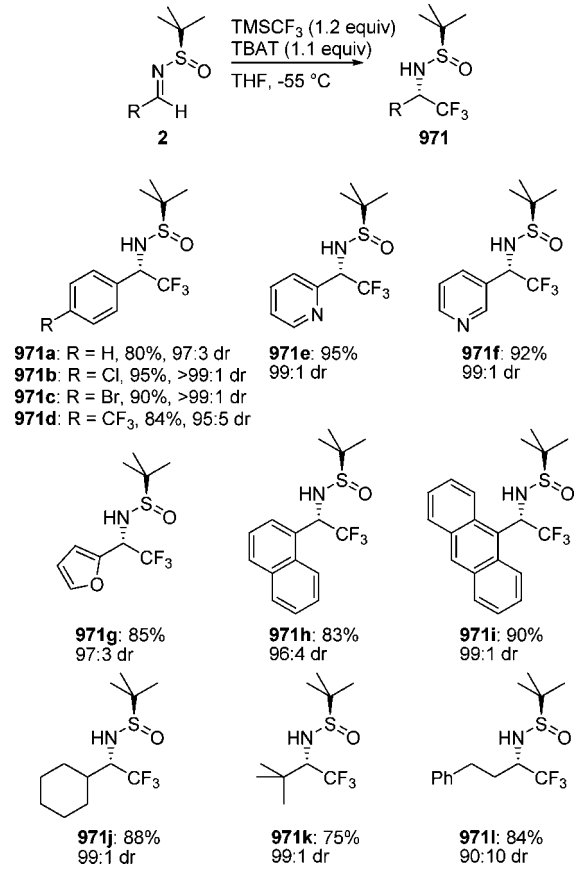
15.1. Synthesis of α-Trifluoromethyl Amines

15.1.1. Addition of a Trifluoromethyl Nucleophile to N-tert-Butanesulfinyl Imines

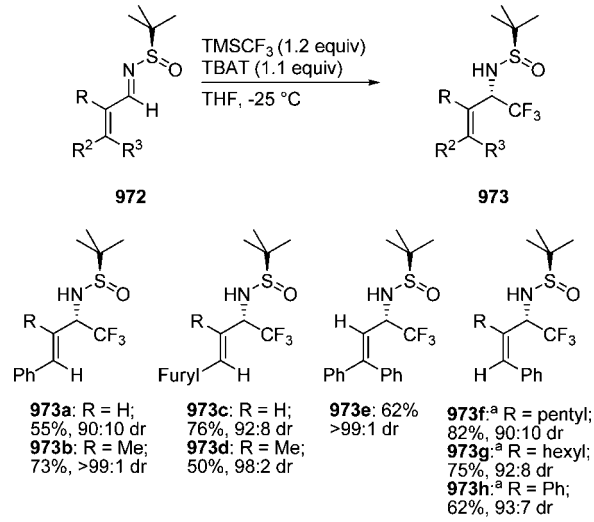
The nucleophilic addition of a fluorinated carbanion to an imine represents a direct and efficient method for the synthesis of fluorinated amines. Prakash, Olah, and Mandal disclosed the first example of a nucleophilic transfer of a "CF_3" anion to *N-tert*-butanesulfinyl aldimines.[319] While in an early study Prakash and co-workers had observed that $TMSCF_3$ in the presence of stoichiometric CsF could act as a nucleophilic trifluoromethylating agent for additions to *N*-sulfonyl aldimines,[320] application of these reaction conditions to *N-tert*-butanesulfinyl aldimines proved problematic. Yields were low due to competitive decomposition of $TMSCF_3$, and imines bearing an α-proton were incompatible coupling partners due to competitive deprotonation by the basic CsF. However, when the fluoride source was changed to the soluble nonmetallic tetrabutylammonium difluorotriphenylsilicate (TBAT),[321] the desired compounds could be obtained in high yields and diastereoselectivities for an array of structurally diverse *N-tert*-butanesulfinyl imines **2** (Scheme 229). *N-tert*-Butanesulfinyl trifluoromethylated aromatic and heteroaromatic amines **971a**−**i** were synthesized in high yields (80−95% yield) and with excellent diastereoselectivities (95:5 >99:1 dr). Branched and linear aliphatic imines **2** were also utilized to provide **971j**−**l** in good yields and with very high diastereoselectivities. The absolute configuration for select products was determined by correlation with known compounds, revealing that the stereochemical outcome was consistent with an open transition state (see Scheme 33, section 4.1).

This methodology was further extended to the addition of $TMSCF_3$ to α,β-unsaturated *N-tert*-butanesulfinyl aldimines.[56] Optimization of the reaction conditions was conducted with the imine derived from cinnamaldehyde. While $TMSCF_3$ and TBAT were still effective sources of a nucleophilic "CF_3" anion (*vide supra*), the lowered reactivity

Scheme 229. Synthesis of Trifluoromethylated *N-tert*-Butanesulfinyl Aldimines



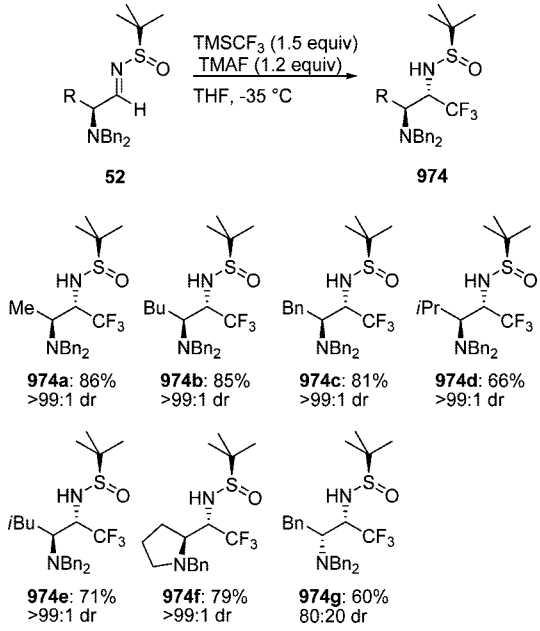
Scheme 230. Synthesis of Allylic *N-tert*-Butanesulfinyl Trifluoromethyl Amines



[a] Reaction was conducted with TMAF as the fluoride source.

of the α,β-unsaturated *N-tert*-butanesulfinyl aldimines **972** required higher temperatures (−25 °C). Under these conditions, **973a** was generated in 55% yield and with 90:10 dr, and none of the corresponding 1,4-addition product was observed (Scheme 230). Methyl substitution at the α-position of **972** increased the diastereoselectivity of the reaction without impacting the yield (**973b** and **d**). Adduct **973e**, with β,β-disubstitution, was also obtained in good yield and with excellent diastereoselectivity. Heteroaromatic substitution at the β-position was also tolerated (**973c** and **d**). However,

Scheme 231. Synthesis of α-Amino *N-tert*-Butanesulfinyl Trifluoromethyl Amines

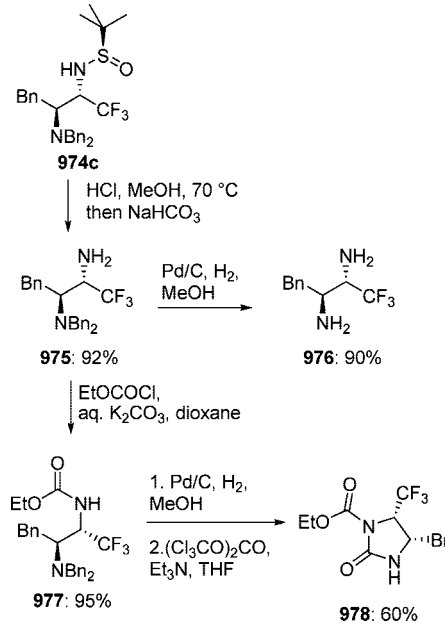


when sterically congested imines **972** with long alkyl chains at the α-position (R = pentyl or hexyl) were utilized under these conditions, the corresponding adducts **973f** and **g** were obtained in unsatisfactory yields (20−25%). When the steric bulk of the nucleophile was decreased by utilizing tetramethylammonium fluoride (TMAF) as the fluoride source, the products **973f−h** were obtained in high yield. The authors also demonstrated that treatment of **973a** with HCl and MeOH removed the sulfinyl group without any loss in stereochemical purity. The stereochemical outcome of the reaction was consistent with the open transition state model (see Scheme 33), and the absolute configuration of **973a** was confirmed by X-ray structural analysis.

The synthesis of α-amino *N-tert*-butanesulfinyl trifluoromethyl amines was also accomplished via the addition of $TMSCF_3$ to α-amino aldimines.[65] The reaction conditions were optimized with imine **52** (R = Me) by evaluating the two fluoride sources that had previously been successful for the addition of $TMSCF_3$ to other *N-tert*-butanesulfinyl aldimines (*vide supra*). While the use of TBAT as the fluoride source for activating $TMSCF_3$ provided a very low yield of **974a**, the less bulky TMAF provided adduct **974a** in 86% yield as a single diastereomer (Scheme 231). Imines **52** bearing linear or branched side chains provided good to excellent yields and diastereoselectivities for the trifluoromethylated vicinal ethylenediamine products **974b−f**. However, when an imine (R = Bn), derived from the opposite enantiomer of the amino aldehyde, was utilized, the corresponding adduct **974g** was obtained with an 80:20 diastereomeric ratio in a 60% isolated yield of the major diastereomer. This demonstrates that both chiral centers influence the diastereoselectivity of this transformation, with **974c** representing the matched case and **974g** the mismatched case. The observed stereoselectivity for imines **52** derived from L-amino aldehydes is consistent with addition via an open transition state. The absolute configuration of **974a** was confirmed by X-ray crystal structural analysis.

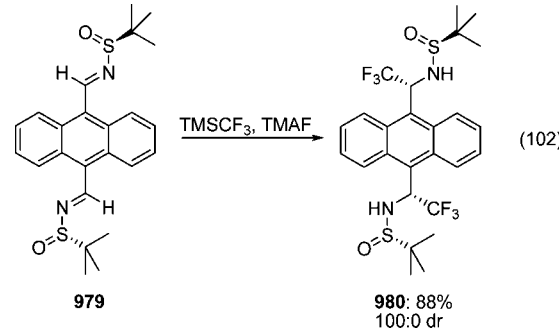
The utility of this method was demonstrated by subjecting compound **974c** to further synthetic transformations (Scheme 232). The sulfinyl group could be cleaved from **974c** to

Scheme 232. Further Synthetic Transformations of 974c



provide **975** in high yield without any epimerization. Catalytic hydrogenation of **975** yielded the free diamine **976** in 90% yield. The amine **975** could also be converted to the carbamate **977** by treatment with ethyl chloroformate under Schotten Bauman conditions. Debenzylation of **977** followed by treatment with triphosgene yielded the cyclic derivative **978** in 60% yield.

Recently, Virgili and co-workers applied the method developed by Prakash and co-workers to the TMAF mediated addition of $TMSCF_3$ to bis(*N-tert*-butanesulfinyl imine) **979** (eq 102).[322] The desired adduct **980** was obtained as a single diastereomer in 88% yield and was then tested as a chiral solvating agent with the chiral carboxylic acid, ibuprofen. Enantiodifferentiation between the proton chemical shifts of the two enantiomers could be achieved and the best results were obtained when a 15:1 ratio of **980** to ibuprofen was used.

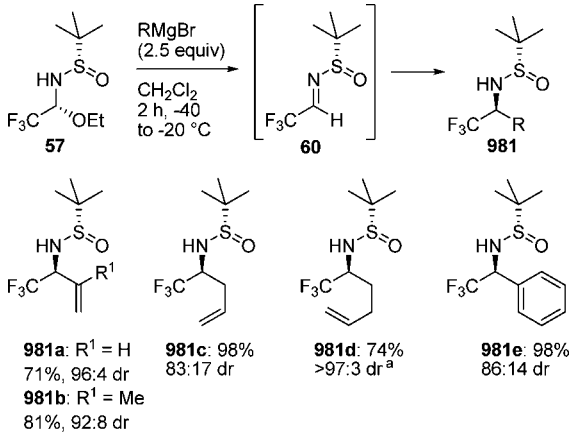


(102)

15.1.2. Addition to Trifluoromethyl N-tert-Butanesulfinyl Imines

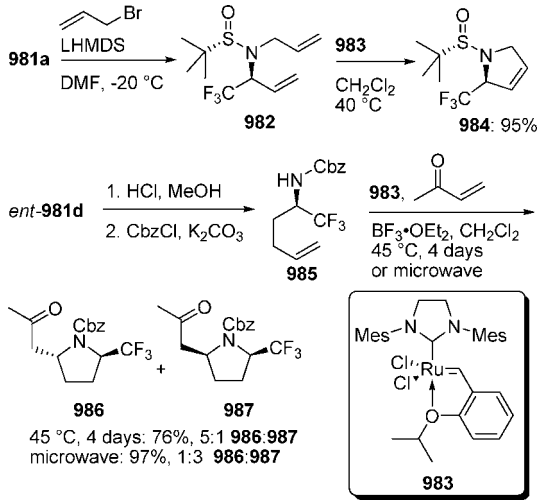
Kuduk and co-workers at Merck provided the first example of a nucleophilic addition to triflouroacetaldimine **60**, which was generated in situ from *N-tert*-butanesulfinyl amino acetal **57** (for the synthesis of this reagent, see section 3.1.3) upon exposure to a Grignard reagent (Scheme 233).[74] Optimization of temperature and solvent revealed that addition of excess Grignard reagent to **57** in CH_2Cl_2 at −40 °C provided the best yield and stereoselectivity. Vinyl, allyl, alkyl, and aryl additions were all demonstrated, providing adducts **981a−e**

Scheme 233. Synthesis of α-Trifluoromethyl Amines



[a] Reaction carried out at −40 to −10 °C.

Scheme 234. Further Transformations of α-Trifluoromethyl Amine Products

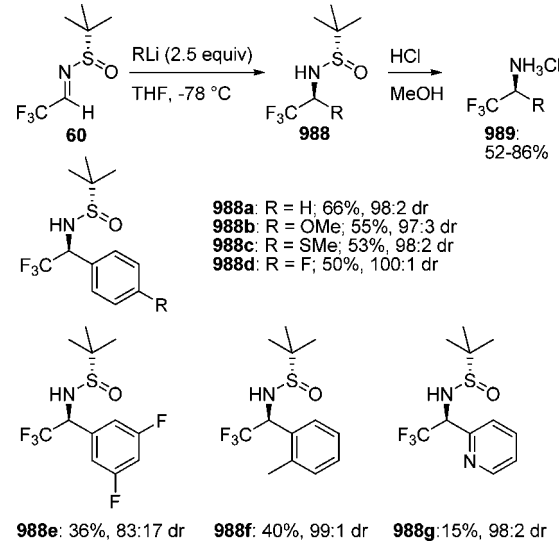


in respectable yields (71−98%) and diastereoselectivities (83:17 to >91:3 dr). The observed stereochemistries of the products, based upon X-ray crystallographic analysis of a derivative of **981a**, are consistent with addition via an open transition state (see Scheme 33, section 4.1, and Figure 13, section 11.1).

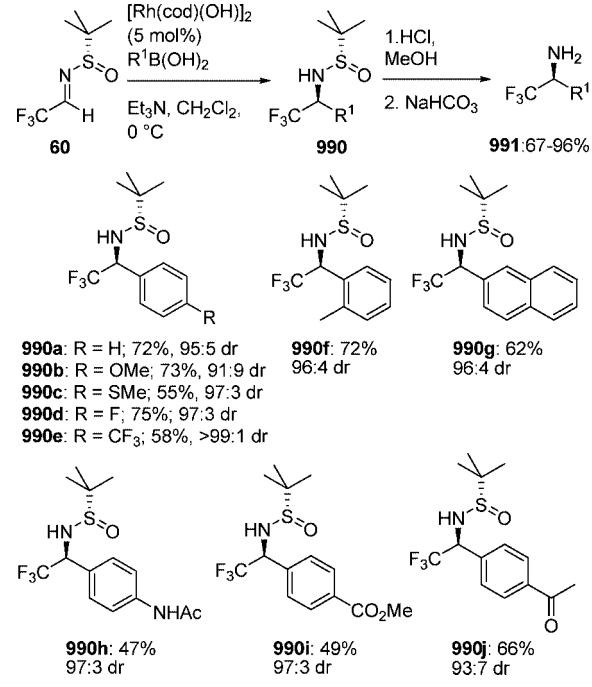
Kuduk and co-workers demonstrated the utility of the addition products by allylation of **981a**, followed by ring closing metathesis using the Hoveyda−Grubbs second generation catalyst **983** to provide chiral dihydropyrrolidine **984** in high yield (Scheme 234).[74] Moreover, Fustero and co-workers utilized the enantiomer of **981d**, after replacing the sulfinyl with the Cbz group, to provide **985**, which, upon a tandem cross-metathesis−intramolecular aza-Michael reaction, provided pyrrolidines **986** and **987** in varying ratios depending on the reaction conditions used (for other substrates for this tandem reaction, see section 4.1.1).[109]

Truong and co-workers reported the synthesis of α-trifluoroacetaldimine **60** (see section 3.1.3) and examined the stereoselective addition of aryl organometallic reagents to this substrate.[75] While Grignard reagents failed to add with the desired level of diastereoselectivity despite extensive solvent and additive optimization, additions of organolithium reagents in THF were found to proceed in moderate yield with high diastereoselectivity (Scheme 235). The product stereochemistry is consistent with addition via an open

Scheme 235. Addition of Aryl Lithium Reagents to *N-tert*-Butanesulfinyl α-Trifluoroacetaldimine



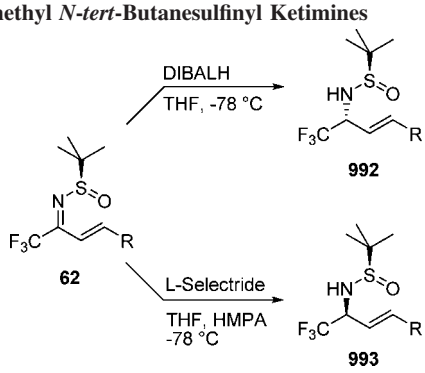
Scheme 236. Addition of Arylboronic Acids to *N-tert*-Butanesulfinyl α-Trifluoroacetaldimine



transition state (see Scheme 33, section 4.1, and Figure 13, section 11.1).

Recently, Truong and Pfeiffer reported the rhodium-catalyzed addition of arylboronic acids to *N-tert*-butanesulfinyl imine **60**, affording diastereomerically enriched *N-tert*-butanesulfinyl trifluoromethyl amines **990** (Scheme 236).[323] Catalysts, solvents, and bases were all examined to reveal that the use of $[Rh(cod)OH]_2$ as the catalyst, CH_2Cl_2 as the solvent, and triethylamine (Et_3N) as a base provided the best combination of yield and diastereoselectivity. The scope of the reaction was probed, and a number of electronically diverse aromatic groups were incorporated into the amine products **990a**−**g** in moderate to good yields (55−75%) and with diastereomeric ratios ranging from 91:9 to >99:1. Arylboronic acids bearing functional groups such as amide, ester, and ketone were also compatible with this methodology, allowing access to the corresponding amines **990h**−**j**.

Table 25. DIBALH and L-Selectride Reductions of Trifluoromethyl *N-tert*-Butanesulfinyl Ketimines



			DIBALH		L-Selectride	
entry	imine	R	dr **992**	yield of **992** (%)	dr **993**	yield of **993** (%)
1	**62a**	Ph	99:1	99	99:1	99
2	**62b**	4-MeO-Ph	99:1	98	98:2	92
3	**62c**	2-MeO-Ph	99:1	97	97:3	96
4	**62d**	4-Me-Ph	>99:1	97	98:2	95
5	**62e**	4-Cl-Ph	99:1	98	99:1	88
6	**62f**	4-Br-Ph	99:1	97	98:2	96
7	**62g**	3-Br-Ph	97:3	93	99:1	90
8	**62h**	1-naphthyl	99:1	96	99:1	94
9	**62i**	2-furyl	>98:2	94	98:2	97
10	**62j**	Ph−C≡C	>96:4	93	95:5	81
11	**62k**	octyl	>99:1	87	96:4	60
12	**62l**	$Ph(CH_2)_3$	>99:1	81	99:1	62

Protodeboration was identified as the major side reaction, causing diminished yields. The authors noted that heteroaromatic boronic acids failed to participate in the reaction and that alkenyl boronic acids only yielded trace amounts of the desired sulfinamide products. Sulfinyl group removal was also demonstrated, and the resulting amines **991a−j** were generated in 67−96% yield. The stereochemical outcome was assigned in analogy to other boronic acid additions to *N-tert*-butanesulfinyl imines.[138]

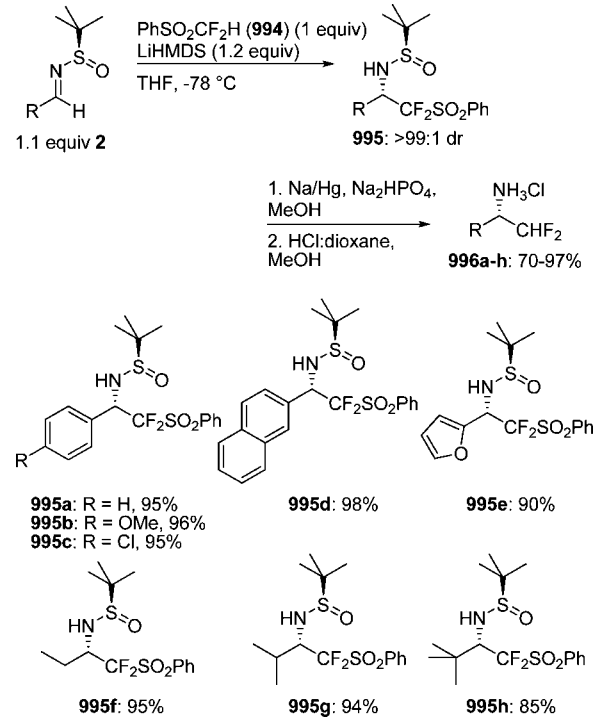
The reduction of trifluoromethyl α,β-unsaturated *N-tert*-butanesulfinyl ketimines **62** was recently demonstrated by Liu and Liu (Table 25).[77] The best yields and diastereoselectivities for the synthesis of **992** were obtained when DIBALH was employed as the metal hydride reagent. In the presence of L-Selectride, the reduction of **62a** provided **993a** as the major product, albeit with moderate diastereoselectivity. However, addition of HMPA as a cosolvent resulted in enhanced diastereoselectivity. The stereochemical outcome was rationalized by invoking a cyclic transition state for the DIBALH reductions and an open transition state for the L-Selectride reactions (see section 4.2.1). Presumably the addition of HMPA serves to disrupt any coordination of the lithium to the sulfinyl oxygen, enhancing access to the open transition state. Under both sets of optimized conditions, aromatic, heteroaromatic, alkynyl, and alkyl substituents were all tolerated, and good to excellent yields and very high diastereoselectivities were achieved for all transformations. Consistent with the observations previously noted by Ellman and co-workers (see section 6.3), the reduction was regiospecific, and no 1,4-adducts were observed in any transformation. The absolute configuration of **993e**, obtained from the L-Selectride reduction of **62e**, was determined by X-ray structural analysis.

15.2. Synthesis of α-Difluoro- and Monofluoromethyl Amines

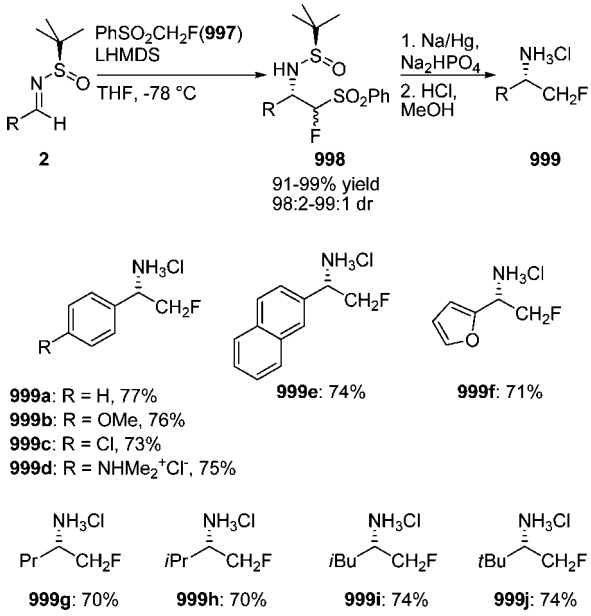
Hu and Li disclosed the asymmetric synthesis of α-difluoromethyl amines via the nucleophilic addition of difluoromethyl phenyl sulfone anion[324] to *N-tert*-butanesulfinyl aldimines (Scheme 237).[325] Generation of the requisite fluorinated carbanion was achieved by deprotonation of **994** with LHMDS *in situ*, followed by rapid addition to *N-tert*-butanesulfinyl aldimines **2** to provide adducts **995**. A variety of electronically diverse *N-tert*-butanesulfinyl aryl imines were reacted with the (phenylsulfonyl)difluoromethyl anion to provide the corresponding chiral *N-tert*-butanesulfinyl amines **995a−e** in very high yields (90−98%) and with excellent diastereoselectivities (>99:1). Despite the basic reaction conditions, adducts **995f** and **g**, derived from imine precursors with α-protons, were synthesized in high yields. The sterically demanding *N-tert*-butanesulfinyl aldimine **2** (R = *t*Bu) also gave a high yield of product **995h** (85%). The absolute configuration of **995a** was determined by X-ray structural analysis, and the configurations of adducts **995b−h** were assigned by analogy. The sense of induction is consistent with addition via an open transition state (see Scheme 33, section 4.1). Each of the (phenylsulfonyl)difluoromethylated *N-tert*-butanesulfinyl amines **995a−h** were deprotected in two steps. Reductive desulfonylation was achieved using Na/Hg amalgam. Subsequent removal of the sulfinyl group with HCl in MeOH then provided the amine hydrochlorides **996a−h** in 70−97% for the two-step procedure. Acylation of amine hydrochloride salt **996a** and chiral HPLC analysis confirmed that no racemization occurred during the deprotection.

Hu and co-workers later extended this methodology to the synthesis of chiral monofluoromethyl amines using fluoromethyl phenyl sulfone (**997**) with *N-tert*-butanesulfinyl aldimines (Scheme 238).[326] A number of aromatic, heteroaromatic, and aliphatic imines **2** were suitable substrates in this methodology, providing the (phenylsulfonyl)fluorom-

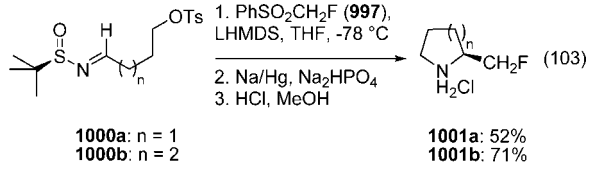
Scheme 237. Synthesis of Difluoromethyl Amines 996



Scheme 238. Synthesis of Monofluoromethyl Amines 999

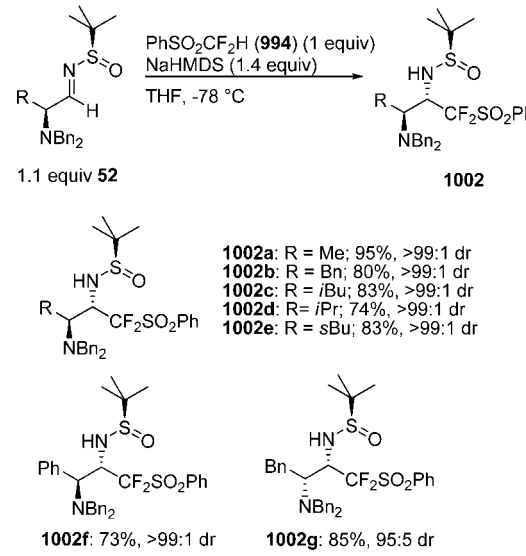


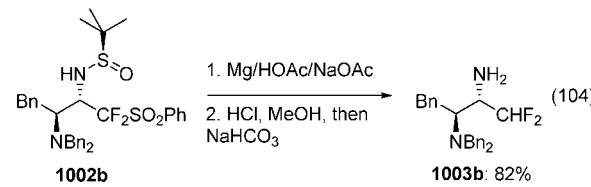
ethyl sulfinamides **998** in excellent chemical yields (91−99%). In all cases, nucleophilic addition of the *in situ* generated (phenylsulfonyl)fluoromethyl anion to the *N-tert*-butanesulfinyl imines proceeded with excellent diastereoselectivity (98:2 to 99:1 dr). A crystal structure of **998a** (R = Ph) was obtained, to establish the relative stereochemistry, which was consistent with addition via an open transition state. Crude intermediates **998** were converted to the α-monofluoromethylamine salts **999a**−**j** via reductive desulfonylation and removal of the *tert*-butanesulfinyl group in good yield over the two-step procedure. Although the initial nucleophilic addition step requires strongly basic conditions, adducts **999g**−**i**, derived from imine precursors with α-protons, were still obtained in high overall yields and with high diastereoselectivities. A tandem nucleophilic addition−substitution sequence was also developed for the synthesis of α-monofluoromethylated pyrrolidine **1001a** and piperidine **1001b** (eq 103). The *N-tert*-butanesulfinyl imines **1000a** and **b** containing a tosylate group were treated with **997** and LHMDS under the optimized reaction conditions, yielding the cyclized products, which were further converted into **1001a** and **b** in overall yields of 52% and 71%, respectively.



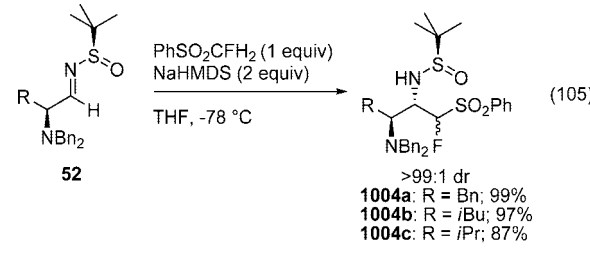
Hu and co-workers also disclosed a highly diastereoselective method for the synthesis of α-amino *N-tert*-butanesulfinyl difluoromethyl amines via the addition of deprotonated **994** to α-amino imines **52** (Scheme 239).[303] A brief survey of reaction conditions revealed that a slight excess of imine **52** and 1.0 equiv of **994** with 1.4 equiv of NaHMDS as the base provided the highest diastereoselectivities. Utilizing these optimized conditions, **1002a**−**f** were generated in good yields and with excellent diastereoselectivities. Consistent with the observations of Prakesh et al.[65] (see section 15.1.1), when imine **52** (R = Bn) was derived from the opposite enantiomer of the amino aldehyde, the corresponding adduct **1002g** was obtained with a lower diastereomeric ratio (95:5 dr), indicating a mismatch between the directing effects of the two chiral centers, with the sulfinyl group serving as the primary controlling element. The absolute configuration of product **1002b** was confirmed by X-ray structural analysis and is consistent with the stereochemistry observed for additions to α-alkoxy imines (see Figure 13, section 11.1). Adduct **1002b** was subjected to reductive desulfonylation with Hu and Ni's previously developed Mg/HOAc/NaOAc reagent,[327] and subsequent cleavage of the sulfinyl group provided the chiral α-difluoromethylated vicinal ethylenediamine **1003b** (eq 104).

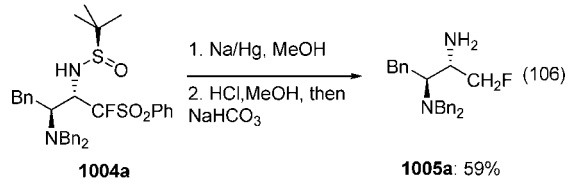
Scheme 239. Preparation of α-(Phenylsulfonyl)difluoromethylated Vicinal Ethylenediamines 1002





These reaction conditions were also amenable to the monofluoromethylation of α-amino imines **52** using fluoromethyl phenyl sulfone **997** (eq 105).[303] The corresponding adducts **1004a**−**c** were obtained in very high yields and with excellent diastereoselectivities. Moderate stereoselectivities were also observed for the formation of the stereogenic center at the fluorine substituted carbon (1.5−3.3:1.0). However, upon desulfonylation, this chiral center is destroyed. The absolute configuration of product **1004a** was confirmed by single crystal X-ray analysis. Desulfonylation and removal of the sulfinyl group was demonstrated by the preparation of **1005a** (eq 106).



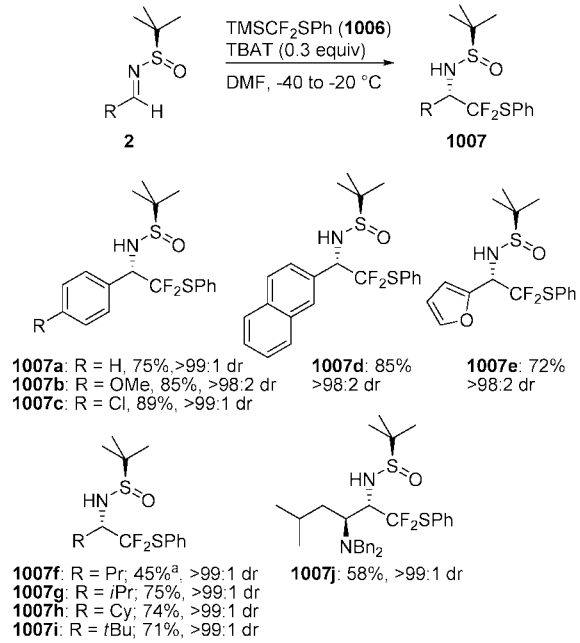


Chiral difluoromethylated amines have also been synthesized using [difluoro(phenylthio)methyl]trimethylsilane (**1006**) and *N-tert*-butanesulfinyl aldimines (Scheme 240).[328] Several Lewis base initiators were tested for the reaction, but use of 0.5 equiv of tetrabutylammonium triphenyldifluorosilicate (TBAT) in DMF at −20 °C provided the highest yield and diastereoselectivity. The scope of the reaction was probed with a number of electronically diverse aryl imines, and good yields and diastereoselectivities were observed for products **1007a**−**e**. Aliphatic imines were also suitable substrates, providing **1007g**−**j** in good yields with excellent diastereoselectivities. However, for adduct **1007f**, whose imine precursor has two α-protons, a lower yield was obtained, presumably due to competitive deprotonation of the starting imine under the reaction conditions. This method provides an alternative approach for the asymmetric synthesis of α-difluoromethyl amines to the previously described difluoromethyl phenyl sulfone route (*vide supra*).

Select products were further transformed into chiral 2,4-*trans*-disubstituted 3,3-difluoropyrrolidines to further demonstrate the utility of this method (Scheme 241). Cleavage of the sulfinyl group followed by *N*-allylation with allyl bromide provided **1008** in 61−78% yield. The CF_2−S bond was homolytically cleaved under radical conditions,[329] resulting in an intramolecular 5-exocylization reaction. This radical cyclization provided a high yield of the diastereomeric mixture of product **1009** with significant preference for the *trans* product.

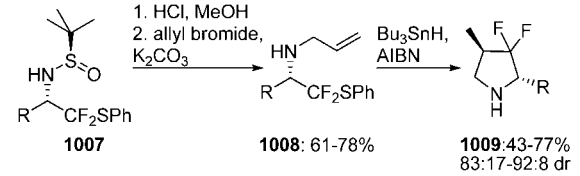
Hu and co-workers have also recently demonstrated a method for the monofluoromethylation of *N-tert*-butanesulfinyl ketimines.[330] When the conditions optimized by Prakash, Olah, and co-workers for the addition of $TMSCF_3$ to *N-tert*-butanesulfinyl aldimines[319] were utilized, no formation of the desired adduct **1010** derived from the *N-tert*-butanesulfinyl ketimine **75** was observed (Scheme 242). The reaction between $PhSO_2CHFLi$, generated *in situ* via the deprotonation of **997** with either LHMDS or *n*BuLi, gave only low yields of the desired product **1012a** (21−32%). However, the authors noted that $PhSO_2CHFLi$ possesses good thermal stability. This reagent was therefore prepared prior to the addition of ketimine **75** to provide adduct **1012a** in 97% yield. Further optimization of the reaction conditions revealed that when *n*BuLi was used as the base in THF, the desired product was obtained with good diastereoselectivity (Table 26, entry 1). Although use of KHMDS resulted in a reduction in yield, even higher diastereoselectivity was observed (entry 1). Ketimines possessing a wide range of electronically diverse aryl substituents were tested under both reaction conditions (entries 2−7), providing the desired adducts **1012** in good yields (60−93%) and diastereoselectivites (91:9–99:1). Heteroaromatic substituents on the ketimine precursor could also be incorporated into the desired product (entries 8−9). *N-tert*-Butanesulfinyl alkyl methyl ketimines were also transformed into the fluorinated products (entries 10−11). The absolute configuration of product **1012a** (R = Ph) was

Scheme 240. Stereoselective (Phenylthio)difluoromethylation of *N-tert*-Butanesulfinyl Imines with $TMSCF_2SPh$

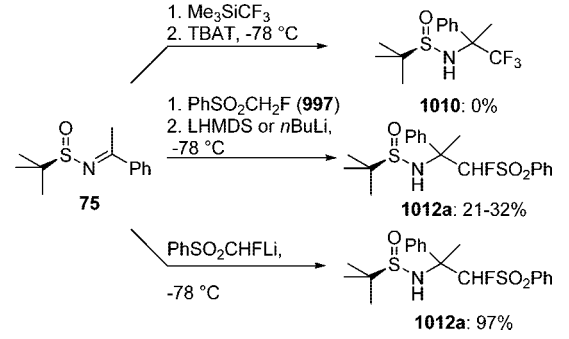


[a] 1.0 equiv of TBAT was used.

Scheme 241. Stereoselective Synthesis of Pyrrolidines 1009

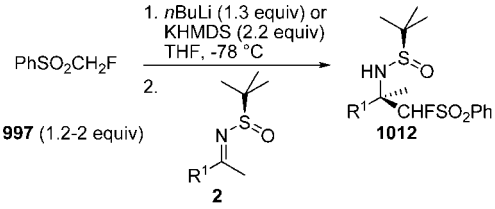


Scheme 242. Optimization of Fluoroalkylation of Ketimine 75

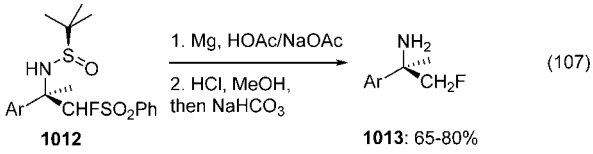


determined by X-ray structural analysis and is consistent with that observed on addition of other organometallic reagents to ketimines (see section 5). Select adducts were further manipulated to produce the chiral fluoromethyl amines **1013**, using their previously described deprotection strategy,[303] in good yields (65−80%) without detectable racemization (eq 107). The authors also attempted to expand this method to include the difluoromethylation of *N-tert*-butanesulfinyl ketimines. Unfortunately, when $PhSO_2CF_2Li$ was pregenerated from **994** and *n*BuLi before addition to ketimine **75**, no desired product was obtained. It appears that the thermal stability, good nucleophilicity, and relatively weak basicity of $PhSO_2CHFLi$ play important roles in the success of this transformation.

Table 26. Diastereoselective Monofluoromethylation of Ketimines



entry	R^1	base	yield (%)	facial selectivity
1	Ph	*n*BuLi	90	95:5
		KHMDS	64	99:1
2	4-F-Ph	*n*BuLi	81	96:4
		KHMDS	65	99:1
3	4-Cl-Ph	*n*BuLi	77	94:6
		KHMDS	69	98:2
4	4-CF_3-Ph	*n*BuLi	86	91:9
		KHMDS	60	97:3
5	4-MeO-Ph	*n*BuLi	85	96:4
		KHMDS	62	99:1
6	4-Me-Ph	*n*BuLi	93	95:5
		KHMDS	68	99:1
7	2-naphthyl	*n*BuLi	72	94:6
		KHMDS	68	99:1
8	2-furyl	*n*BuLi	81	95:5
		KHMDS	77	94:6
9	pyridyl	*n*BuLi	81	87:13
		KHMDS	74	99:1
10	*i*Pr	*n*BuLi	81	95:5
		KHMDS	73	94:6
11	*t*Bu	*n*BuLi	77	95:5
		KHMDS	47	99:1



(107)

15.3. Synthesis of Fluorinated α-Amino Acid Derivatives

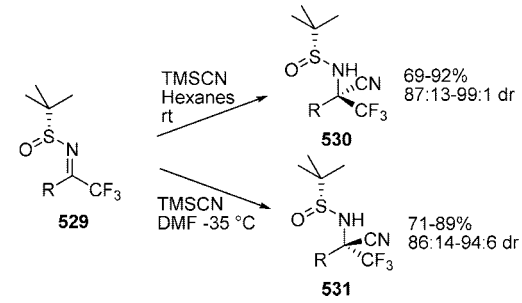
The asymmetric Strecker reaction for the synthesis of α-trifluoromethyl α-amino acids from CF_3-substituted *N-tert*-butanesulfinyl ketimines **529** has been demonstrated by Lu and co-workers (Scheme 243; for details, see section 9.2.1).[76]

15.4. Synthesis of Fluorinated *β*-Amino Acid Derivatives

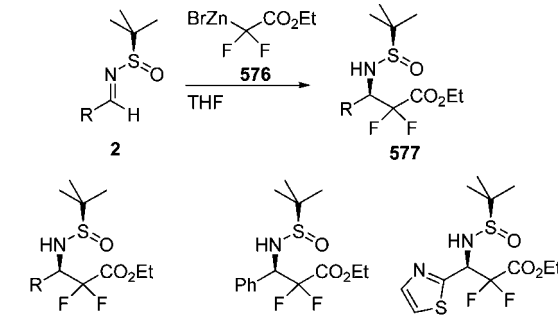
Staas and co-workers at Merck developed a synthetic route to α,α-difluoro *β*-amino esters via addition of the Reformatsky reagent **576** to aryl and alkyl imines **2** (Scheme 244).[229] Treatment of a number of *N-tert*-butanesulfinyl aldimines at ambient temperature with an excess of **576** provided adducts **577a**−**e** in moderate to good yields (51−82%) and with good to excellent diastereoselectivities (80:20 to 95:5 dr). The absolute configuration of a derivative of **577c** was determined by X-ray structural analysis, and the stereochemical outcome of the reaction was rationalized by a chelated transition state.

The utility of this methodology was exemplified by demonstrating its compatibility with standard peptide coupling techniques. Treatment of **577c** with ammonia provided the corresponding primary amide, which was converted to the primary amine **1014** in the presence of BH_3·DMS (Scheme 245). Acylation with Fmoc-L-Pro afforded peptide **1015** in 92% yield. Further synthetic manipulations yielded

Scheme 243. Strecker Reaction with Trifluoromethyl *N-tert*-Butanesulfinyl Ketimines

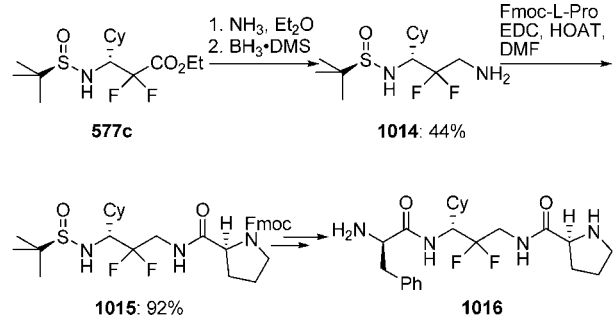


Scheme 244. Synthesis of *N-tert*-Butanesulfinyl Protected α,α-Difluoro *β*-Amino Esters

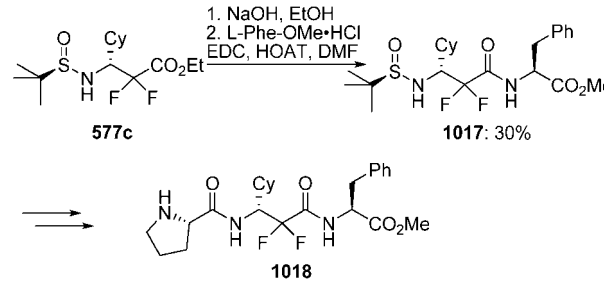


577a: R = Pr; 55%; 80:20 dr **577d**: 82%, 90:10 dr **577e**: 58%, 95:5 dr
577b: R = *i*Bu; 51%, 81:19 dr
577c: R = Cy; 81%; 87:13 dr

Scheme 245. Synthesis of Pseudotripeptide 1016 from α,α-Difluoro-*β*-amino Ester 577c



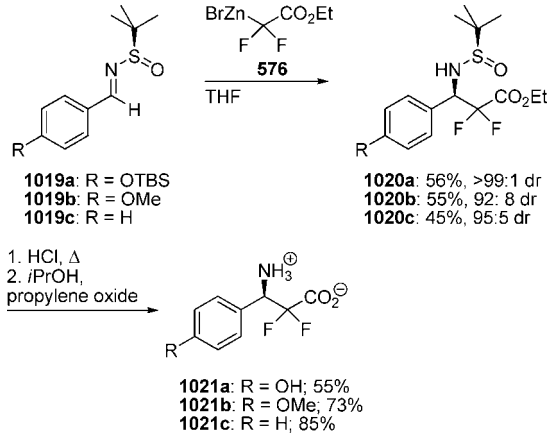
Scheme 246. Synthesis of Pseudotripeptide 1018 from α,α-Difluoro-*β*-amino Ester 577c



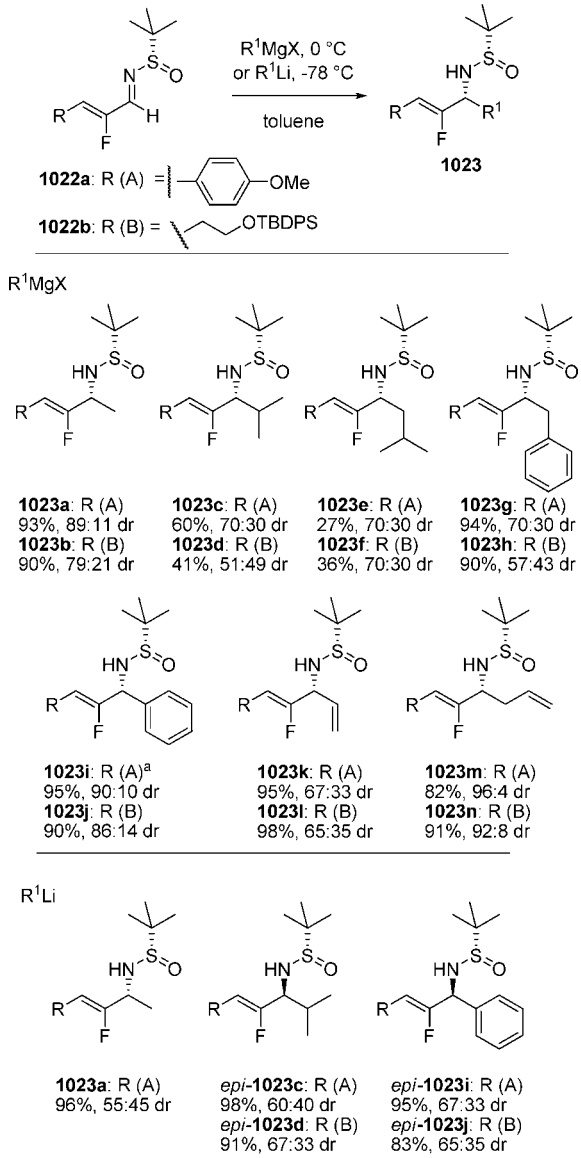
the pseudotripeptide **1016**. Alternatively, ester **577c** was hydrolyzed with NaOH to the free carboxylic acid, which was then coupled with L-Phe-OMe, providing **1017** in 30% yield (Scheme 246). Pseudotripeptide **1018**, bearing an α,α-difluoro-*β*-amino acid linker, was obtained after further chemical transformations.

Bruner and co-workers applied the methodology developed at Merck in their synthesis of α,α-difluoro-*β*-tyrosines **1021a** and **b** as well as α,α-difluoro-*β*-phenylalanine **1021c** (Scheme

Scheme 247. Synthesis of α,α-Difluoro-Based Inhibitors of *Sg*TAM



Scheme 248. Organometallic Additions to *N-tert*-Butanesulfinyl α-Fluoroenimines

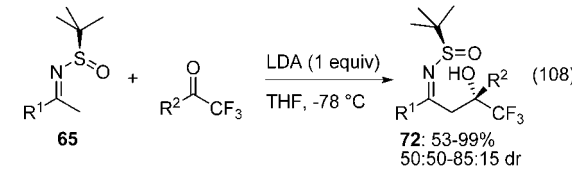


[a] Reaction conducted at −30 °C.

247).[331] These adducts were explored as mechanism-based inhibitors of *Sg*TAM, an aminomutase that utilizes 4-methylideneimidazole-5-one (MIO) as a cofactor and catalyzes the conversion of L-tyrosine to (*S*)-β-tyrosine. Addition of the Reformatsky reagent **576** to the appropriate imine precursors provided the desired *N-tert*-butanesulfinyl protected α,α-difluoro-β-amino esters **1020a**−**c** in moderate yield (45−56%) and with good diastereoselectivity (92:8 to >99:1). Global deprotection yielded the requisite β-tyrosine analogues **1021**, which were cocrystallized with *Sg*TAM to probe the binding of these substrates in the active site and elucidate the mechanism of the 1,2-amino shift catalyzed by *Sg*TAM.

15.5. Synthesis of β-Imino α-Trifluoromethyl Alcohols

The synthesis of β-hydroxy-β-trifluoromethyl imines **72** was described by Liu and co-workers. These imines were synthesized via the addition of the metalloenamine derived from ketimines **65** to a number of trifluoromethyl ketones (eq 108; see section 3.2.1 for details).[85]



15.6. Synthesis of Fluorinated Allylic Amines

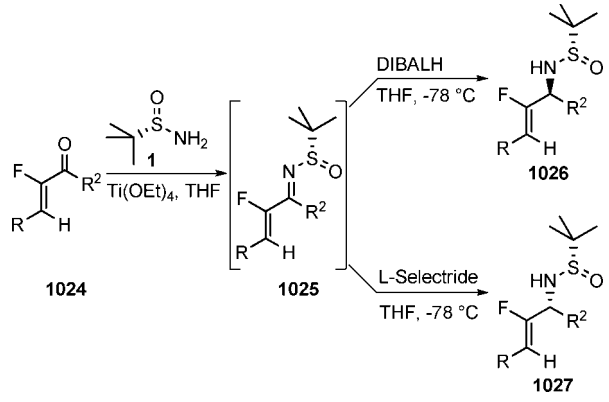
15.6.1. 1,2-Addition to α-Fluoro α,β-Unsaturated Imines

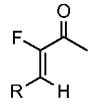
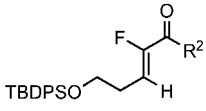
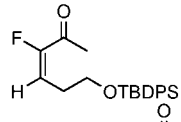
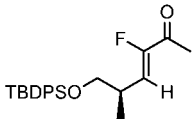
Pannecoucke and co-workers reported the addition of organometallic reagents to α-fluoro α, β-unsaturated imines **1022a** and **1022b** (Scheme 248).[332] This method is complementary to the work by the same group on reductions of the corresponding *N-tert*-butanesulfinyl ketimines (see section 15.6.2).[333] The best diastereoselectivities were obtained for Grignard additions carried out in toluene as a reaction solvent. Methyl, benzyl, aryl, vinyl, and allyl additions all proceeded to give products **1023a**−**b** and **g**−**n** in high yields (82−98%) with variable levels of diastereoselectivity. In contrast, addition of *i*PrMgCl and *i*BuMgBr provided low yields of the desired products due to competitive imine reduction. This is consistent with results obtained for similar reactions of unfunctionalized aldimines (section 4.1.1).[92] Therefore, additions of organolithium reagents were also investigated, providing the desired adducts **1023** in high yield but with low stereoselectivity, in many cases favoring the opposite diastereomer from that observed for the corresponding Grignard addition. The absolute stereochemistry of major diastereomer **1023a** was established via X-ray crystallographic analysis of the minor diastereomer, and the other Grignard additions were presumed to proceed with analogous stereoselectivity. This is consistent with addition of Grignard reagents via a chelated transition state and addition of organolithium reagents via an open transition state, as observed for most additions to unfunctionalized aldimines (see Scheme 33). An isolated example of enolate addition to an α-fluoroenimine was reported by Edmondson and co-workers (see Scheme 158, section 10.1.2).[242]

15.6.2. Reduction of α-Fluoro α,β-Unsaturated Ketimines

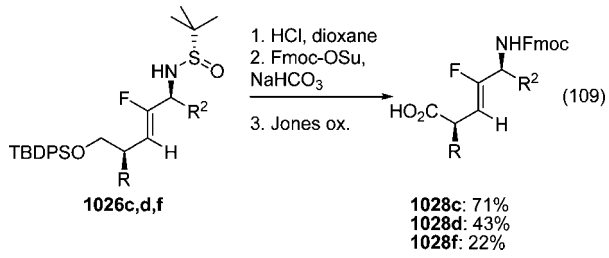
A one-pot protocol for reductive amination of α-fluoro α,β-unsaturated ketones using (*S*)-*tert*-butanesulfinamide was described by Pannecoucke and co-workers (Table 27).[333] A series of metal hydride reagents were screened, revealing

Table 27. Diastereoselective Reductive Aminations of α-Fluoro Enones 1024 with *tert*-Butanesulfinamide



Ketone **1024**		DIBALH yield (%)	DIBALH dr **1026**	L-Selectride yield (%)	L-Selectride dr **1027**
	**1024a**: R = 4-MeOPh	79	98:2	72	98:2
	1024b: R = $Ph(CH_2)_2$	57	98:2	46	97:3
	**1024c**: R^2 = Me	65	97:3	67	97:3
	1024d: R^2 = Bn	58	99:1	57	99:1
	**1024e**	60	98:2	86	99:1
	**1024f**	61	98:2	62	95:5

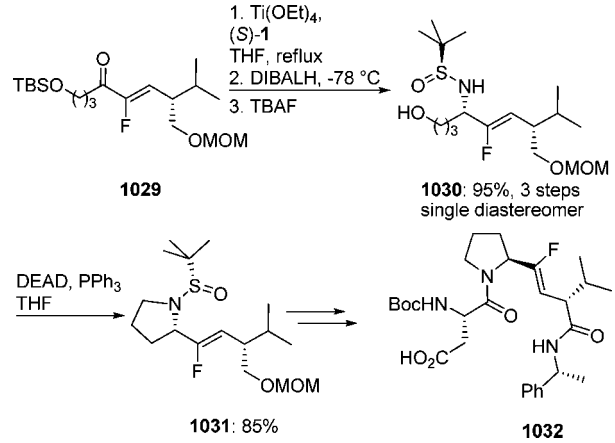
that excellent yields and diastereoselectivities for diastereomer **1026** were obtained in the presence of DIBALH while **1027** was obtained in the presence of L-Selectride. A series of α-fluoro enones **1024a**−**f** were evaluated under both sets of reaction conditions, and uniformly good yields and very high diastereoselectivities were observed. A three-step procedure consisting of concomitant acidic deprotection of the sulfinyl and silyl groups, FMOC protection of the amine group, and Jones oxidation of the alcohol to the carboxylic acid was devised and tested on select substrates for the synthesis of fluoroolefin-containing peptidomimetics **1028** (eq 109).



(109)

To probe the role of the Pro-D-Val amide bond in their aspartic-acid containing peptidic expoxidation catalyst, Miller and co-workers developed a route to the fluoroolefin peptidomimetic analogue **1032** by utilizing sulfinamide chemistry

Scheme 249. Synthesis of Fluoroolefin Analogue 1032 of an Aspartate-Based Epoxidation Catalyst

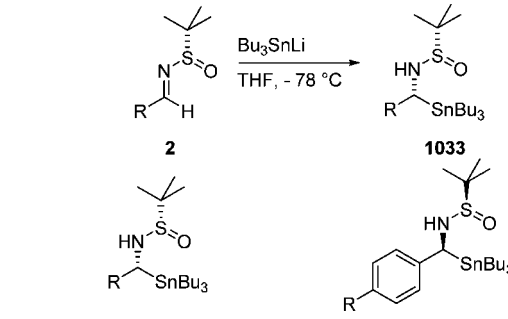


(Scheme 249).[334] Imine condensation, stereoselective reduction of the resulting ketimine with DIBALH, and deprotection of the silyl-protected primary alcohol provided **1030** as a single diastereomer in 95% yield over three steps. Cyclization to **1031** was achieved under Mitsunobu conditions, and the relative stereochemistry was established by X-ray structural analysis of the amino alcohol derived from **1031**. Further synthetic transformations provided the desired fluoro-substituted alkene isostere epoxidation catalyst **1032**, which was evaluated to gain mechanistic insight into the structure–selectivity relationships present in this class of peptidic epoxidation catalysts.

16. Synthesis of α-Organometallic Amines

The first report of a 1,2-addition of a non-carbon or hydride nucleophile to an *N*-*tert*-butanesulfinyl imine was disclosed by Chong and Kells in 2003 in their synthesis of α-aminoorganostannanes **1033** (Scheme 250).[335] Addition of Bu_3SnLi to *N*-*tert*-butanesulfinyl aliphatic imines at −78 °C followed by quenching at low temperature provided the desired adducts **1033** in high yields as single diastereomers (Scheme 250). Bu_3SnLi was also an effective nucleophile for addition to electron-rich aromatic imines, while electron-poor aromatic imines required the use of $Bu_3SnZnEt_2Li$ to

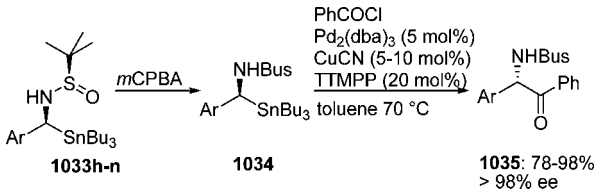
Scheme 250. Synthesis of Functionalized α-Amino Organostannanes



1033a: R = Me; 83%, 99:1 dr
1033b: R = Et; 92%, >99:1 dr
1033c: R = pentyl; 84%, >99:1 dr
1033d: R = *i*Pr; 96%, >99:1 dr
1033e: R = Cy; 89%, >99:1 dr
1033f: R = *t*Bu; 94%, >99:1 dr
1033g[a]: R = $(CH_2)_7OBn$; 80%, >99:1 dr
1033h: R = H; 73%, >99:1 dr
1033i: R = Me; 77%, >99:1 dr
1033j: R = OMe; 84%, >99:1 dr
1033k: R = NMe_2, 91%, >99:1 dr
1033l[b]: R = Cl; 94%, >99:1 dr
1033m[b]: R = Br; 59%, >99:1 dr
1033n[b]: R = CF_3; 80%, >99:1 dr

[a] (*R*)-*tert*-Butanesulfinyl imine **2** was used. [b] $Bu_3SnZnEt_2Li$ was used.

Scheme 251. Stille Cross-coupling from α-Aminoorganostannanes



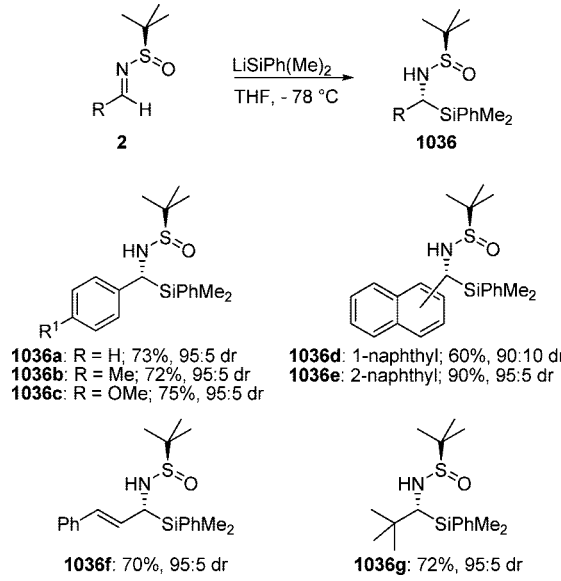
maintain high levels of diastereoselectivity.[336] The *N-tert*-butanesulfinyl α-aminoorganostannanes **1033** were found to be stable to silica gel chromatography and could be stored at ambient temperatures for extended periods of time without discernible decomposition. The absolute configuration of **1033c** was determined by chemical correlation. The observed sense of induction is in accordance with the chelated transition state suggested by Ellman and co-workers for the addition of Grignard reagents to *N-tert*-butanesulfinyl imines (Scheme 33, section 4.1). Direct deprotection of the sulfinyl group was not possible due to the instability of α-stannylamines under acidic conditions. However, protecting group manipulation was possible, yielding the Boc-protected α-aminoorganostannanes after several synthetic transformations (see section 19.1.2 for further details on this transformation).

Chong and Kells also demonstrated that aromatic *N-tert*-butanesulfinyl α-aminoorganostannanes were viable precursors for Stille cross-coupling reactions with acid chlorides.[336] While all attempts to couple sulfinamides **1033** with electrophiles under Stille-type conditions failed, coupling with benzoyl chloride could be achieved after oxidation to provide the corresponding *tert*-butanesulfonyl (Bus) protected derivatives **1034** (Scheme 251). A brief survey of ligands revealed that the highly basic tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) was the most effective, providing the products **1035** in good yields without loss of stereochemical integrity. Comparison of **1035** (Ar = Ph) with an identical sample of known stereochemistry demonstrated that Stille coupling proceeded with inversion of stereochemistry.

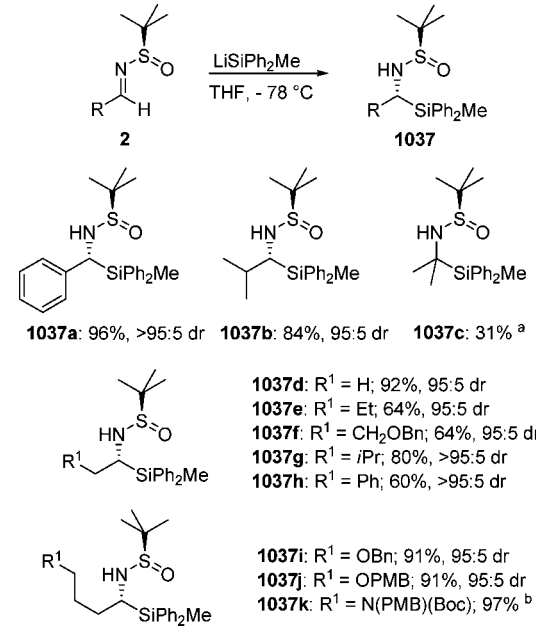
The 1,2-addition of noncarbon or hydride nucleophiles to *N-tert*-butanesulfinyl aldimines was expanded to include the synthesis of α-silylamines by Scheidt and co-workers.[337] They utilized dimethylphenylsilyllithium as the nucleophile at low temperatures in THF. These conditions were applicable for a variety of aryl aldimines, an alkenyl aldimine, and a nonenolizable alkyl (R = *t*Bu) aldimine, generating the α-silylamines **1036** in 60−90% yield and with >90:10 dr (Scheme 252). Scheidt and co-workers obtained a crystal structure of α-silylamine **1036g**. The observed stereochemistry corresponds to an open transition state, similar to organolithium additions (see Scheme 33, section 4.1). They also demonstrated that the sulfinyl group of adduct **1036a** could be replaced with a Boc group (by treatment with HCl/dioxane followed by Boc_2O addition), without degradation of the silyl group or epimerization of the newly formed stereogenic center.

Later Lindsay, Skrydstrup, and co-workers expanded the scope of this reaction to include aldimines with enolizable protons by using $LiSiPh_2Me$ as the nucleophile (Scheme 253).[338] Under these conditions, alkyl aldimines incorporating protected alcohols or amines could also be converted to α-silylamines. The aldimines used were chosen to mimic naturally occurring amino acid side chains. Moreover, addition of the silyl nucleophile to the ketimine derived from

Scheme 252. Synthesis of *N*-Sulfinyl α-Silylamines



Scheme 253. Synthesis of *N*-Sulfinyl α-Silylamines

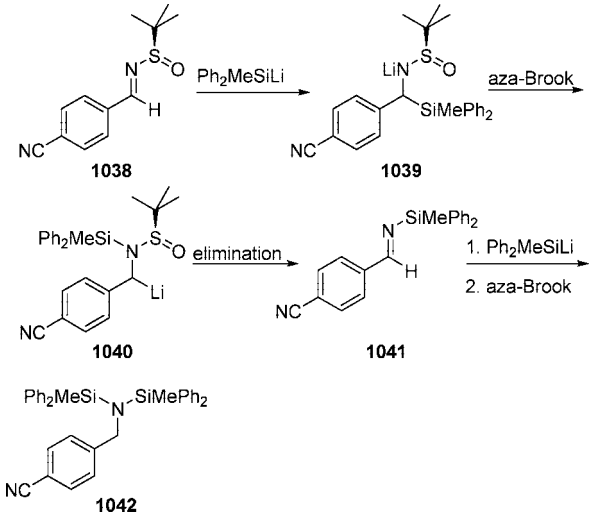


[a] The ketimine derived from acetone was used. [b] The dr was not determined.

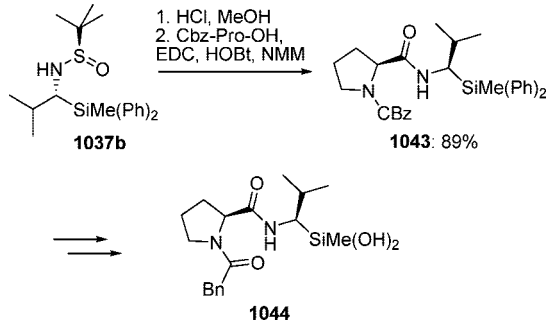
acetone was demonstrated, providing a 31% yield of adduct **1037c**. While no product arising from an aza-Brook rearrangement was observed for the silyllithium during additions to electron-rich or electron-neutral aldimines, when the *N-tert*-butanesulfinyl imine derived from 4-cyanobenzaldehyde was employed, product **1042**, arising from a double aza-Brook rearrangement, was obtained in 56% yield (Scheme 254).

In their efforts to synthesize silanediol peptidomimetics, Lindsay, Skrydstrup, and co-workers elaborated several *N*-sulfinyl α-silylamines, including **1037b**, by cleaving the sulfinyl group, followed by coupling the resulting free amine with protected amino acids (Scheme 255).[338] Further extension of these peptides with additional amino acids was also performed. The diphenylsilyl moiety was then converted over several steps to the corresponding silanediol to provide peptidomimetics such as **1044**. The silanediol motif has been

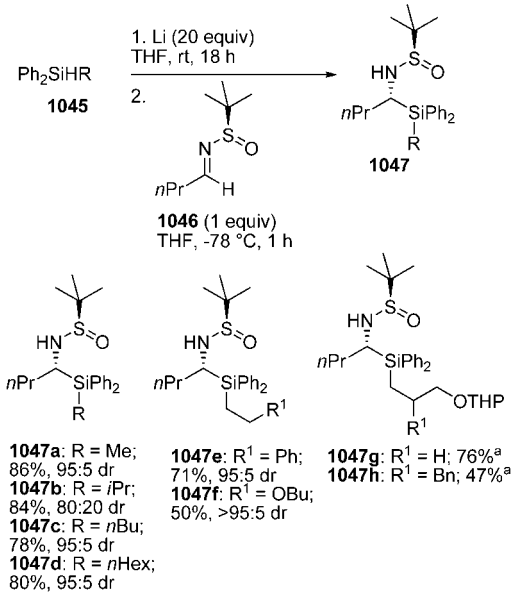
Scheme 254. Aza-Brook Rearrangement with Electron-Deficient Imine Substrate



Scheme 255. Synthesis of Silane-Containing Peptide Isosteres



Scheme 256. Lithiation of Hydridosilanes Followed by Addition to an Imine

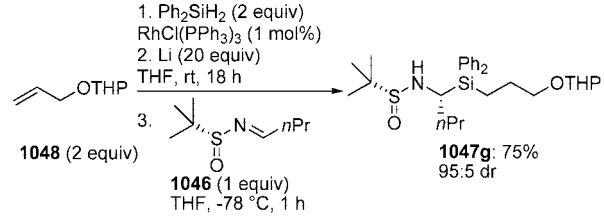


[a] The dr was not determined.

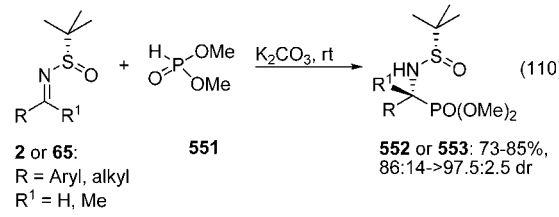
shown to be a stable mimetic of the tetrahedral intermediate for aspartic and metalloprotease inhibition.[339]

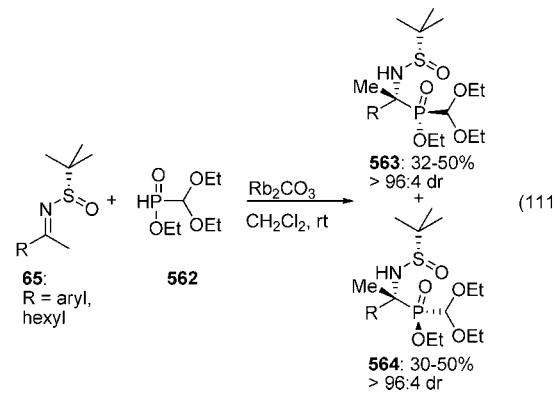
More recently, Skrydstrup has used diverse alkyl diphenylsilanes, synthesized from the hydrosilylation of alkenes using either a radical initiator with a thiol catalyst or Wilkinson's catalyst, for the synthesis of *N-tert*-butanesulfinyl α-silylamines.[340] The hydridosilane precursors are more stable than the chlorosilanes that they had used previously to generate $LiSiPh_2Me$ or $LiSiMe_2Ph$ (*vide supra*) and can be purified by column chromatography, making them a more attractive choice of starting material. Treatment of the hydridosilane intermediates **1045** with lithium followed by addition to *N-tert*-butanesulfinyl imine **1046** provided an array of *N*-sulfinyl α-silylamines **1047** in yields ranging from 47 to 84% and diastereoselectivities from 80:20 to >95:5 (Scheme 256). While most of the synthesized products were obtained after isolation of the intermediate alkyldiphenylsilanes, this method was also amenable to a one-pot hydrosilylation of **1048**, lithiation, and addition to imine **1046**, generating **1047g** in 75% yield and with 95:5 dr (Scheme 257).

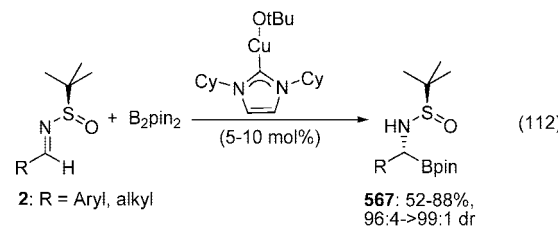
Scheme 257. One-Pot Hydrosilylation, Lithiation, and Addition to an Imine



The synthesis of α-amino phosphonates by addition to both aldimines and ketimines (eqs 110 and 111; for details, see section 9.3), as well as the synthesis of α-amino boronate esters (eq 112; for details see section 9.4), has also been reported.



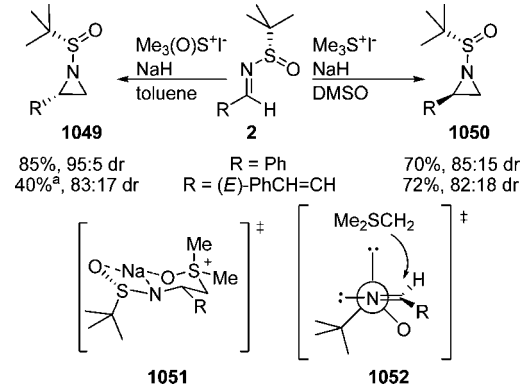




17. Synthesis of Aziridines

Aziridines not only are present in bioactive natural products and drugs but also are versatile intermediates for

Scheme 258. Synthesis of *N-tert*-Butanesulfinyl Aziridines



[a] *n*BuLi as the base and THF as the solvent were employed.

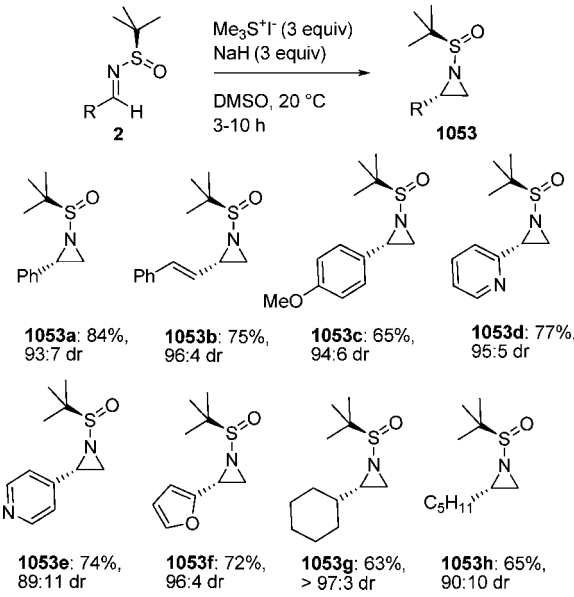
the synthesis of amine-containing compounds. As reviewed in this section, *N-tert*-butanesulfinyl imines have served as very useful starting materials for the asymmetric synthesis of a diverse set of aziridines.

17.1. Addition of Ylides to *N-tert*-Butanesulfinyl Imines

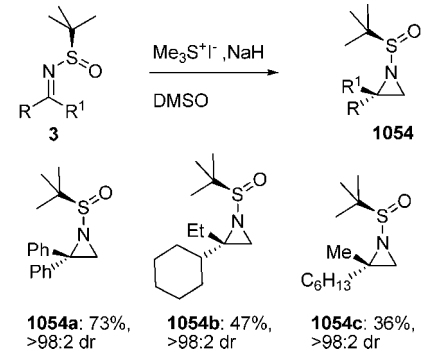
In 1996 Garcia Ruano and co-workers reported the first method for the preparation of aziridines from *N-tert*-butanesulfinyl aldimines via the addition of activated sulfur ylides.[32] Upon investigating the effect of the substituent on the sulfinyl sulfur, they determined that the more sterically bulky *tert*-butanesulfinyl group resulted in higher levels of diastereoselectivity than the corresponding *N-p*-toluenesulfinyl or *N*-naphthalenesulfinyl groups. In particular, the reaction between the *in situ* generated dimethylsulfonium methylide or dimethyloxosulfonium methylide and the *N-tert*-butanesulfinyl imines derived from benzaldehyde or cinnamaldehyde yielded the corresponding aziridines **1050** in 70−72% yield and >82:18 dr and **1051** in 40−85% yield and 83:17 to 95:5 dr, respectively (Scheme 258). Interestingly, a switch in diastereoselectivity was observed in the formation of the aziridines that was dependent on the methylene-transfer reagent employed. This reversal in stereoselectivity was also observed by Khiar and co-workers.[341] Garcia Ruano and co-workers hypothesize that the reaction utilizing the nonchelating dimethylsulfonium methylide is under kinetic control, where nucleophilic addition to the C═N bond occurs from the least hindered face, as shown in transition state **1052**. In contrast, the oxygen present in the dimethyloxosulfonium methylide can promote chelated transition state **1051**, in which both the sulfinyl oxygen and the dimethyloxosulfonium methylide oxygen chelate to the sodium ion. In this transition state, the R group is held in an equatorial position to minimize steric interactions with the axial methyl of the ylide, thereby generating diastereomer **1049**.

Later, Stockman and co-workers extended the scope of the aziridination reaction with dimethylsulfonium methylide to include a variety of electron-rich and electron-poor aryl and branched and unbranched alkyl *N-tert*-butanesulfinyl aldimines.[342] After screening several reaction conditions, they determined that deprotonation with NaH in DMSO, the same protocol utilized by Garcia Ruano and co-workers, provided the highest yields and selectivities (Scheme 259). Significantly, Stockman observed good yields (63−84%) and diastereoselectivities (>89:11 dr) of products **1053** at much

Scheme 259. Synthesis of Aziridines from Diverse *N-tert*-Butanesulfinyl Aldimines

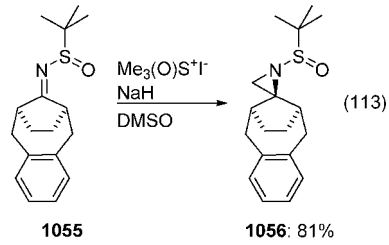


Scheme 260. Synthesis of Aziridines from *N-tert*-Butanesulfinyl Ketimines



shorter reaction times than those reported by Garcia Ruano and co-workers (3−10 h versus 48−168 h). Indeed, comparison of the two reaction times for formation of products **1053a** and **1053b** reveals that the use of shorter reaction times resulted in improved yields. More recently, these conditions were utilized to synthesize a limited number of aziridines derived from *N-tert*-butanesulfinyl ketimines (Scheme 260).[343] For the ketimine substrates, exposure to NaH resulted in undesired side reactions, and many of the substrates that were evaluated yielded little or no desired product. However, for those ketimines that gave appreciable amounts of the terminal aziridines **1054a**−**c**, excellent diastereoselectivity was observed (>98:2 dr). The stereochemical outcome, as based on an X-ray crystal structure of **1053b**, was consistent with the findings of Garcia Ruano (*vide supra*). Dimethyloxosulfonium methylide has also been utilized to produce aziridines from *N-tert*-butanesulfinyl ketimines. In their studies on inhibitors of γ-secretase for the treatment of Alzheimer's disease, Madin and co-workers synthesized the spiro-aziridine **1056** from racemic *N-tert*-butanesulfinyl ketimine **1055** in 81% yield (eq 113).[344]

Recently, Forbes, Stockman, and co-workers utilized the methylene transfer reagent **1057**, which generates a sulfur ylide *in situ* upon thermally induced decarboxylation of the carboxymethylsulfonium betaine precursor, in their synthesis of terminal *N-tert*-butanesulfinyl aziridines **1058** (Scheme



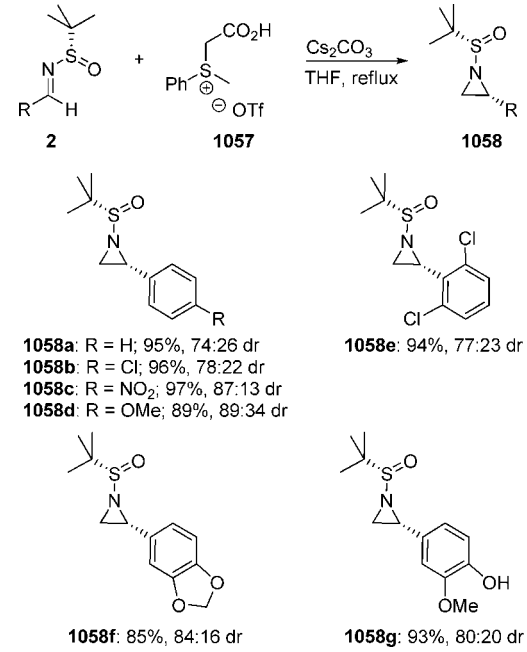
261).[345] Aryl *N-tert*-butanesulfinyl aldimines were first examined as the π-acceptors, and while the isolated yields for products **1058a**−**g** were excellent (85−97%), diastereoselectivities remained moderate under the reaction conditions employed (Cs_2CO_3, refluxing THF). Improved diastereoselectivity for **1058a** was obtained when the reaction was conducted at ambient temperature, but the yield was significantly lowered (50% conversion, 90:10 dr). While this method has the distinct advantage that strong bases are not required for the generation of the ylide, superior diastereoselectivity was achieved using the $Me_3{}^+I^-$/NaH protocol previously reported by Stockman and co-workers (*vide supra*).

The reaction was also studied using butanediacetal-protected *N-tert*-butanesulfinyl imines derived from enantiomerically pure aldehyde precursors (Scheme 262).[346] In order to explore the matched/mismatched scenarios in the methylene transfer reaction, both diastereomers of the imines were prepared and reacted with **1057**. A high yield and high levels of diastereocontrol were achieved for **1059a**. For the mismatched scenario, **1059b**, a lower diastereoselectivity was observed. The source of asymmetry was probed by examining the reaction between the *N-tert*-butanesulfinyl imine derived from cyclohexanecarboxaldehyde and **1057**. The resulting aziridine **1059c** was generated in high yield, but with modest diastereoselectivity (61:39). Experiments were conducted suggesting that epimerization of the aziridine was not a competitive pathway. Unfortunately, the relative configurations of the aziridine products were not determined in this study.

Building on their previous work for the synthesis of terminal *N-tert*-butanesulfinyl aziridines, Stockman and co-workers have also reacted allyl sulfur ylides with *N-tert*-butanesulfinyl imines to generate chiral vinyl aziridines.[347] An investigation of several bases and solvents to identify the optimal conditions for the aziridination reaction between the *N*-sulfinyl imine and *S*-allyl tetrahydrothiophenium bromide **1060** established that deprotonation of the sulfur salt should be carried out with lithium *tert*-butoxide in THF at room temperature. Aromatic and heteroaromatic imines were suitable substrates for this reaction (entries 1−6, Table 28). An example of an alkenyl imine was reported (entry 7), and linear, β-branched, and α-branched alkyl aldimines could also be used (entries 8−12). Most reactions were complete within 25−45 min, and yields were generally good (44−82%). Moderate levels of *cis*/*trans* selectivity and high diastereoselectivities were observed for a wide range of imine substrates. A preference for the *trans* configuration in all aziridine products (**1061a**−**l**) was observed.

Stockman and co-workers have also reacted *S*-allyl tetrahydrothiophenium bromide **1060** with *N-tert*-butanesulfinyl ketimines **3**, obtaining aziridine products **1063** in good yields and with excellent diastereoselectivities (≥95:5 dr) and moderate *trans*:*cis* selectivity (Scheme 263).[343] While the reactivity of several of the ketimine substrates was unacceptably low in THF (the optimal solvent for addition to aldimines), DMSO as a solvent resulted in higher yields, albeit with diminished stereocontrol (**1063d** was obtained in a 55% yield and with a 72:28 *trans*:*cis* ratio in THF). The milder reaction conditions employed for the formation

Scheme 261. Synthesis of *N-tert*-Butanesulfinyl Aziridines from Sulfonium Salt 1057



Scheme 262. Methylene Transfer onto *N-tert*-Butanesulfinyl Imines

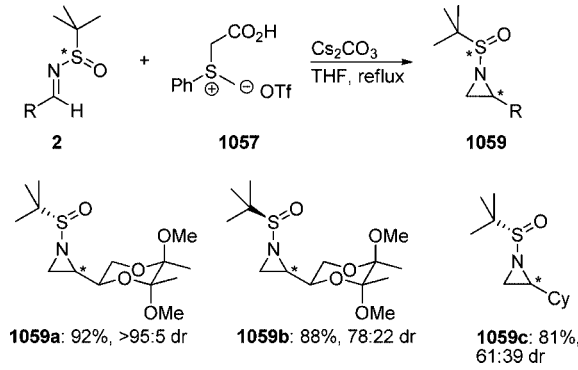
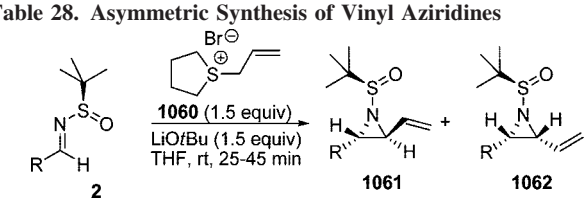
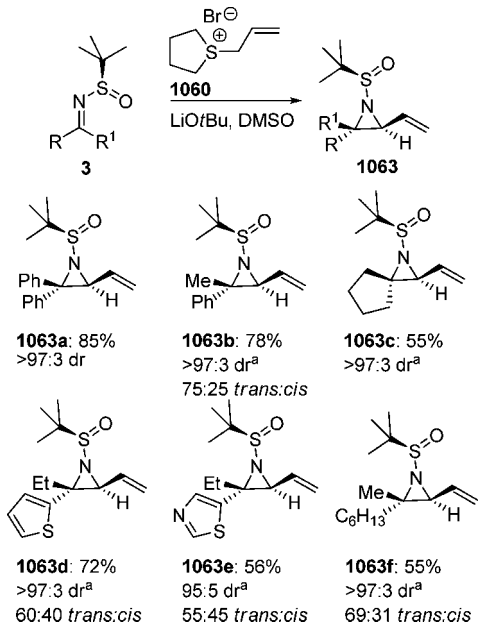


Table 28. Asymmetric Synthesis of Vinyl Aziridines



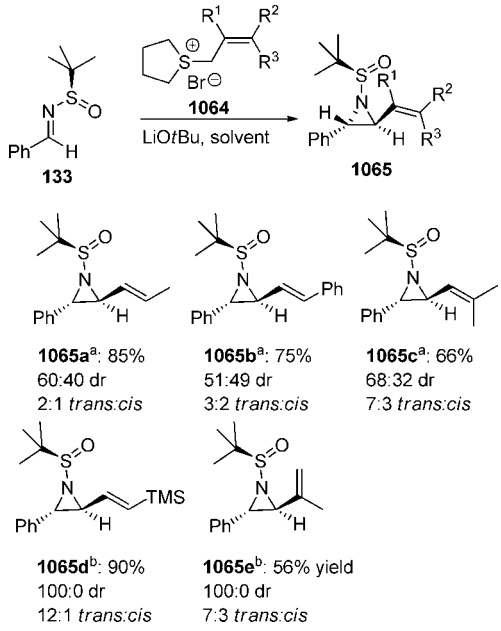
entry	R	product	**1061**/**1062**	yield (%)	**1061** dr
1	Ph	**1061a**	71:29	68	95:5
2	4-MeO-Ph	**1061b**	82:18	76	96:4
3	4-NO_2-Ph	**1061c**	59:41	74	92:8
4	2-naphthyl	**1061d**	80:20	64	>97:3
5	2-pyridyl	**1061e**	88:12	54	94:6
6	2-furyl	**1061f**	67:33	55	>97:3
7	cinnamyl	**1061g**	83:17	82	>97:3
8	Et	**1061h**	80:20	44	95:5
9	pentyl	**1061i**	82:18	67	>97:3
10	*i*Bu	**1061j**	83:17	62	>97:3
11	cyclopropyl	**1061k**	72:28	61	93:7
12	cyclohexyl	**1061l**	83:17	78	>97:3

Scheme 263. Synthesis of Vinyl Aziridines from *N-tert*-Butanesulfinyl Ketimines



[a] The diastereomeric ratios provided are for the *trans* aziridine product.

Scheme 264. Synthesis of Substituted Vinyl Aziridines

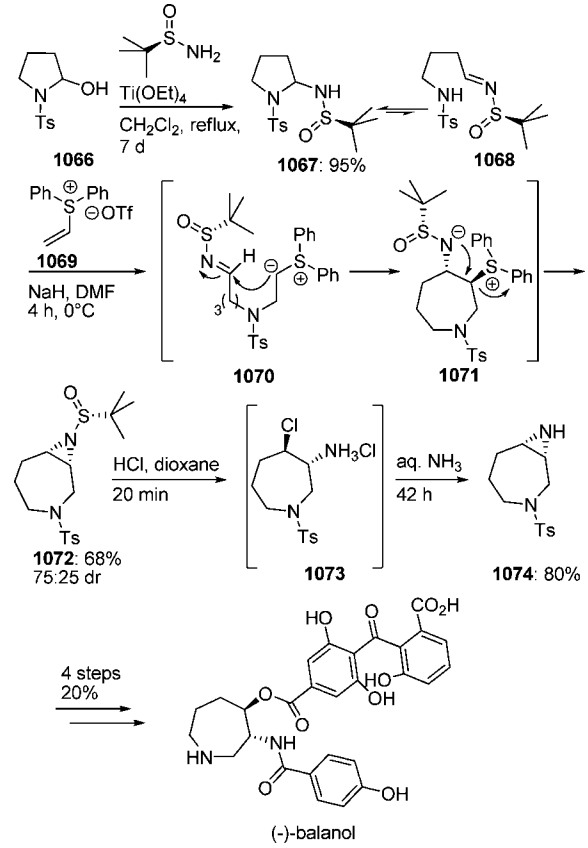


[a] Reaction run in DMSO. [b] Reaction run in THF.

of the vinyl aziridines with the allyl sulfur ylide as compared to the dimethylsulfonium methylide protocol (see Scheme 260 and related text) resulted in a broader substrate scope with respect to the ketimine, and improved yields, particularly for enolizable ketimines.

Stockman and co-workers have also demonstrated that vinyl aziridines derived from *N-tert*-butanesulfinyl aldimines can be obtained using substituted allyl sulfonium salts (Scheme 264).[348] As previously observed, solvent had a dramatic impact on the outcome of the reaction. While THF consistently provided better stereoselectivities, DMSO resulted in significantly higher yields and shorter reaction times for substituted ylides. Indeed, only trace amounts of products **1065a**−**c** were observed in THF after several hours for the

Scheme 265. Formal Synthesis of (−)-Balanol

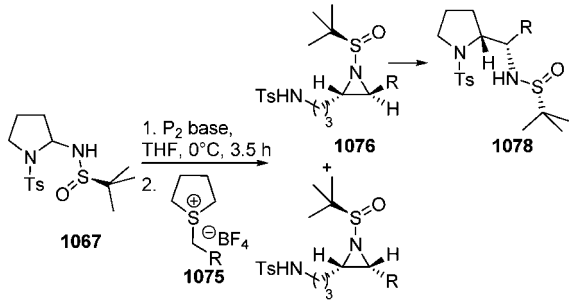


reaction between *N-tert*-butanesulfinyl benzaldimine **133** and several substituted sulfonium salts **1064**. For the electronically activated ylide that provided **1065d**, THF could be used as the solvent; however, prolonged reaction times were required. When the very sterically encumbered ylide was utilized leading to **1065e**, both THF and DMSO gave 100:0 dr for the *trans* isomer, but the *trans* selectivity was diminished in DMSO. In general, the addition of sulfur allyl ylides to *N-tert*-butanesulfinyl benzaldimine proceeded in good yields with highly variable stereoselectivities (51:49 to 100:0 dr and 2:1 to 12:1 *trans*:*cis*).

Aggarwal and co-workers utilized an *N-tert*-butanesulfinyl aziridine fused heterocycle in their elegant formal synthesis of (−)-balanol, a protein kinase C inhibitor.[349] Aminal **1067** was synthesized from hemiaminal **1066** and (*R*)-*N-tert*-butanesulfinamide and then was treated with the diphenyl vinyl sulfonium salt under basic conditions (Scheme 265). Deprotonation of the tosyl amide in the ring-opened **1068** followed by conjugate addition to **1069** produced the carbanion **1070**, which then added to the *N-tert*-butanesulfinyl imine to generate the desired nitrogen-containing seven-membered ring. Displacement of diphenyl sulfide by the newly formed sulfinamide anion then yielded the desired hexahydroazepine **1072**, which was obtained in 68% yield as a 75:25 mixture of diastereomers that could be separated by column chromatography. A crystal structure of the minor diastereomer established the absolute configuration of **1072**. Treatment with HCl in dioxane afforded ring-opened product **1073**, which upon workup with aqueous ammonia generated the known chiral aziridine **1074** to complete the formal synthesis of (−)-balanol in the shortest route (nine steps) to this target.

Later, Aggarawal and Kokotos demonstrated that *N-tert*-butanesulfinyl aminal **1067** could also react with other

Table 29. Synthesis of Aminoalkyl Substituted Aziridines



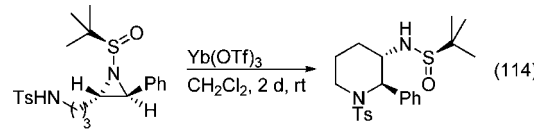
entry	R	sulfonium salt	aziridine yield (%)[a]	*trans*:*cis*[b]	dr **1076**	yield of **1078** (%)
1	Ph	**1075a**	77	13:1	70:30	
2[c]	Ph	**1075a**		12:1		46
3	4-MeO-Ph	**1075b**	43	4.5:1	65:35	
4	4-Cl-Ph	**1075c**	66	11.5:1	85:15	
5	CH=CH$_2$	**1075d**	73	1.3:1	>95:5	
6	C(O)NHPh	**1075e**	63[d]	1.1:1	>95:5	29
7[e]	C(O)NHPh	**1075e**	45	1.1:1		47

[a] Combined yield of **1076** + **1077**. [b] Ratio of (**1076** + **1078**):**1077**. [c] Product **1078** was isolated as a single diastereomer after heating at reflux for 15 h. Piperidine **1079** was also isolated in 12% yield. [d] Aziridines **1076** and **1077** isolated as a 1:4 *trans*:*cis* mixture. [e] Reaction time was increased to 48 h.

stabilized sulfur ylides to produce amine-substituted aziridines **1076** and **1077** (Table 29).[350] An initial screen of conditions revealed that the P$_2$-phosphazene base, *N*,*N*,*N*′,*N*′-tetraethyl-*N*′-[tris(dimethylamino)phosphoranylidene]phosphoric triamide ethylamine, was critical for obtaining the desired aziridines in high yields. Addition of the phenyl stabilized sulfonium salt **1075a** to aminal **1067** at 0 °C for 3.5 h provided a 13:1 mixture of the *trans*-aziridine **1076** to the *cis*-aziridine **1077** (entry 1). The diastereoselectivity for each aziridine with respect to the *N*-*tert*-butanesulfinyl group (70:30 for **1076a** and >95:5 for **1077a**) is consistent with nucleophilic addition to the more sterically accessible face of the sulfinyl imine via an open transition state. Modification of the reaction conditions (reflux, 48 h) resulted in complete conversion of the intermediate *trans*-aziridine **1076** to pyrrolidine **1078** in 46% isolated yield (entry 2).

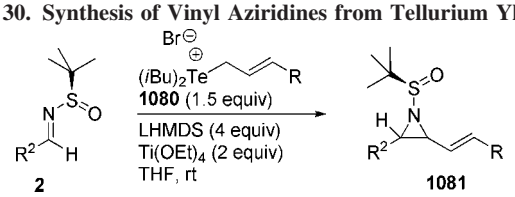
Addition of other aryl sulfonium salts **1075b** and **c** to **1067** proceeded in a *trans*-selective manner, providing mixtures of **1076** and **1077** with moderate to high dr with respect to the *N*-*tert*-butanesulfinyl substituent (entries 3 and 4). In contrast, additions of allyl and amide stabilized sulfonium salts were less *trans*-selective, but the chiral sulfinyl group imparted very high diastereocontrol (entries 5−7). While the low *trans*:*cis* ratio from the allyl stabilized ylide **1075d** is potentially due to the substituent's small size, making the transition states for production of each aziridine comparable, the authors hypothesize that betaine formation could be reversible for the amide stabilized ylide **1075e**. Under the standard reaction conditions, addition of amide stabilized ylide **1075e** generated a mixture of aziridine products and pyrrolidine **1078** (entry 6), while increasing the reaction time promoted complete conversion of *trans*-aziridine **1076e** to pyrrolidine **1078e** (entry 7; the *cis*-aziridine **1077** does not undergo further reaction).

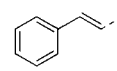
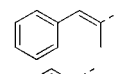
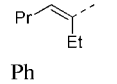
While heat and extended reaction times promoted the conversion of *trans*-aziridine **1076a** to pyrrolidine **1078a**, the authors demonstrated that **1076a** could instead be converted to piperidine product **1079** in high yield in the presence of the Lewis acid Yb(OTf)$_3$ (eq 114). Efficient sulfinyl cleavage from both aziridine **1076a** and piperidine **1079** using HCl in EtOH also was demonstrated (81−88% yield).



In 2005, Tang and co-workers published an isolated example of a reaction between a telluronium ylide and a racemic *N*-*tert*-butanesulfinyl α,β-unsaturated imine to exclusively form the aziridine.[351] This method was further explored in the synthesis of chiral vinyl aziridines from enantiomerically pure *tert*-butanesulfinyl imines.[352] Interestingly, the use of allyl telluronium ylides **1080** as opposed to the allyl sulfur ylide resulted in a reversal in selectivity, generating the 2-substituted vinyl aziridines **1081** with very high selectivity for the *cis*-isomer. After screening several reaction parameters, Tang, Deng, and co-workers determined that deprotonation of the telluronium salt was best achieved with LHMDS. Addition of the Lewis acid Ti(OEt)$_4$ also influenced the reaction, providing higher yields and better *trans*:*cis* selectivity. The reaction between TMS substituted ylide **1080** and *N*-*tert*-butanesulfinyl aldimines **2** was quite general with respect to the aldimine substituent (entries 1−11, Table 30). The scope of the reaction with respect to the telluronium ylide was also explored, and both the simple allylic and the cinnamyl telleronium ylides gave the aziridine products in high yields and with high diastereoselectivities

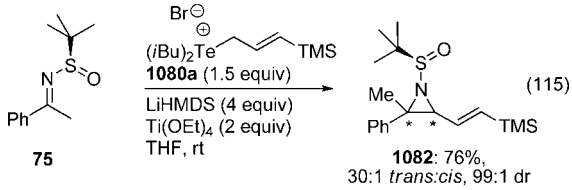
Table 30. Synthesis of Vinyl Aziridines from Tellurium Ylides



entry	R^2	R	product	yield (%)	*cis*: *trans*	*cis* dr
1	Ph	TMS	**1081a**	98	20:1	>99:1
2	4-Me-Ph	TMS	**1081b**	98	20:1	99:1
3	4-Cl-Ph	TMS	**1081c**	96	20:1	>99:1
4	4-CF$_3$-Ph	TMS	**1081d**	98	20:1	>99:1
5	1-naphthyl	TMS	**1081e**	98	22:1	>99:1
6	2-furyl	TMS	**1081f**	93	19:1	97:3
7[a]	Cy	TMS	**1081g**	83	9:1	>99:1
8[a]	*t*Bu	TMS	**1081h**	53	>30:1	>99:1
9		TMS	**1081i**	88	10:1	94:6
10		TMS	**1081j**	98	25:1	94:6
11		TMS	**1081k**	91	12:1	93:7
12	Ph	H	**1081l**	91	14:1	98:2
13	Ph	Ph	**1081m**	89	>30:1	>99:1

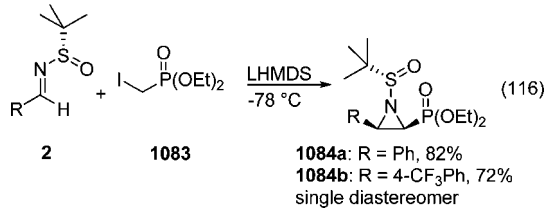
[a] No Ti(OEt)$_4$ was added, and the BPh$_4$ counterion for the tellurium salt was used.

(entries 12 and 13). An example of addition to ketimine **75** was also described, further demonstrating the versatility of this reaction (eq 115).



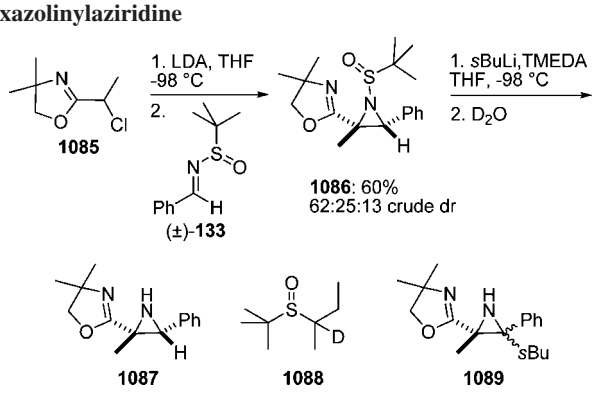
17.2. Aza-Darzens Reaction

Davis and co-workers briefly explored the use of *N-tert*-butanesulfinyl aldimines as substrates in a one-pot aza-Darzens reaction to form *N-tert*-butanesulfinyl aziridine 2-phosphonates (**1084a** and **b**, eq 116). While the focus of this study was the addition of the anion of iodomethylphosphonate **1083** to *N-p*-toluenesulfinyl aldimines, the influence of the sulfinyl group was investigated by examining the reaction between **1083** and *N-tert*-butanesulfinyl aldimines **2** (eq 116).[353] Two aryl *N-tert*-butanesulfinyl imines **2** were examined, and the reaction proceeded in the presence of LHMDS to directly produce aziridines **1084a** and **b** in 72−82% yield as single diastereomers. Although the *tert*-butanesulfinyl group provided higher diastereoselectivity than the *p*-toluenesulfinyl group, all attempts to cleave the *tert*-butanesulfinyl group using either acid or MeMgBr without aziridine ring-opening were unsuccessful. In contrast, the *p*-toluenesulfinyl group could be removed from the aziridine phosphonates in good yields in the presence of MeMgBr at low temperature.



Florio and co-workers reported a synthesis of *N-tert*-butanesulfinyl oxazolinylaziridine **1086** via an aza-Darzens reaction between imine (±)-**133** and lithiated 2-(1-chloroethyl)oxazoline **1085** (Scheme 266).[354] The aziridine was obtained as a 62:25:13 mixture of diastereomers, and the major diastereomer (±)-(*R**,*R**)-**1086** was isolated in 60% yield after recrystallization. Attempts to deprotonate (±)-(*R**,*R**)-**1086** with *s*BuLi/TMEDA at low temperature (−98 °C) and trap the resulting carbanion with deuterium resulted

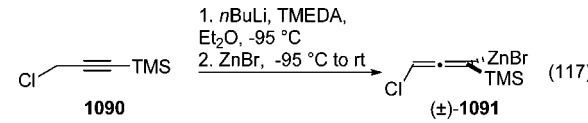
Scheme 266. Synthesis of *N-tert*-Butanesulfinyl Oxazolinylaziridine



in a mixture of **1087**, **1088**, and **1089**, as detected by ^{1}H NMR and GC-MS analysis. The authors noted that compound **1087** was the major product but that it could not be separated from **1088** and **1089**.

17.3. Addition of Allenylzinc Reagents to *N-tert*-Butanesulfinyl Imines

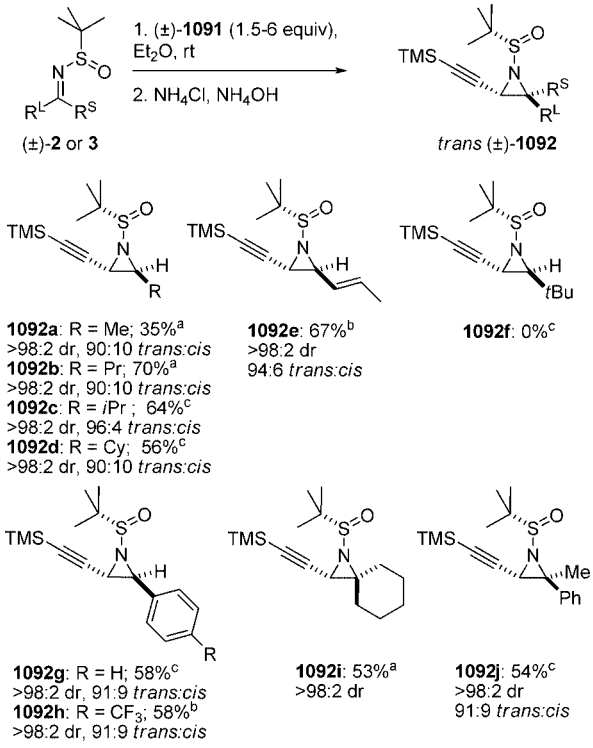
The addition of allenes to *N-tert*-butanesulfinyl imines was first explored by Ferreira and Chemla in the context of developing a stereoselective synthesis of alkynylaziridines.[355] Previous studies had demonstrated that the condensation of allenylzinc (±)-**1091**, generated *in situ* from 3-chloro-1-trimethylsilylpropyne **1090** (eq 117), with *N*-trimethylsilyl or *N*-benzyl imines provided *trans-N*-H and *N*-benzyl ethynylaziridines.[356] This methodology was then applied to the addition of (±)-**1091** to racemic *N-tert*-butanesulfinyl aldimines **2** or ketimines **3** (Scheme 267). A brief optimization of the reaction conditions revealed that the highest conversions were achieved in Et_2O at ambient temperature. Additionally, the amount of (±)-**1091** (1.5−6.0 equiv) required for reaction completion was dependent on the reactivity of the starting *N-tert*-butanesulfinyl imines. When the highly hindered aldimine **2** (R = *t*Bu) was employed, none of the desired aziridine **1092f** was observed, and only starting imine was recovered even with excess (±)-**1091**. The authors propose that, as the reactivity of the *N-tert*-butanesulfinyl imine **2** is attenuated, the decomposition of (±)-**1091** becomes an increasingly competitive side reaction. Ketimines **3** could also be employed, providing **1092i** and **1092j** in 53−54% yield. All alkynyl aziridines were formed with very high *trans*:*cis* ratios. The imine facial selectivity was also very high, and only one major *trans*-isomer was detected by ^{1}H NMR for aziridines **1092a**−**e** and **g**−**j** (>98:2 dr). The relative stereochemistry (S_S*,2*S**,3*S**) was determined by X-ray structural analysis of **1092g**.



This methodology was extended to the reaction between (±)-**1091** and enantiomerically pure *N-tert*-butanesulfinyl imines (Scheme 268).[357] However, because the equilibration of (±)-**1091** was slow relative to the reaction time scale, to achieve the same levels of stereoselectivity (≥90:10 *trans*/*cis*) observed with racemic *N-tert*-butanesulfinyl imines, a larger excess of (±)-**1091** was required to enable efficient kinetic resolution of this substrate. A series of alkyl, alkenyl, and aryl aldimines **2** were evaluated, and *trans*-aziridines **1093a**−**e** were isolated in 50−69% yields and with ≥89:11 *trans*:*cis* ratios and >98:2 diastereomeric ratios. Two ketimines **3** were also studied, and the corresponding products **1093f** and **g** were also obtained in good yields and with high diastereoselectivities. In the case of **1093f**, a predilection for the *trans*-isomer was observed. The sulfinyl group was removed from select substrates using HCl/MeOH (see section 19.1.3).

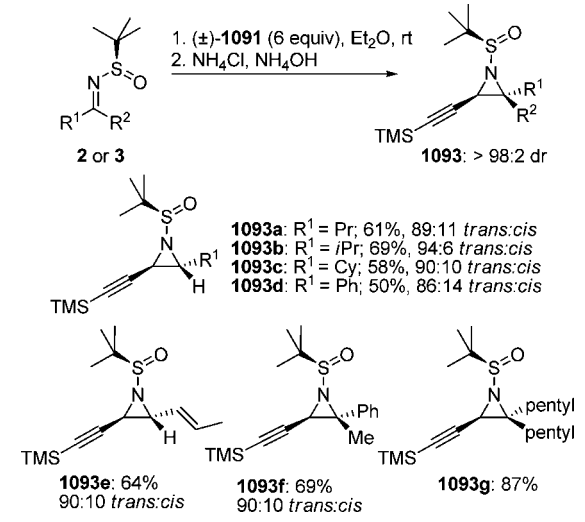
Both the high *trans*-selectivity and the facial stereodifferentiation can be explained by kinetic resolution of allenylzinc (±)-**1091** (Figure 14), where the major *trans* isomer **1093** is the result of the reaction between the matched pair (S_a)-**1091** and (R_S)-**2** or **3** via the cyclic chelate model **1094**. The authors postulate that the two enantiomers of the

Scheme 267. Reaction of (±)-1091 with Racemic *N-tert*-Butanesulfinyl Imines 2 or 3



[a] 1.5 equiv of (±)-**1091** was used. [b] 3.0 equiv of (±)-**1091** was used. [c] 6.0 equiv of (±)-**1091** was used.

Scheme 268. Reaction of (±)-1091 with (R_S)-*N-tert*-Butanesulfinyl Imines



allenylzinc reagent (±)-**1091** could equilibrate under the reaction conditions to provide a dynamic kinetic resolution, but equilibration is not necessary to explain the product stereochemistry given that a 6-fold excess of (±)-**1091** is used. In the proposed transition state, **1094**, the zinc is coordinated both to the nitrogen of the imine and to the oxygen of the sulfinyl group. The mismatched pair (R_a)-**1091** and (R_S)-**2** or **3**, which reacts more slowly than the matched pair, can be rationalized by the open transition state model **1095**, and provides the observed minor diasteromer **1096**.

Ferreira and Chemla also explored modification of the reaction conditions to favor the formation of the *cis*-isomers of the *N-tert*-butanesulfinyl alkynylaziridines (Scheme 269).[358] Lewis acids were first screened to determine their

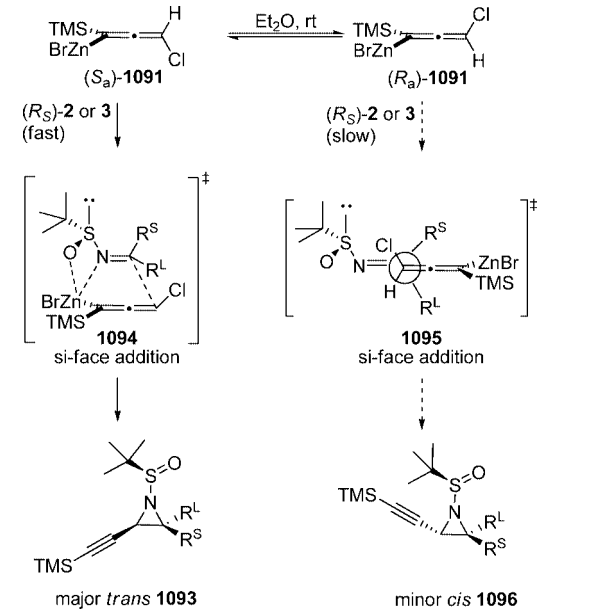
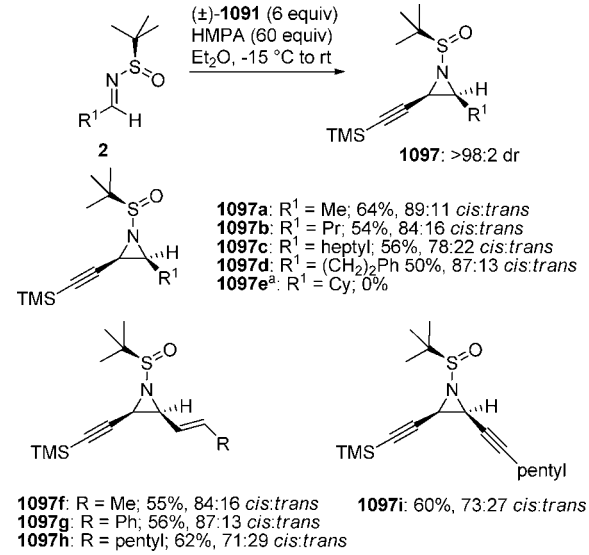


Figure 14. Proposed transition states for the addition of (±)-**1091** to *N-tert*-butanesulfinyl imines.

Scheme 269. Synthesis of *cis*-Alkynyl Aziridines 1097 in the Presence of HMPA



[a] Eight equivalents of HMPA were utilized.

effect on the stereochemical outcome of the reaction. However, the precoordination of *N-tert*-butanesulfinyl imines with several Lewis acids afforded the *trans*-aziridines **1093** as the major products. Conversely, when 8 equiv of hexamethylphosphoric triamide (HMPA) was used as a cosolvent in the addition of (±)-**1091** to *N-tert*-butanesulfinyl imines **2**, the *cis*-isomer **1097** was generated as the major product. The stereoselectivity in favor of the *cis*-isomer was further improved by increasing the amount of HMPA to 60 equiv (10 equiv with respect to allenylzinc (±)-**1091**). Aziridines were synthesized from a number of primary alkyl, alkenyl, and alkynyl imine precursors to give **1097a**−**d** and **f**−**i** with *cis*/*trans* ratios ranging from 71:29 to 89:11. The major *cis*-isomer was formed as a single diastereomer, within the limits of detection by ^{1}H NMR analysis of the crude reaction mixtures. All products were obtained in moderate yields (50−64%) as single isomers after purification. However, no

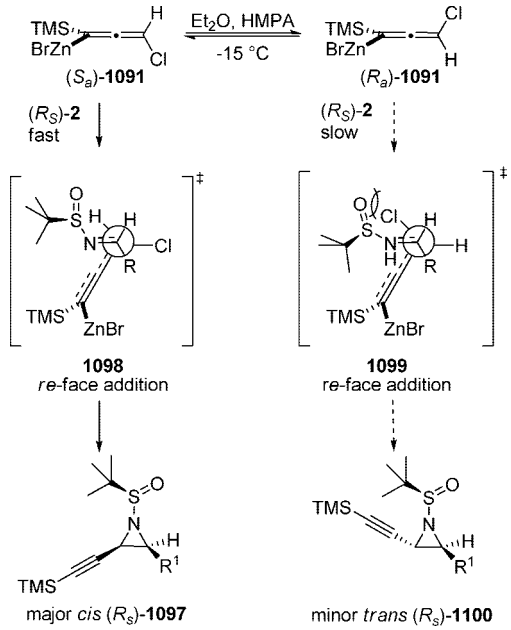


Figure 15. Proposed transition states for the addition of (±)-**1091** to *N*-*tert*-butanesulfinyl imine **2** in the presence of HMPA.

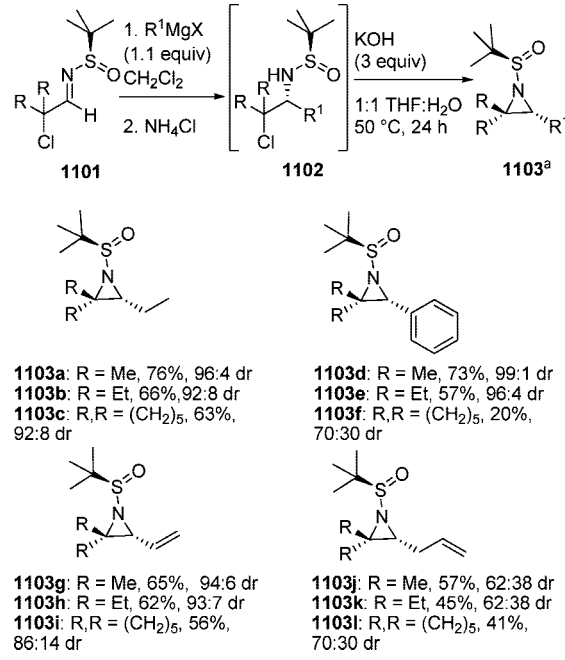
reaction was observed when an α-branched imine was utilized (**1097e**).

The absolute configuration of the *cis*-aziridine **1097g** was determined to be (R_S,2*R*,3*S*) by X-ray structural analysis. This corresponds to addition of (±)-**1091** to the *Re*-face of *N*-*tert*-butanesulfinyl imine **2**, which is opposite to that observed for the minor *cis* isomer **1096** (Figure 14) when the reaction was conducted without HMPA.[357] The observed stereochemistry for the *cis*-aziridines **1097** was rationalized by the suprafacial synclinal model **1098** (Figure 15). As each enantiomer of **1091** gives a single *cis* or *trans* product (**1097** and **1100**, respectively), the analogous suprafacial synclinal transition state **1099** was evoked to rationalize the formation of the minor *trans*-isomer. Transition state **1098** corresponds to the matched pair (S_a)-**1091** and (R_S)-**2**, where the steric interactions between the chlorine atom on the allenylzinc and the *tert*-butanesulfinyl group are minimized. Ferreira and co-workers also converted both *trans*- and *cis*-*N*-*tert*-butanesulfinyl aziridines **1093** and **1097** to enantiomerically pure acetylenic 1,2-amino alcohols (see section 11.3).[289]

17.4. Addition/Cyclization with α-Chloro *N*-*tert*-Butanesulfinyl Imines

The addition of a Grignard reagent to an *N*-*tert*-butanesulfinyl α-chloro aldimine followed by cyclization to form the resulting chiral aziridine was first disclosed by de Kimpe and co-workers (Scheme 270).[67] A screen of several reaction parameters revealed that the best results were obtained by adding 1.1 equiv of Grignard reagent in CH_2Cl_2 at −78 °C (−97 °C for PhMgCl addition). For reactions of imine **1101** (R = Me), the intermediate *N*-sulfinyl β-chloro amine product **1102** could be obtained by quenching the reaction at −78 °C with NH_4Cl. Phenyl, ethyl, and vinyl additions were more stereoselective (94:6 to 99:1 dr) than allyl addition (62:38 dr). Cyclization could be effected either by warming the reaction mixtures to room temperature without quenching ($R^1 \neq$ Ph) or by heating the *N*-sulfinyl β-chloro amine **1102** with aqueous KOH in THF to form the aziridines **1103**. Each of the aziridines was isolated in reasonable yields (57−76%) after chromatographic separation of the diastereomers.

Scheme 270. Synthesis of Chiral Aziridines from *N*-Sulfinyl α-Chloro Aldimines



[a] Crude dr and isolated yield of major diastereomer.

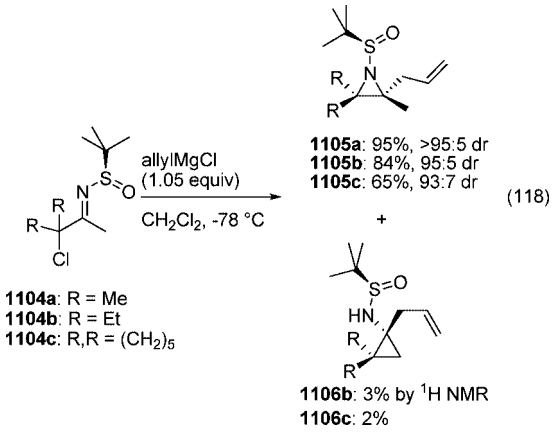
Consistent with previous results on α-unfunctionalized imines (section 4.1.1),[92] the use of *i*PrMgCl as a nucleophile resulted in reduction rather than addition in high yield (95%).

For Grignard additions to the more sterically hindered imines **1101** (R = Et or -$(CH_2)_5$-), mixtures of *N*-*tert*-butanesulfinyl β-chloro amines **1102** and aziridines **1103** were obtained after performing the reaction and quenching at −48 °C (Scheme 270). Again, addition of allylMgCl proceeded with lower stereoselectivity than addition of ethyl, vinyl, or phenyl reagents. Treatment of the reaction mixture with the optimized cyclization conditions (heating with aqueous KOH in THF) followed by chromatographic separation of the aziridine diastereomers allowed isolation of diastereomerically pure **1103** in 20−66% yield.

The absolute stereochemistry of aziridine product **1103d** determined by X-ray structural analysis, and the stereochemical outcome was rationalized by the α-coordinating ability of the chlorine atom, in a transition state analogous to the one proposed for additions to α-alkoxy imines (see Figure 13, section 11.1).

De Kimpe and co-workers also reported the synthesis of *N*-*tert*-butanesulfinyl aziridines via the addition of allyl Grignard reagent to α-chloro *N*-*tert*-butanesulfinyl ketimines **1104a**−**c** (eq 118).[68] The aziridine products **1105a**−**c** were obtained in good yields (65−95%) and with high diastereoselectivities (93:7 to >95:5). In addition to the aziridine products, minor amounts of *N*-*tert*-butanesulfinyl cyclopropyl amines **1106b**−**c** were either isolated or observed by ^{1}H NMR (see section 5.1 for the optimized synthesis of cyclopropyl amines). While the absolute configurations of **1105a**−**c** were not rigorously determined, they were assigned by analogy to the related reaction with α-chloro *N*-*tert*-butanesulfinyl aldimines (*vide supra*).

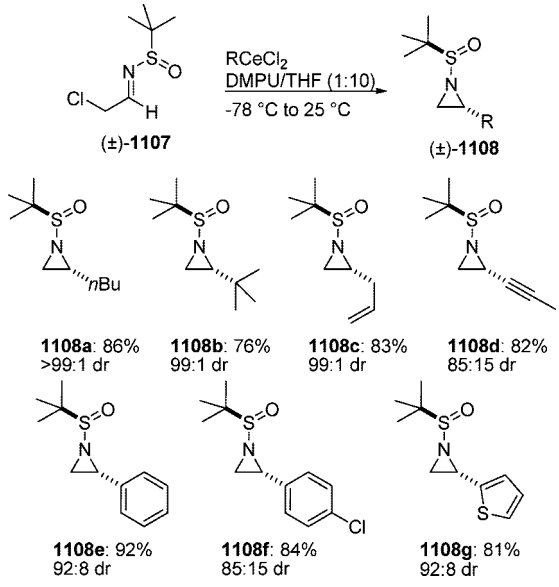
The synthesis of terminal *N*-*tert*-butanesulfinyl aziridines has also been achieved via addition of an organocerium reagent to α-chloro aldimine **1107** (Scheme 271).[359] After observing no diastereoselectivity in the addition of BuMgCl



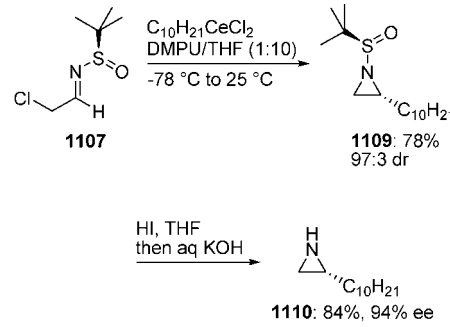
to *N*-sulfinyl α-chloro imine **1107**, Hodgson and co-workers examined organocerium reagents as coupling partners. Although the addition of an organocerium reagent to an unfunctionalized *N-tert*-butanesulfinyl imine has been reported to give lower diastereoselectivities than the corresponding Grignard addition,[92] the use of an organocerium reagent in THF for the addition to imine **1107** dramatically improved the diastereomeric ratio, which was further optimized by addition of DMPU to the reaction mixture. The addition of nBuCeCl$_2$ to racemic imine **1107** followed by cyclization proceeded in 86% yield and with >99:1 dr (**1108a**). Branched and allyl cerium reagents also gave very high levels of diastereoselectivity (**1108b**−**c**), but the reaction was less diastereoselective when aryl, heteroaryl, and alkynyl reagents were utilized (**1108d**−**g**). Hodgson and co-workers also applied their method to the addition of $C_{10}H_{21}CeCl_2$ to enantiomerically pure imine **1107** to provide aziridine **1109** with high diastereoselectivity (Scheme 272). The sulfinyl group could then be removed in high yields without racemization by treating with aqueous HI in THF, followed by neutralization with KOH. Alternatively, oxidation to the *N-tert*-butanesulfonyl (Bus) aziridine was also demonstrated.

Yuan and co-workers explored the reaction between dimethylphosphite and chloro-substituted aldimines and ketimines **556** with varying tether lengths, including α-chloro imines. Depending on the base and substitution patterns,

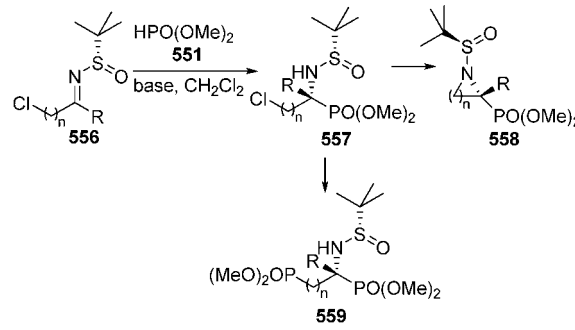
Scheme 271. Aziridines from Diastereoselective Organocerium Additions to α-Chloro Imine 1107



Scheme 272. Organocerium Addition to Enantiomerically Pure Imine Followed by Sulfinyl Deprotection



Scheme 273. Reaction of Dimethylphosphite with Chloro-Substituted Imines



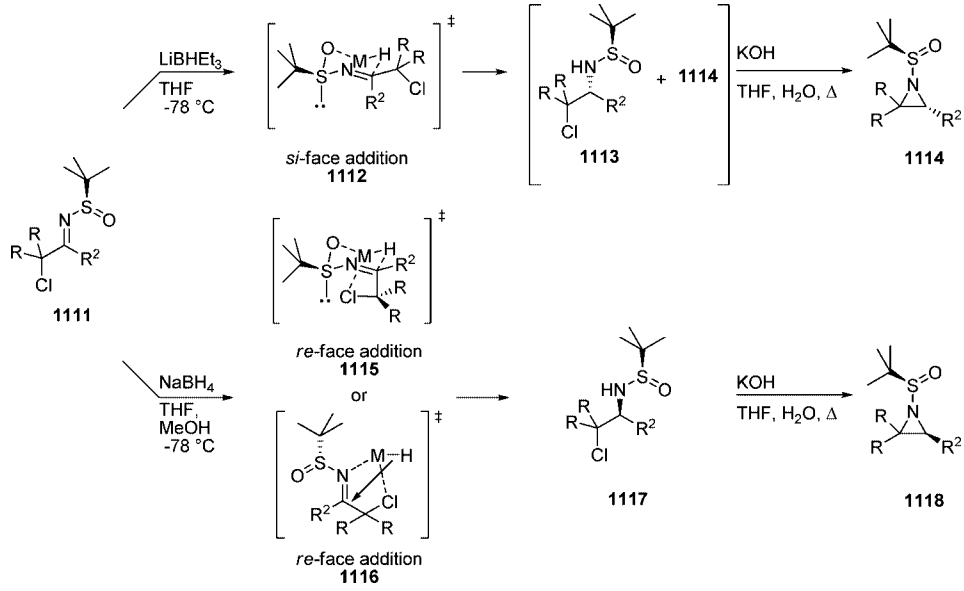
different products were obtained (Scheme 273; for details, see section 9.3)[220]

17.5. Reduction/Cyclization with α-Chloro *N-tert*-Butanesulfinyl Imines

The hydride reduction of *N-tert*-butanesulfinyl α-chloro aldimines and ketimines and subsequent cyclization to *N-tert*-butanesulfinyl aziridines under basic conditions was described by De Kimpe and co-workers (Table 31).[360,361] When $NaBH_4$ was employed for the reduction of aldimines **1111a** and **1111b**, β-chloro *N-tert*-butanesulfinyl amines **1117** were generated in excellent yields (>95%), and subsequent cyclization to the aziridines **1118** proceeded smoothly. In contrast, for these substrates, the use of $LiBHEt_3$ yielded a complex mixture of **1113**, aziridine **1114**, and other reaction byproducts (entries 1−2). For the reduction of ketimines, $NaBH_4$ provided the β-chloro amine **1117** with excellent diastereoselectivity, while $LiBHEt_3$ gave a mixture of the opposite diastereomer **1113** and aziridine **1114** with moderate diastereoselectivity. Aziridines **1114** or **1118** were isolated in good yields after treatment with KOH in THF/H_2O at reflux followed by recrystallization. The stereochemistry of the aziridine product **1114e** was confirmed by chemical correlation.

The authors noted that the $NaBH_4$ reductions proceeded with opposite selectivity from the previously described reductions of unfunctionalized *N-tert*-butanesulfinyl ketimines (see Figure 4, section 4.2.1). To explain this reversal, they proposed transition states **1115** or **1116**, which invoke coordination of the chlorine atom to the borohydride reagent. With the more reactive reagent $LiBHEt_3$, the authors hypothesize that the reduction occurs more rapidly than the *E*/*Z* isomerization required for transition state **1116**, and the chelated transition state **1112** is proposed.

Table 31. Reduction of *N-tert*-Butanesulfinyl α-Chloro Imines by $NaBH_4$ or $LiBHEt_3$



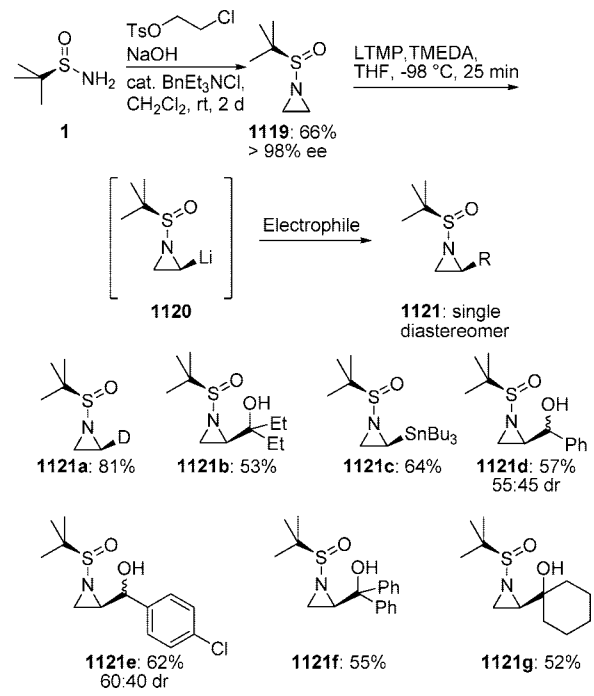
				$LiBHEt_3$		$NaBH_4$		
entry	imine	R	R^2	dr	yield of **1114** (%)	dr	yield of **1117** (%)	yield of **1118** (%)
1	**1111a**	Me	H				99	95
2	**1111b**	Et	H				97	95
3	**1111c**	Me	Me	78:22	61	98:2	98	88
4	**1111d**	Et	Me	80:20	57	99:1	92	92
5	**1111e**	H	Ph	87:13	62	>98:2	95	90
6	**1111f**	H	4-Cl-Ph	89:11	66	>98:2	94	89
7	**1111g**	H	4-Br-Ph	92:8	71	>98:2	98	91
8	**1111h**	H	4-F-Ph	98:2[a]	79	>98:2		86
9	**1111i**	H	4-Me-Ph	>99:1[a]	80	>97:3		76

[a] Diastereomeric ratio after recrystallization of **1114**.

17.6. Stereoselective Functionalization of *N-tert*-Butanesulfinyl Aziridine Anions

Recently, Hodgson and co-workers have developed a very efficient method for the synthesis of terminal aziridines by the α-deprotonation of *N-tert*-butanesulfinyl aziridine followed by subsequent trapping with an electrophile (Scheme 274).[291] The requisite *N-tert*-butanesulfinyl aziridine **1119** was synthesized in enantiomerically pure form in one step from (*R*)-*tert*-butanesulfinamide, 2-chloroethyl-*p*-toluenesulfonate, sodium hydroxide, and a catalytic amount of benzyltriethylammonium chloride. Treatment of **1119** with lithium 2,2,6,6-tetramethylpiperdine (LTMP) and *N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA) provided **1120**, which was subsequently trapped with a variety of electrophiles to provide the functionalized terminal aziridines **1121a**−**g** as single observable diastereomers in good yields. Indeed, addition of **1120** to the symmetrical ketone pentan-3-one gave **1121b** with greater than 99:1 diastereomeric ratio. While addition of **1120** to prochiral aldehdyes resulted in low asymmetric induction at the carbinol carbon (**1121d** and **e**), Swern oxidation of **1121d** to the ketone gave the diastereomerically pure sulfinyl aziridine. For all other substrates, **1121a**, **c**, **f**, and **g**, no minor diastereomer was detected by ^1H or ^{13}C NMR analysis of the crude material. The absolute configuration of **1121b** was confirmed by X-ray structural analysis. The diastereoselectivity of the reaction was rationalized by coordination of LTMP to the sulfinyl oxygen of the *N-tert*-butanesulfinyl aziridine and subsequent deprotonation of the proximal *pro-R* hydrogen of the aziridine ring (Figure 16). Addition of lithiated aziridine **1120** to the electrophile occurs with retention of configuration. Regioselective aziridine ring-opening with 2-thionaphthalene or phenyl magnesium bromide was also demonstrated, providing secondary *N-tert*-butanesulfinyl amines in good

Scheme 274. Electrophilic Trapping of *N-tert*-Butanesulfinyl Aziridines



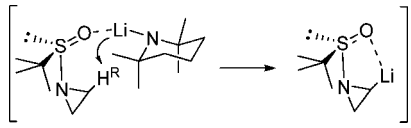
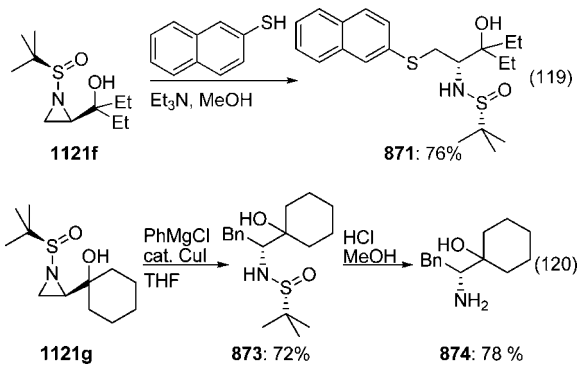


Figure 16. Proposed transition state.

yields (eqs 119 and 120). Cleavage of the sulfinyl group from the ring-opened product **874** was also demonstrated.

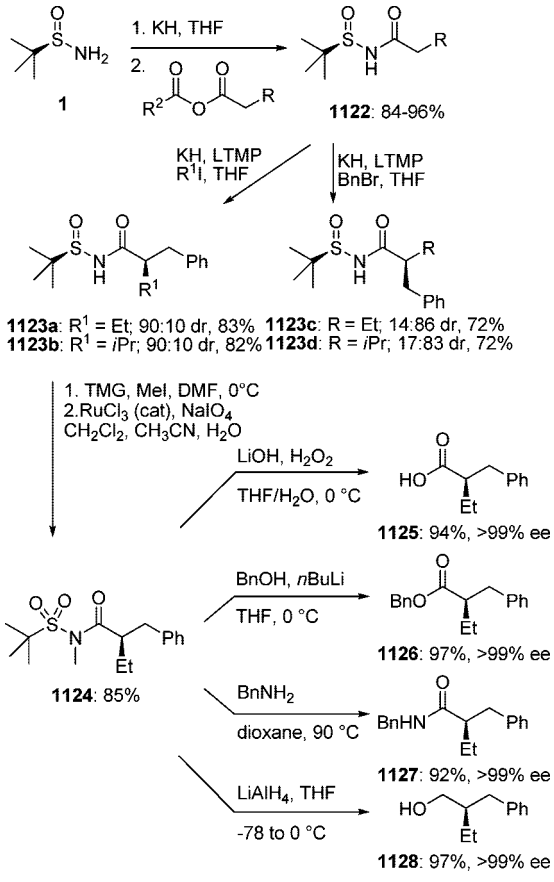


18. Miscellaneous Transformations

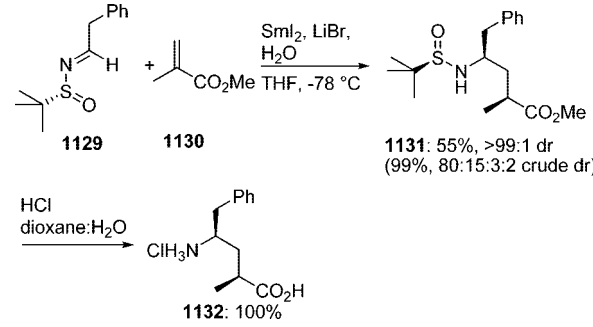
18.1. Diastereoselective Enolate Alkylations

Ellman and co-workers reported the use of *N*-acyl *tert*-butanesulfinamides **1122** as substrates for enolate alkylation (Scheme 275).[362] The substrates were prepared by treating *tert*-butanesulfinamide **1** with KH, followed by reaction with an anhydride. Under the optimum conditions, the resulting *N*-acyl sulfinamides were then treated with KH to deprotonate

Scheme 275. Diastereoselective Enolate Alkylation and Product Elaboration



Scheme 276. Reductive Coupling of *N-tert*-Butanesulfinyl Imine 1129 and Methyl Methacrylate



the acidic N−H and then the sterically hindered base, lithium 2,2,6,6-tetramethylpiperidide (LTMP) to generate the enolate. Addition of an alkylating agent (an alkyl iodide or benzyl bromide) then afforded products **1123a−d** with moderate to high diastereoselectivity. Chromatographic isolation of the major diastereomer provided 72−83% yield of each desired product in diastereomerically pure form. Activation of the sulfinamide moiety of **1123a** for nucleophilic displacement was achieved by *N*-methylation with tetramethylguanidine (TMG) and methyl iodide followed by catalytic oxidation to the corresponding *tert*-butanesulfonamide **1124**. Cleavage with several different nucleophiles was demonstrated, providing a variety of enantiomerically pure derivatives **1125−1128** in high yields and without any racemization.

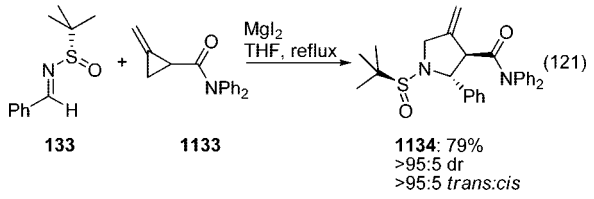
18.2. Reductive Coupling with a Vinylogous Ester

Ellman and co-workers employed a SmI_2 mediated reductive coupling between imine **1129** and methyl methacrylate (**1130**) as an isolated example of an asymmetric coupling between an *N-tert*-butanesulfinyl imine and an α,β-unsaturated ester (Scheme 276).[312] Optimization of the solvent and additives revealed that LiBr and H_2O were essential for achieving a high yield. Employing these conditions, coupling product **1131** was produced in 99% yield with good selectivity (80:15:3:2). Subsequent purification by column chromatography provided diastereomerically pure **1131** in 55% yield. The relative and absolute stereochemistries of **1131** were established by X-ray structural analysis. Concomitant hydrolysis of the methyl ester and cleavage of the sulfinyl group then provided **1132** in quantitative yield. This fragment was subsequently incorporated into tubulysin D (see section 13.1 for additional *tert*-butanesulfinamide chemistry toward this natural product).

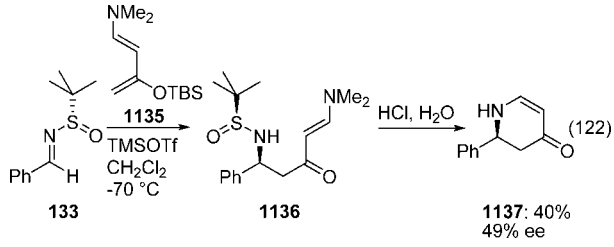
18.3. Cycloaddition Reactions with *N-tert*-Butanesulfinyl Imines

Lautens and Scott explored the synthesis of 2,3-disubstituted pyrrolidines via an iodide-mediated ring expansion from *N-tert*-butanesulfinyl imine **133** and methylenecyclopropyl amide **1133** (eq 121).[363] Under the reaction conditions optimized for the analogous *p*-toluenesulfinyl imine, a good yield and excellent diastereoselectivity of the *trans*-pyrrolidine **1134** was achieved.

Kawecki reported the reaction of aryl *N-tert*-butanesulfinyl aldimine **133** with the highly reactive Rawal's diene **1135** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to provide the open chain product **1136**, which



upon treatment with acid underwent cyclization to form the dihydropyridone **1137** in 40% yield and with 49% ee (eq 122).[364]



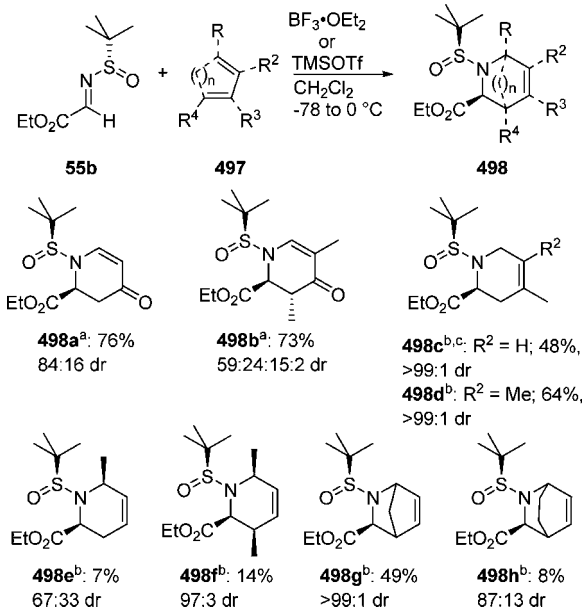
The diastereoselective aza-Diels−Alder with *N-tert*-butanesulfinyl imines was developed by Gautun and co-workers (Scheme 277).[205] To expand the scope of the reaction to include dienes other than Rawal's diene **1135** (*vide supra*), the highly activated *N-tert*-butanesulfinyl imino ester **55b** was employed as the dieneophile. The *p*-toluenesulfinyl chiral directing group was also evaluated, but higher diastereoselectivities were achieved with the *tert*-butanesulfinyl group in all cases. 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 **55b** and a number of dienes was evaluated, providing **498a**−**h** in variable yields (7−76%), with 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 **498c** in moderate yield. The absolute configurations of **498a** and **b** were established by X-ray structural analysis, while the configurations of **498c**, **d**, and **g** were determined by chemical correlation. The (*S*)-configurations of the α-carbon of **498e**, **f**, and **h** were assigned by analogy while ^{1}H NMR analysis was used to determine the relative configuration between the ester and methyl groups.

18.4. Synthesis of Cyclic Sulfinamides

A novel synthesis of cyclic sulfinamides using *N-tert*-butanesulfinyl imino ester **55b**, a Lewis acid, and allyl benzene was reported by Davis and co-workers (Scheme 278).[365] A variety of Lewis acids were screened, with tin tetrachloride providing the best results. Employing the optimized reaction conditions, a mixture of cyclic sulfinamides **1138** and **1139** was produced, which were separated by preparative thin layer chromatography. This transformation was also attempted with the analogous *N-p*-toluenesulfinyl imino ester, but the allyl benzene exclusively attacked the sulfur atom. The relative stereochemistry of **1138** was determined by X-ray structural analysis, and the absolute configuration was established by chemical correlation studies. Although the mechanism for the formation of either product is unclear, the authors propose the concerted elimination of isobutylene to furnish the major isomer **1138**.

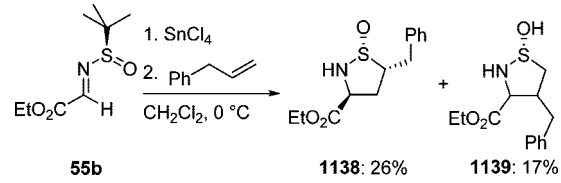
Malacria, Lacote, Fensterbank, and co-workers developed an innovative synthesis of cyclic sulfinamides by treatment

Scheme 277. Aza Diels−Alder Reaction of 55b with Dienes

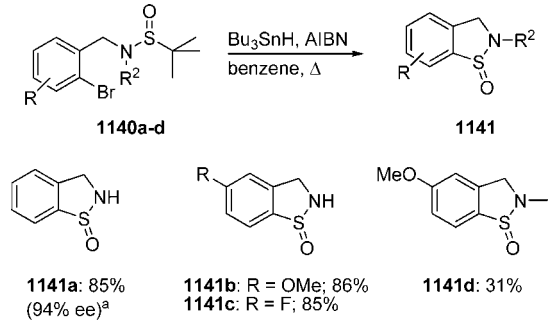


[a] $BF_3 \cdot OEt_2$ was used as the Lewis acid. [b] TMSOTf was used as the Lewis acid. [c] Twenty equivalents of diene was used.

Scheme 278. Synthesis of Cyclic Sulfinamides

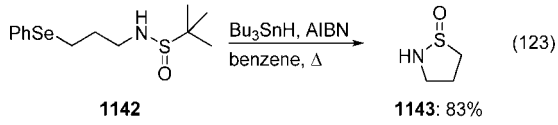


Scheme 279. Synthesis of Cyclic Sulfinamides



[a] Reaction performed using **1140a** with 100% ee.

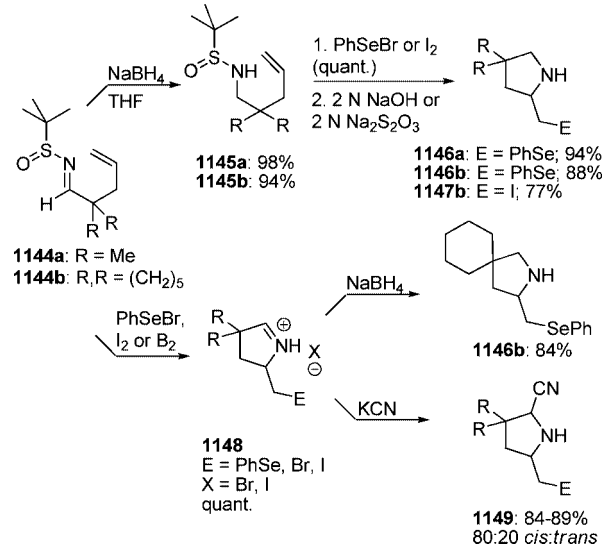
of aryl bromides **1140** with tributyltin hydride (Bu_3SnH) and α,α-azoisobutyronitrile (AIBN) (Scheme 279).[366] Generation of the aryl radical, followed by intramolecular homolytic substitution at sulfur with a *tert*-butyl radical as the leaving group provided **1141a**−**c** in 85−86% yield. When the reaction was carried out starting with enantiomerically pure sulfinamide **1140a**, only a small degradation in ee was observed (100% to 94%). While the absolute stereochemistry of the sulfinamide product **1141a** was not determined, cyclization of the analogous sulfinate ester was found to proceed with inversion of chemistry. Radical cyclization of the *N*-methyl derivative **1140d** provided **1141d** in a lower yield (31%). The method was also applicable to the cyclization of aliphatic sulfinyl amine **1142**, providing cyclic sulfinamide **1143** in 83% yield (eq 123).



18.5. Electrophilic Cyclization

The preparation of cyclic or spirocyclic pyrrolidines via electrophile-induced cyclization of *N-tert*-butanesulfinyl imines or amines was demonstrated by De Kimpe and Dondas (Scheme 280).[367] Reduction of **1144a** and **b** provided *N-tert*-butanesulfinyl amines **1145** in high yields, which upon exposure to PhSeBr or I_2 cyclized to the corresponding pyrrolidinium salts with concomitant sulfinyl deprotection in quantitative yield. Treatment with 2 N aqueous NaOH (E = SePh) or aqueous $Na_2S_2O_3$ (E = I) afforded the cyclic and spirocyclic pyrrolidines **1146** and **1147** in 77−94% yield. Alternatively, cyclization and cleavage of the sulfinyl group was achieved directly from imines **1144a** and **b**, providing the pyrrolidinium salts **1148** in quantitative yields. Reduction of the imminium salts **1148** with $NaBH_4$ or addition of KCN provided pyrrolidines **1146** or **1149** in 84−89% yield. Notably, the cyclization could be rendered asymmetric by preparing enantiomerically pure **1144b** and reacting it with phenylselenyl bromide followed by reduction with $NaBH_4$, providing spiropyrrolidine **1146b**, albeit with a modest 20% ee.

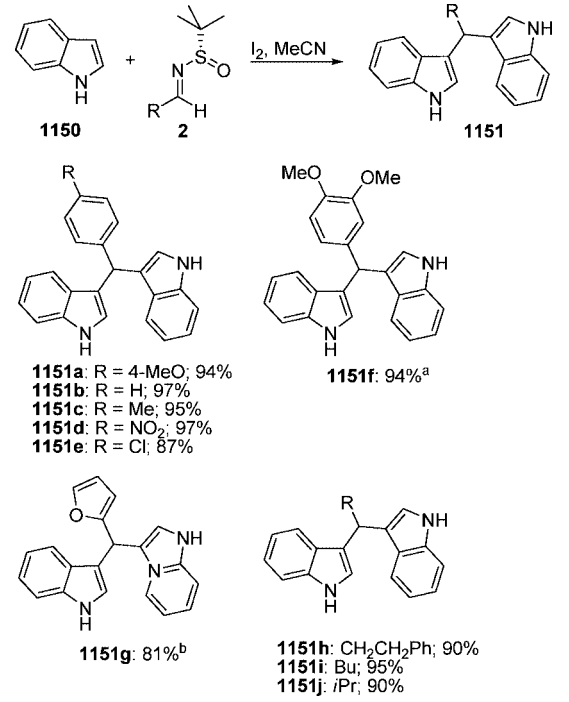
Scheme 280. Electrophile Induced Cyclization of *N-tert*-Butanesulfinyl Imines and Amines



18.6. S_N1 Displacement of Sulfinamide

Qin, Wang, and co-workers developed a new method for the preparation of bisindolylalkanes via a nucleophilic addition of indole to a number of *N-tert*-butanesulfinyl aldimines **2** (Scheme 281).[368] Optimization of the reaction conditions revealed that additives were necessary to promote product formation. The desired bisindolylalkanes **1151** were obtained in the best yields upon addition of 1 equiv of iodine, amberlyst, or $KHSO_4$, with iodine, in general, being the most efficient additive. Electron-rich, electron-poor, and heteroaromatic substituents were all incorporated into the bisindolylalkanes **1151a**−**g** in very high yields (81−97%). Aliphatic *N-tert*-butanesulfinyl aldimines were also excellent substrates, providing **1151h**−**j** in ≥90% yield.

Scheme 281. Addition of Indole to *N-tert*-Butanesulfinyl Aldimines



[a] Reaction conducted at 60 °C in MeOH with $KHSO_4$ as an additive. [b] Reaction conducted with amberlyst as an additive.

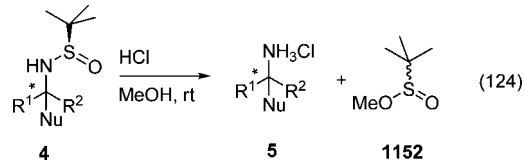
19. Manipulation of the N-tert-Butanesulfinyl Group

19.1. Deprotection of *N-tert*-Butanesulfinyl Amines

19.1.1. Acidic Deprotection of N-tert-Butanesulfinyl Amines

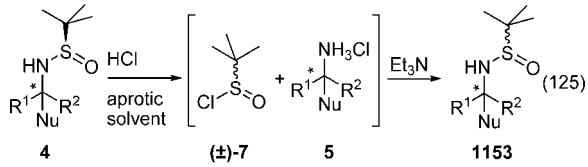
The initially reported method for the removal of the *N-tert*-butanesulfinyl group from *N-tert*-butanesulfinyl amines was by treatment with one or more equivalents of HCl, typically added using commercially available 4 M HCl solution in dioxane with MeOH as a cosolvent. The amine hydrochloride salt is then isolated in a straightforward fashion often in analytically pure form by precipitation from the reaction mixture with Et_2O or related ethereal solvents such as cyclopentyl methyl ether (eq 124).[16] These conditions have proven to be widely applicable, and the vast majority of examples in the literature follow this protocol. The side product from this reaction is *tert*-butanesulfinyl methyl ester **1152**, which is volatile. Therefore, isolation of the amine hydrochloride by removal of the solvent *in vacuo*, instead of precipitation, is also possible. While methanol is the most frequently used nucleophilic solvent in this deprotection, the use of HCl with either water or other alcohols, including ethanol,[230] isopropanol,[241] or *n*-butanol[227] has also been reported. Sulfinyl group hydrolysis under harsher conditions (refluxing aqueous HCl) has been reported in cases where simultaneous hydrolysis of another functional group (including esters,[181,312] nitriles,[76,87,213,214] or phosphonate esters[218]) was desired.

It is noteworthy that despite the acid lability of both the *N-tert*-butanesulfinyl group and the *N*-Boc group, one of the most popular of nitrogen protecting groups, orthogonal

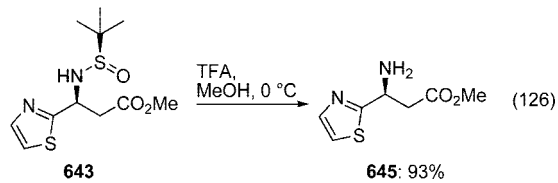


cleavage of the *N-tert*-butanesulfinyl group in the presence of the Boc group by HCl treatment has been amply demonstrated.[117,118,122,123,127] Correspondingly, the Boc group can be removed without cleavage of the *N-tert*-butanesulfinyl group by treatment with non-nucleophilic trifluoroacetic acid.[117,118,120,122]

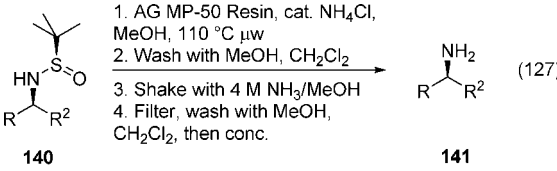
In the absence of a hydroxylic solvent, the sulfinyl group is cleaved by treatment with HCl to provide *tert*-butanesulfinyl chloride in solution. Both the Ellman[45] and Aggarwal[46] groups have developed methods for recycling of the *tert*-butanesulfinyl group that take advantage of this intermediate (see section 2.3 for details). Recently, Ellman and co-workers reported a one-pot procedure for epimerization of the *N-tert*-butanesulfinyl group via the configurationally unstable sulfinyl chloride **7** (eq 125).[369] This mixture provides a useful standard for the analysis of the diastereomeric purity of sulfinyl amine products.



Sulfinyl group cleavage using other acids has also been demonstrated. For example, in their work on the synthesis of bottromycin A2, Omura, Sunazuka, and co-workers utilized TFA with MeOH to cleave the *tert*-butanesulfinyl group of intermediate **643** (eq 126).[244]



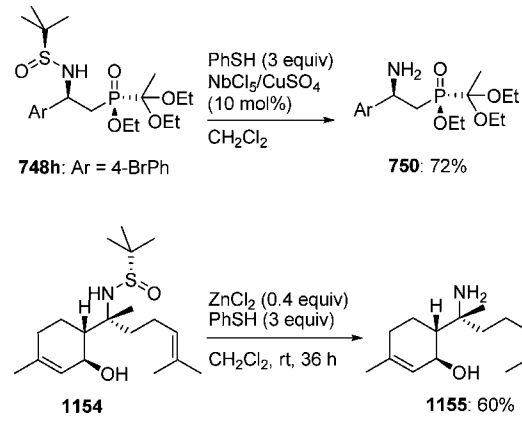
In their publication on the parallel solution-phase asymmetric synthesis of α-branched amines (section 4.1.1), Ellman and co-workers disclosed an alternate protocol to cleave the sulfinyl group.[98] Microwave irradiation of a mixture of **140** with a macroporous sulfonic acid resin in the presence of a catalytic amount of ammonium chloride, followed by purification of the product by washing it with methanol followed by elution with methanolic ammonia, provided the products **141** (eq 127).



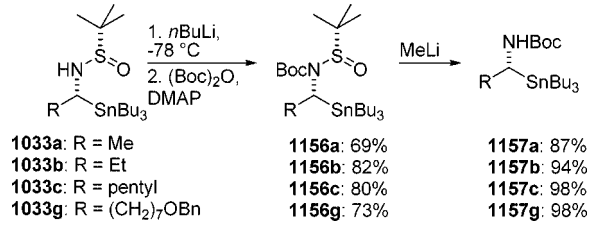
19.1.2. Nonacidic Conditions for Deprotection of N-tert-Butanesulfinyl Amines

In some cases, acidic removal of the sulfinyl group is not possible due to incompatibility with other functional groups.

Scheme 282. Thiophenolysis of the *tert*-Butanesulfinyl Group



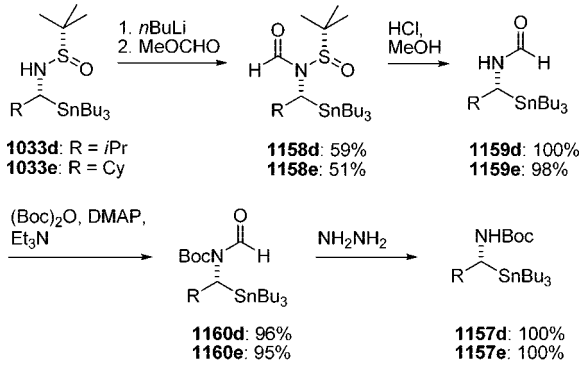
Scheme 283. Conversion of *N-tert*-Butanesulfinyl Amines 1033a−c and g to Boc-Protected Stannanes



In their work on the synthesis of α-amino phosphinates, Yuan and Zhang reported an alternative protocol for the removal of the sulfinyl group.[267] Thiophenolysis of the sulfinyl group in **748h** was achieved in the presence of 10 mol % $NbCl_5$ and 10 mol % $CuSO_4$, providing **750** in 72% yield (Scheme 282). These conditions were developed based upon the work by Hou and co-workers on the Lewis acid catalyzed thiophenolysis of *p*-toluenesulfinyl amines.[370] An example of thiophenol-mediated cleavage of the *tert*-butanesulfinyl group in a complex molecule containing a highly acid labile substituted secondary allylic alcohol was also provided by Schenkel and Ellman (Scheme 282).[371]

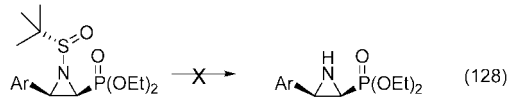
Chong and Kells noted in their development of a method for the synthesis of α-amino organostannanes from *N-tert*-butanesulfinyl imines that direct deprotonation of the sulfinyl group under a variety of conditions failed, presumably due to the instability of the resulting α-stannylamines.[335] Deprotonation of the sulfinyl amine at low temperature followed by treatment with Boc anhydride and 4-(dimethylamino)pyridine (DMAP) provided the mixed imides **1156a−c** and **g** in good yields (Scheme 283). Cleavage of the sulfinyl group employing methyllithium then yielded the Boc-protected amines **1157**. Unfortunately, for *N-tert*-butanesulfinyl α-amino organostannanes possessing branched substituents (**1033d** and **e**, Scheme 284), this method provided the desired products in very low yields. For these substrates, an alternative protocol was developed to introduce the Boc protecting group (Scheme 284). Because direct incorporation of the Boc group after deprotonation of the sulfinyl amine proved problematic due to steric crowding, the smaller formyl group was first introduced, providing **1158d** and **e** in moderate yields. Cleavage of the sulfinyl group, introduction of the Boc protecting group, and hydrazinolysis of the formyl group generated the desired Boc-protected α-amino organostannanes **1157** in excellent yields over three steps.

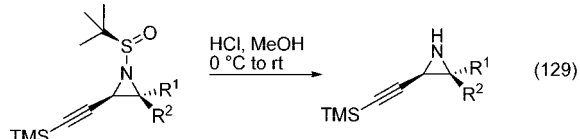
Scheme 284. Conversion of Branched *N-tert*-Butanesulfinyl Amines 1033d and e to Boc-Protected Stannanes

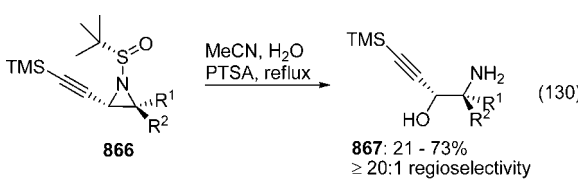


19.1.3. Removal of the N-tert-Butanesulfinyl Group from N-Sulfinyl Aziridines

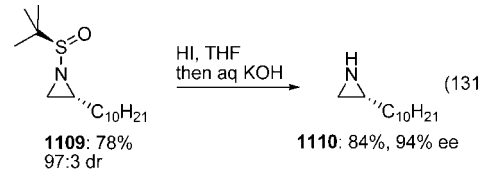
Attempts to deprotect *N-tert*-butanesulfinyl aziridines have met with mixed success, depending on the aziridine substitution pattern. Davis and co-workers reported that all attempts to cleave the *tert*-butanesulfinyl group of *N-tert*-butanesulfinyl aziridine 2-phosphonates **1084** using either acid or MeMgBr without aziridine ring-opening were unsuccessful (eq 128). Chemla and Ferriera reported success in the HCl mediated methanolysis of the sulfinyl group of *N-tert*-butanesulfinyl alkynyl aziridines **1093** (eq 129).[357] Using 5 equiv of HCl in methanol, deprotection was achieved within 30 min, providing alkyl 3-substituted and 3,3-disubstituted aziridines **1162a−c** in 66−100% yield. However, when these conditions were attempted with *N-tert*-butanesulfinyl protected aziridines bearing an alkenyl or aryl substituent, only the products resulting from aziridine ring-opening were observed. In a separate study, Ferreira and co-workers reported the concomitant aziridine ring-opening and removal of the sulfinyl group of **866** by treatment with *p*-toluenesulfonic acid (PTSA) (1 equiv) at reflux in 7:1 MeCN/H_2O to provide the fully deprotected acetylenic 1,2-amino alcohols **867** (eq 130; for details, see section 11.3).[289]



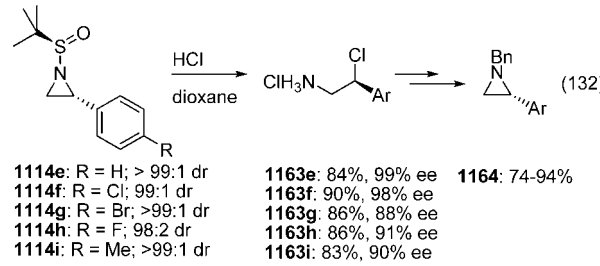


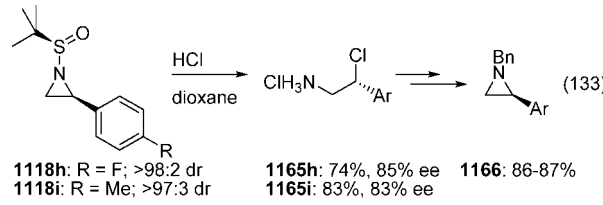


Hodgson and co-workers found that the sulfinyl group of aziridine **1109** could be cleaved in high yield without racemization by treating with aqueous HI in THF, followed by neutralization with KOH (eq 131).[359]



De Kimpe and co-workers reported that attempts to remove the sulfinyl group from recrystallized aziridines **1114e−i** or **1118h−i** by treatment with HCl in dioxane resulted in concomitant sulfinyl cleavage and regioselective nucleophilic ring-opening to provide the 2-aryl-2-chloroethylamine salts **1163** and **1165** in good yields (eqs 132 and 133).[361,372] The enantiomeric purities of **1163e−i** and **1165h** and **i** were ascertained after subsequent chemical transformations and evaluation by ^{1}H NMR with a chiral solvating reagent. While ring-opening of **1114e** and **f** proceeded without any epimerization, some racemization occurred for the other *para*-substituted compounds (eq 132). Some racemization was also observed in the ring-opening of aziridines **1118h** and **i** (eq 133). All ring-opened adducts were converted to 2-aryl-1-benzylaziridines **1164** or **1166** without further loss of configurational integrity.

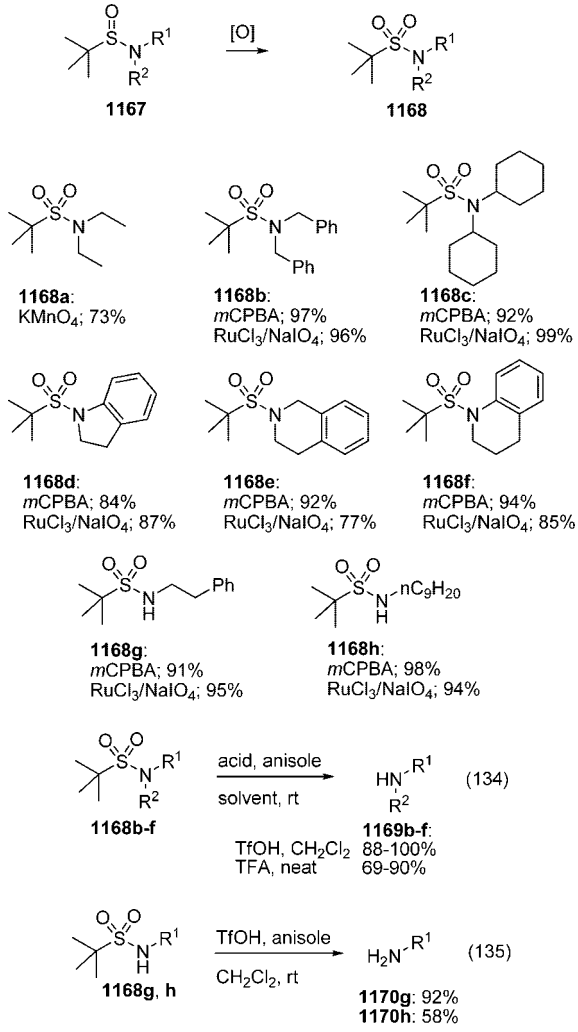




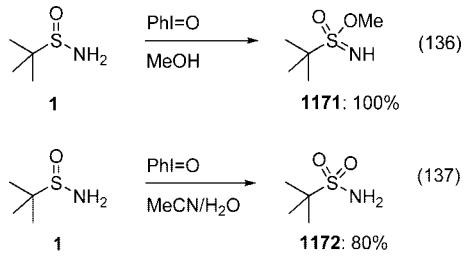
19.2. Oxidation of the *N-tert*-Butanesulfinyl Group

The *tert*-butanesulfonyl (Bus) group was described by Weinreb and co-workers in 1997 as a new protecting group for primary and secondary amines.[373] The Bus group was introduced by formation of an *N-tert*-butanesulfinyl amine, followed by oxidation. In this work, the *N-tert*-butanesulfinyl amines **1167** were synthesized by treating amines with *tert*-butanesulfinyl chloride. As an alternative to the previously disclosed oxidation conditions ($KMnO_4$, **1168a**, Scheme 285),[374] Weinreb and co-workers demonstrated the use of either *m*-chloroperbenzoic acid (*m*CPBA) or catalytic $RuCl_3$ with stoichiometric $NaIO_4$. It was also noted that dimethyldioxirane was an effective reagent for this oxidation. The *N*-Bus group was found to be stable to strong bases and metalation conditions, as well as to 0.1 N HCl/MeOH, 0.1 N TFA/CH_2Cl_2 (rt, 1 h), and pyrolysis (180 °C, neat, 3 h). Secondary Bus amines can be cleaved using either TFA or TfOH/CH_2Cl_2/anisole (eq 134) while primary amines could only be cleaved with TfOH/CH_2Cl_2/anisole (eq 135).

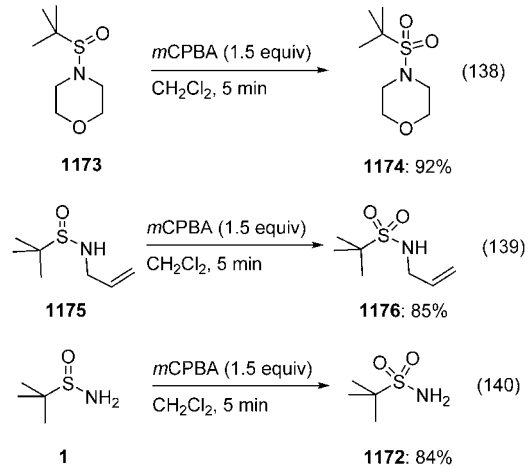
Scheme 285. Oxidation of *N-tert*-Butanesulfinyl Amines



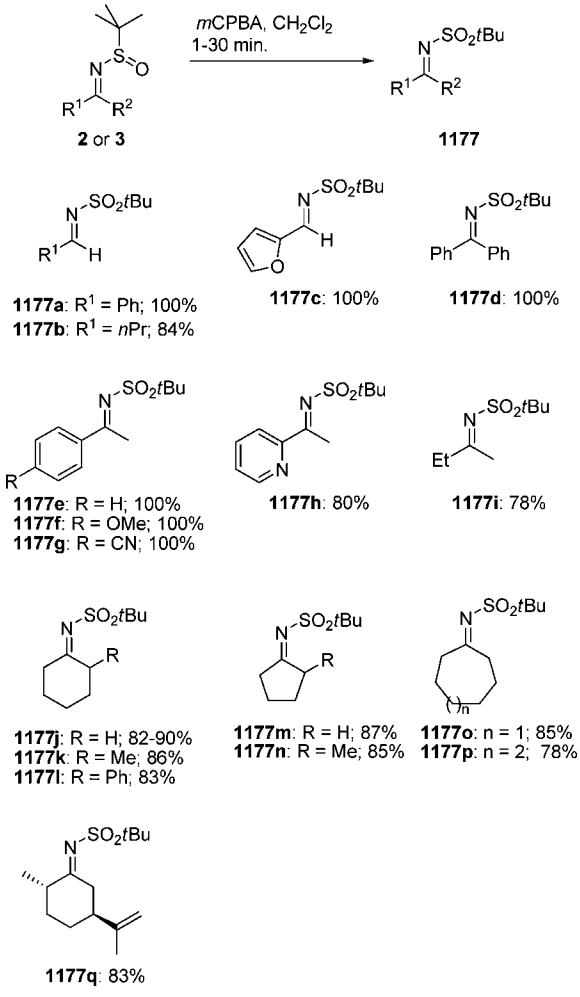
Malacria and co-workers reported the oxidation of *tert*-butanesulfinamide **1** with iodosobenzene to provide either sulfinimidate **1171** (eq 136, in the presence of MeOH) or sulfonamide **1172** (eq 137, in the absence of MeOH).[375] Garcia Ruano, Yuste, and co-workers reported the oxidation of *tert*-butanesulfinyl amines **1173** to Bus amines **1174** using 1.5 equiv of *m*CPBA (eq 138).[376] Moreover, they demonstrated the selective oxidation of the sulfur in the presence of an alkene in substrate **1175** (eq 139). The oxidation of *tert*-butanesulfinamide (**1**) under the same conditions to provide *tert*-butanesulfonamide **1172** in 85% yield was also disclosed (eq 140).

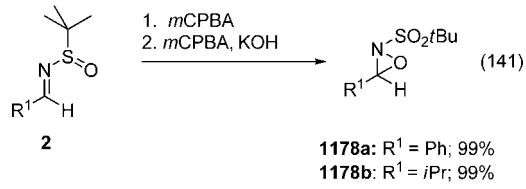


The oxidation of *N-tert*-butanesulfinyl aldimines **2** and ketimines **3** to *N*-Bus imines **1177a−j** using *m*CPBA was developed by Garcia Ruano and co-workers (Scheme 286).[377] This is an attractive general method for the two-step synthesis of sulfonyl imines from aldehydes and ketones due to the ease of isolation of the *N-tert*-butanesulfinyl imine intermediates. The successful oxidation to provide **1177q**, which contains a disubstituted alkene, demonstrated the chemoselectivity obtained under these oxidation conditions. Wang and co-workers utilized this method for the preparation of cyclic *N*-Bus ketimines **1177j−p**, which were used as substrates in a new rhodium-mediated ring expansion method.[58] Garcia Ruano and co-workers also demonstrated further oxidation of the *N*-Bus imines to *N*-Bus oxaziridines **1178** by treating with *m*CPBA in the presence of KOH (eq 141).[378]

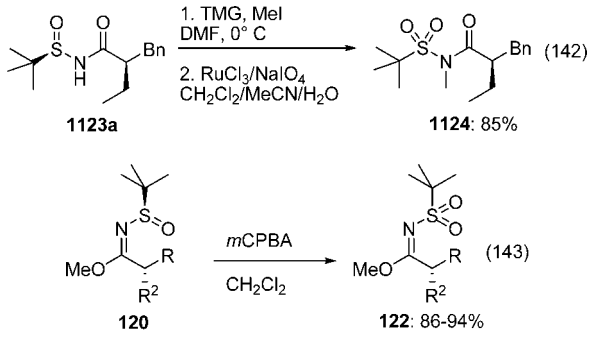


Scheme 286. Preparation of *N*-Bus Imines from *N-tert*-Butanesulfinyl Imines

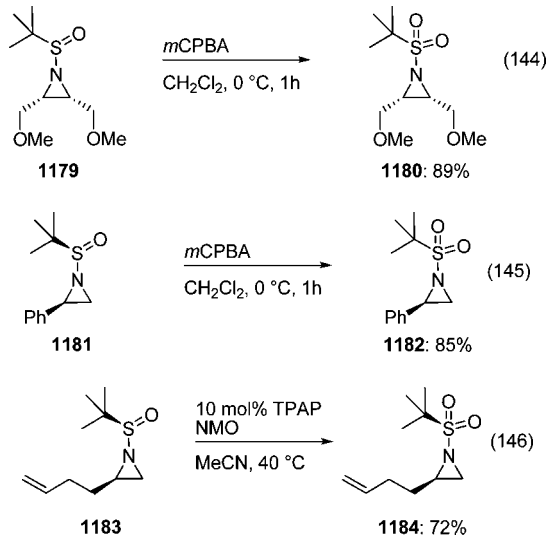




Ellman and co-workers reported *N*-methylation followed by oxidation of *N*-acyl-*tert*-butanesulfinamide **1123a** (eq 142).[362] De Kimpe and co-workers demonstrated the oxidation of the *N*-*tert*-butanesulfinyl imidates **120** to the corresponding *N*-Bus imidates (eq 143).[78]

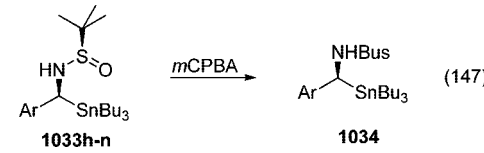


Hodgson and co-workers reported the use of *m*CPBA for the oxidation of *N*-*tert*-butanesulfinyl aziridines **1179** and **1181** to *N*-Bus aziridines **1180** and **1182** (eqs 144 and 145).[379,380] They noted that for *N*-*tert*-butanesulfinyl aziridines bearing pendant alkenes, such as **1183**, competitive oxidation occurred. Therefore, they reported the use of catalytic tetrapropylammonium perruthenate (TPAP) with excess *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant to effect a chemoselective oxidation of the sulfinyl group (eq 146).[380]

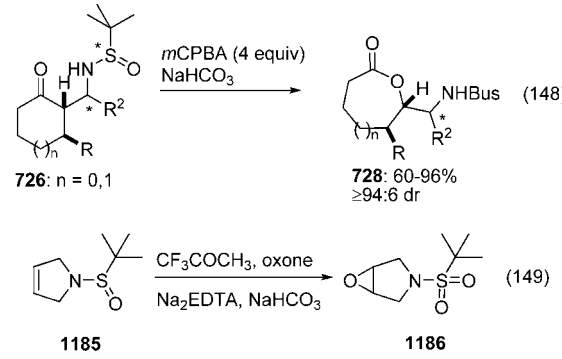


Chong and Kells reported use of mCPBA for sulfinyl oxidation of aromatic *N*-sulfinyl α-aminoorganostannanes, and subsequent application of the resulting *N*-Bus α-aminoorganostannanes **1034** in Stille cross-coupling reactions with acid chlorides (eq 147; see section 16).[336]

Concomitant oxidation of the *tert*-butanesulfinyl group as well as another functional group has been demonstrated by a number of researchers to access complex structures. For



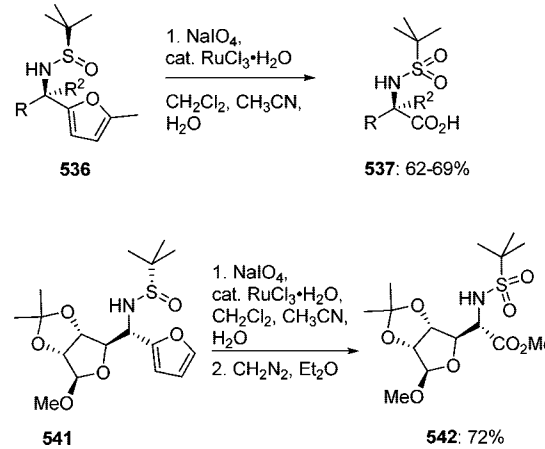
example, Ellman and co-workers reported the synthesis of α,α-disubstituted amino acids **537** by the 1,2-addition of 5-methylfuryllithium to *N*-*tert*-butanesulfinyl ketimines to provide adducts **536**, followed by concomitant oxidation of the *N*-*tert*-butanesulfinyl group and oxidative cleavage of the furan using $NaIO_4$ and catalytic $RuCl_3$ (Scheme 287; for details, see section 9.2.2).[215] Xu and co-workers utilized a modification of this method in the synthesis of **542**.[212,216] Gonzalez-Gomez, Foubelo, and Yus reported the concomitant oxidation of the *N*-*tert*-butanesulfinyl group and Baeyer−Villiger oxidation of a number of *β*-amino ketones **726** in the presence of *m*CPBA and $NaHCO_3$ (eq 148).[258] In addition, the concomitant oxidation of both the *N*-*tert*-butanesulfinyl group and the olefin of **1185** by methyl(trifluoromethyl)-dioxirane (generated in situ) to provide dihydropyrrole epoxide **1186** was reported by Hodgson and co-workers (eq 149).[381] Foubelo, Yus, and co-workers also reported the concomitant sulfinyl oxidation and alkene epoxidation of homoallylic *N*-*tert*-butanesulfinyl amines **1187** to *N*-Bus amino epoxides **1188** using 3 equiv of *m*CPBA (eq 150).[382] The further transformation of these products to azetidines and pyrrolidines was also disclosed.

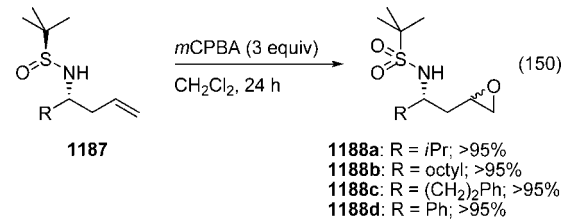


19.3. Conversion of *N*-*tert*-Butanesulfinyl Imines to Nitriles

The conversion of *N*-*tert*-butanesulfinyl imines to nitriles has been reported. The thermal decomposition pathway of *N*-*tert*-butanesulfinyl imines at high temperatures (>130 °C)

Scheme 287. Synthesis of *N*-Bus α-Amino Acids



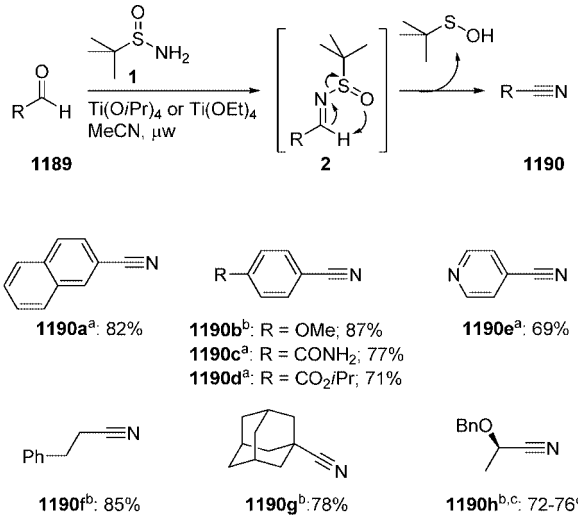


was first observed by Ellman and co-workers during their studies on microwave-mediated imine synthesis.[98] This transformation was then applied to the synthesis of the biologically important amine compounds *trans*-2-aminocyclopentanecarboxylic acid and SC-53116 (see section 3.2.3).[87] Later, a general method for the direct conversion of aldehydes to nitriles using *tert*-butanesulfinamide was developed by Ellman and co-workers (Scheme 288).[383] Optimization of the reaction conditions revealed that irradiating the reaction mixture containing **1**, aldehyde **1189**, and $Ti(OiPr)_4$ or $Ti(OEt)_4$ at 100 °C in the microwave for 10 min promoted complete conversion to the *N*-*tert*-butanesulfinyl imine. Increasing the reaction temperature to 200 °C for an additional 15 min facilitated the extrusion of sulfenic acid, providing the desired nitrile **1190**. Alkyl, heteroaryl, and aryl aldehydes, including ether-, amide-, and ester-functionalized aldehydes, were suitable substrates, generating nitriles **1190a**−**h** in 71−87% yield. Notably, when an aldehyde with an α-stereocenter was employed, no epimerization of the stereocenter was observed under the reaction conditions.

19.4. Hydrolysis of *N*-*tert*-Butanesulfinyl Imines

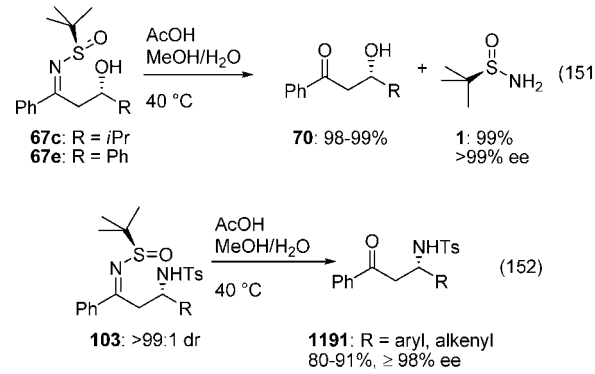
The acidic hydrolysis of *N*-*tert*-butanesulfinyl imines to the corresponding ketones or aldehydes is a simple and robust reaction. This has been demonstrated by a number of researchers, particularly following the functionalization of imines via an *N*-*tert*-butanesulfinyl metalloenamine intermediate. The first example was reported by Ellman and coworkers, who heated β-hydroxy *N*-*tert*-butanesulfinyl imines **67c** and **67e** in a mixture of acetic acid, water, and methanol to yield the corresponding β-hydroxy ketones **70** in almost quantitative yield with minimal racemization (<2%, eq 151).[83]

Scheme 288. Synthesis of Nitriles via *N*-*tert*-Butanesulfinyl Imines

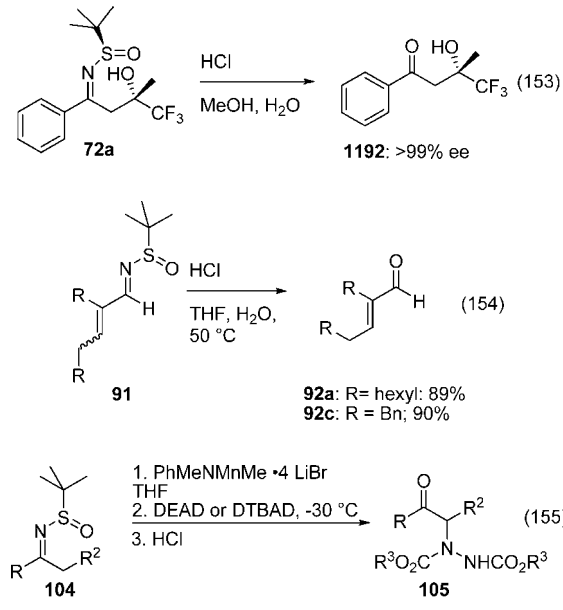


[a] $Ti(OiPr)_4$ was used. [b] $Ti(OEt)_4$ was used. [c] The (*R*)- and (*S*)-enantiomers of *tert*-butanesulfinamide provided the desired product in 72% and 76%, respectively.

Under these conditions, enantiomerically pure *tert*-butanesulfinamide (**1**) was also recovered in quantitative yield. Wang, Chen, and co-workers utilized the same conditions for the acidic hydrolysis of β-amino imines **103** to the corresponding β-amino ketones **1191** in 80−91% yield without racemization (eq 152).[90]

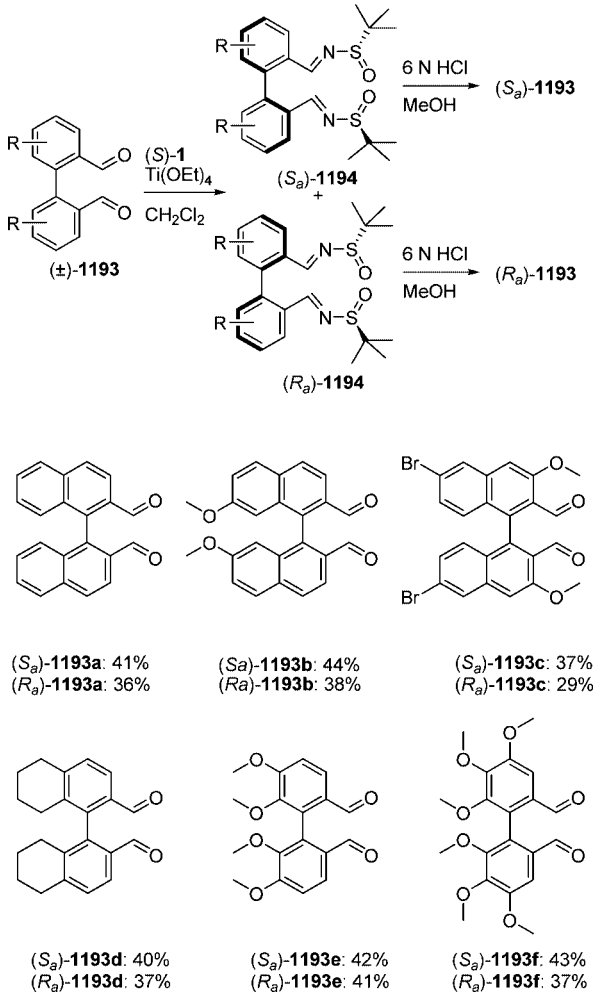


Alternatively, the use of HCl instead of acetic acid has been reported. Liu and co-workers demonstrated the hydrolysis of **72a** using aqueous HCl and MeOH to afford the enantiomerically pure β-hydroxy-β-trifluoromethyl ketone **1192** (eq 153).[85] Qin and co-workers demonstrated the hydrolysis of imines **91** to the corresponding enals **92** as single isomers in excellent yields by treatment with HCl in THF/H_2O (eq 154).[88] The one-pot α-amination of *N*-*tert*-butanesulfinyl ketimines followed by acidic hydrolysis to the corresponding α-hydrazino ketones was reported by Ricci and co-workers (eq 155; for details, see section 3.2.4).[91]



Xu, Lin, and co-workers demonstrated the use of *tert*-butanesulfinamide as a chiral resolving reagent (Scheme 289).[384] In this application, racemic axially chiral dialdehydes were condensed with *tert*-butanesulfinamide to form diastereomeric *bis*-imines **1194**, which were readily separated from each other by silica gel chromatography. Treatment of each diastereomerically pure *bis*-imine with 6 N HCl and MeOH resulted in hydrolysis of the imines to provide enantiomerically pure dialdehydes **1193** in high yield (29−44% of each enantiomer over two steps).

Scheme 289. Resolution of Axially Chiral Dialdehydes via *N-tert*-Butanesulfinyl Imine Intermediates



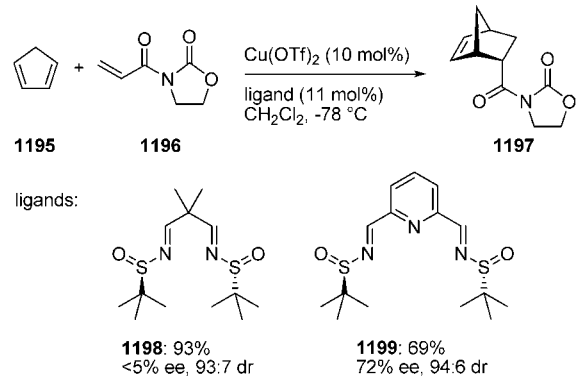
20. Ligands and Catalysts Incorporating *tert*-Butanesulfinamide

20.1. Metal−Ligand Complexes

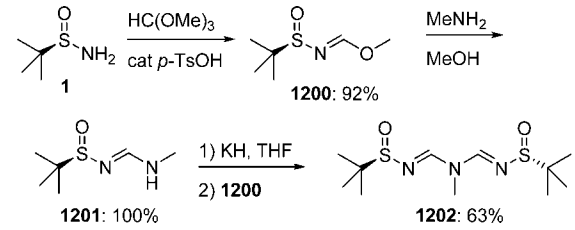
20.1.1. Catalytic Metal−Ligand Complexes

The ease of synthesis, stability, resident chirality, and potential for metal coordination of the S, N and O atoms of *N-tert*-butanesulfinyl imines and amines also provides excellent opportunities for the development of *N*-sulfinyl-based ligands for asymmetric catalysis.[385] In 2001, Ellman and co-workers published the first study on the use of *N*-sulfinyl imine ligands for asymmetric Lewis acid catalysis of the Diels−Alder reaction.[82] This work was expanded upon in a subsequent full paper.[80] Initially, ligands such as **1198** and **1199** (Scheme 290) were designed in analogy to the highly successful bisoxazoline ligands.[386] The synthesis of these C_2-symmetric *N-tert*-butanesulfinyl imine ligands was carried out by condensing the appropriate bis-aldehyde precursors with enantiomerically pure *tert*-butanesulfinamide, utilizing $Ti(OEt)_4$ or $CuSO_4$ as a Lewis acid and water scavenger. Metal complexes of these ligands (along with several others) were tested in the Diels−Alder reaction of cyclopentadiene with *N*-acryloyl oxazolidinone **1196**. This transformation was chosen because it has served as a benchmark reaction for the evaluation of asymmetric Lewis acid catalysts.[387] While the $Cu(OTf)_2$ complex of ligand **1198** provided high conversion, low enantioselectivity was obtained. The corresponding

Scheme 290. Initial Ligand Screening for the Diels−Alder Reaction



Scheme 291. Preparation of Bis(sulfinyl)imidoamidine Ligand 1202



complex of ligand **1199** was less active but provided the desired product with moderate enantioselectivity.

Extensive ligand optimization led to the design of bis-(sulfinyl)imidoamidine ligand **1202**. The synthesis of this ligand was carried out in three straightforward steps (Scheme 291). As the $Cu(SbF_6)_2$ complex, this ligand was found to efficiently catalyze the Diels−Alder reaction with very high stereoselectivity. The substrate scope of this reaction, outlined in Table 32, includes the reaction of cyclopentadiene (entries 1−4) or cyclohexadiene (entry 5) with several dienophiles with varying electronic properties, giving products with high selectivity. Modulation of temperature and extended reaction times were successful in providing acceptable yields for less active substrates.

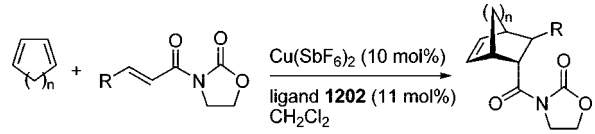
The scope of the reaction, particularly for acyclic dienes, was further investigated (Scheme 292). While terminal diene substitution resulted in poor yields and selectivities (**1207a**), internal substitutions were well tolerated. However, internal substitution with increased steric bulk resulted in diminished enantioselectivity.

The crystal structure of a $CuCl_2$−ligand **1202** complex was obtained, revealing a M_2L_4-helicate structure in which each ligand is coordinated to a copper center via the oxygen of the sulfinyl group (Figure 17). Additionally, IR data suggests that, both in the solid state and in freshly prepared solutions of the $Cu(SbF_6)_2$−**1202** complex, the primary species is oxygen bound. Nonlinearity was also observed with respect to the enantiomeric purity of the ligand,[388] suggesting that the active catalytic species is not a simple monomer.

The utility of this catalyst in complex molecule synthesis was demonstrated by Murai and co-workers, who applied **1202** to the synthesis of **1210**, the spirocyclic core of gymnodimine. In this transformation, a single diastereomer of the Diels−Alder product was observed (Scheme 293).[389]

A variety of ligands incorporating both phosphorus and *tert*-butanesulfinamide as binding elements have been developed.[390] The first report in this area was the development of *P,N*-sulfinyl imine ligands for Pd-catalyzed allylic alky-

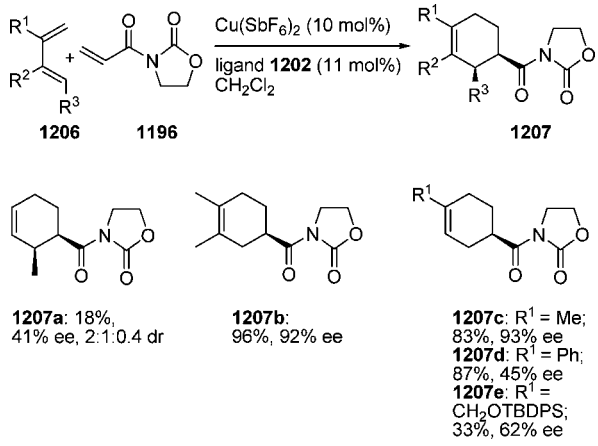
Table 32. Cu-Catalyzed Diels−Alder Reaction with Ligand 1202



1203 1204 1205

entry	*n*	R	time (h)	temp (°C)	yield (%)	ee (%)	dr (%)
1	1	H	0.1	−78	96	98	99:1
2	1	Me	8	−40	76	97	98:2
3	1	Ph	16	0	58	94	95:5
4	1	CO_2Et	2	−78	85	96	97:3
5	2	H	16	0	50	90	98:2

Scheme 292. Diels−Alder Reaction with Acyclic Dienes



lation.[391] In this study, the *N-tert*-butanesulfinyl imines were prepared via $Ti(OEt)_4$-mediated condensation of phosphine-containing aldehydes to give ligands of type **1212** (eq 156). A crystal structure was obtained of a Pd−π-allyl complex of **1212** (R = Ph), verifying the bidentate binding mode of this ligand via the phosphorus and the imine nitrogen.[391] Optimization of catalyst structure and reaction conditions

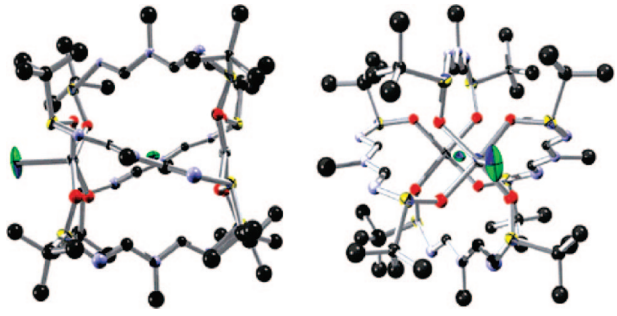
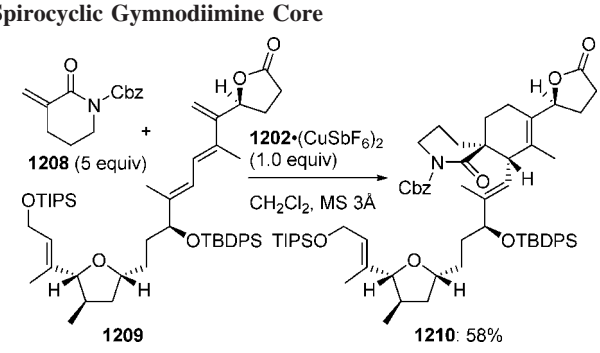
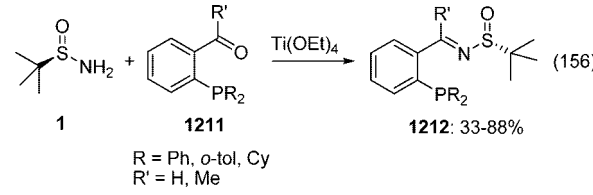


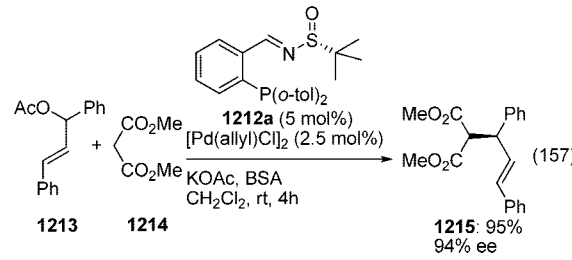
Figure 17. Crystal structure of the $CuCl_2$−**1202** complex. The $Cu_2Cl_6^-$ counterion was omitted for clarity.[80]

Scheme 293. Diels−Alder Reaction for the Synthesis of the Spirocyclic Gymnodiimine Core



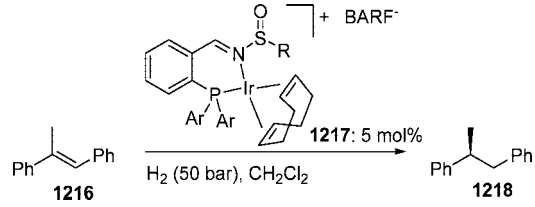
revealed that imine ligand **1212a** was capable of providing allylic alkylation product **1215** (eq 157) in high yield and with excellent enantioselectivity.





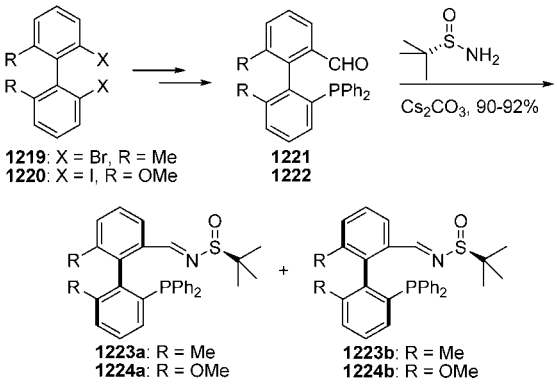
Having established the ability of *P*,*N*-sulfinyl imine ligands to induce enantioselectivity in transition metal catalyzed reactions, Ellman and co-workers turned their attention to the application of this ligand class to Ir-catalyzed asymmetric hydrogenation.[392] While only the *tert*-butanesulfinyl and *p*-toluenesulfinyl substituents had been explored in the allylic alkylation study (*vide supra*), a wide variety of *N*-sulfinyl substituents were investigated for the hydrogenation reaction to determine the steric and electronic influence of the sulfinyl group in this modular ligand scaffold. The imine ligands were prepared by condensation of the corresponding aldehyde with sulfinamide mediated by $Ti(OEt)_4$ (75−95% yield). The Ir complexes **1217a−g** were then prepared in a high-yielding, two-step, one-pot procedure involving ligand complexation with $[Ir(cod)Cl]_2$ followed by replacement of the chloride with the noncoordinating $BARF^-$ ($[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$) counterion (90−95% yield). These complexes were then tested in the catalytic hydrogenation of an unfunctionalized olefin, α-methylstilbene **1216** (Table 33). Under the optimized reaction conditions, complex **1217a**, derived from ligand **1212a**, which was previously reported for Pd-catalyzed allylic alkylation, provided quantitative conversion to product **1218** with very high enantioselectivity (entry 1). While it was expected that increasing the steric bulk of the *N*-sulfinyl substituent would further improve the enantioselectivity observed for this transformation, unfortunately, neither the adamantanesulfinyl nor 3-ethylpentanesulfinyl substituents were effective toward this goal and each resulted in both attenuated reactivity and selectivity (entries 2 and 3). The catalyst bearing the *p*-toluenesulfinyl substituent did provide quantitative conversion, but the product was obtained

Table 33. Hydrogenation of α-Methylstilbene

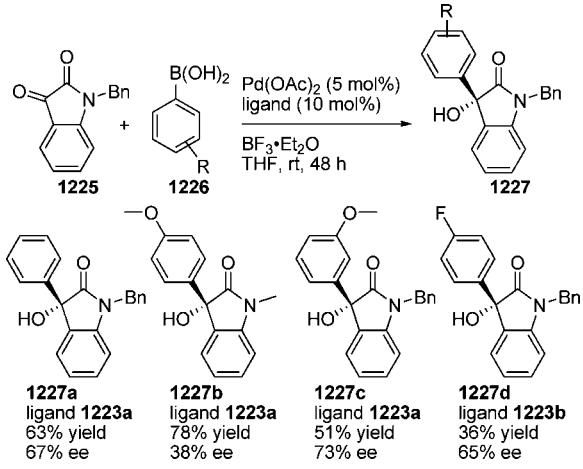


entry	1217	R	Ar	conversion (%)	ee (%)
1	**1217a**	(*R*)-*t*Bu	*o*-tol	>99	94
2	**1217b**	(*S*)-1-adamantyl	*o*-tol	58	84
3	**1217c**	(*S*)-3-ethylpentane	*o*-tol	75	84
4	**1217d**	(*S*)-*p*-tolyl	*o*-tol	>99	5
5	**1217e**	(*S*)-mesitylene	*o*-tol	52	7
6	**1217f**	(*R*)-*t*Bu	3,5-Me_2Ph	53	57
7	**1217g**	(*R*)-*t*Bu	Ph	20	55

Scheme 294. Synthesis of Biaryl *P*,*N* Ligands



Scheme 295. Phenylboronic Acid Addition to Isatins



as a nearly racemic mixture (entry 4). The mesitylenesulfinyl substituent had the same detrimental effect on enantioselectivity and also resulted in much lower conversion (entry 5). Examination of the effects of substitution on the phosphorus aryl groups confirmed that the *o*-tolyl substituent was required for high conversion and selectivity (entries 1, 6, and 7), consistent with previous studies with oxazoline-based *P*,*N* ligands.[393]

Recently, Qin and co-workers have reported the development of biaryl *P*,*N*-sulfinyl imine ligands and their application in Pd-catalyzed addition of arylboronic acids to *N*-benzyl isatin.[394] While previously explored *N*-sulfinyl imine ligands relied solely on the chirality at sulfur for asymmetric induction, these novel structures (**1223** and **1224**, Scheme 294) incorporate the chiral sulfinyl group in conjunction with

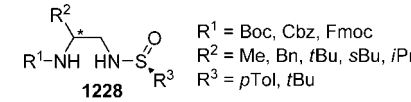
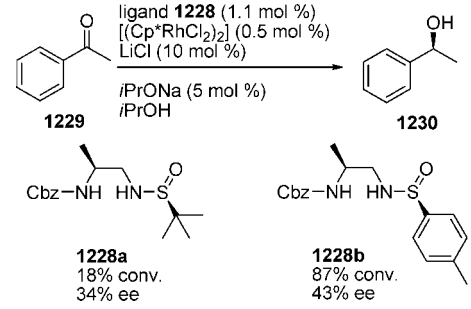


Figure 18. Amino-acid derived sulfinyl ligands.

Scheme 296. Transfer Hydrogenation of Acetophenone



an axially chiral biaryl component. The multistep synthesis of these ligands, beginning with C_2-symmetric biaryl compounds **1219** and **1220**, proceeded via Cs_2CO_3-mediated condensation of enantiomerically pure *tert*-butanesulfinamide (**1**) with biaryl aldehydes **1221** and **1222**, followed by chromatographic separation of the imine diastereomers.

Reaction of ligand **1223a** with $[Pd(allyl)Cl]_2$ followed by counterion replacement of the Cl^- with SbF_6^- yielded a Pd−π-allyl complex that was analyzed by X-ray crystallography, allowing assignment of the stereochemistry of the ligand as well as confirming the expected *P*,*N*-chelate binding mode.

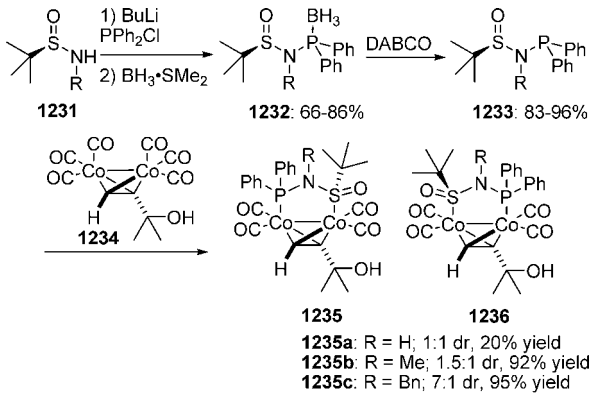
Biaryl ligands **1223**−**1224** were screened in the transition-metal catalyzed addition of phenylboronic acid to *N*-benzyl isatin **1225** (Scheme 295). After optimization of reaction conditions, ligand **1223a** was identified as the most active for this transformation. Comparison of the performance of ligand diastereomers **1223a** and **1223b** revealed that product stereochemistry was predominantly controlled by the ligands' axial chirality rather than the sulfinyl stereocenter. A brief survey of arylboronic acid coupling partners demonstrated the synthesis of **1227a**−**d** in variable yields and with moderate selectivities.

Adolfsson and co-workers investigated the use of amino-acid derived sulfinamide ligands of general structure **1228** (Figure 18) in the enantioselective transfer hydrogenation of ketones.[395] Ligand **1228a**, bearing the *N*-*tert*-butanesulfinyl group, proved to be inferior to the analogous *p*-toluenesulfinyl ligand **1228b** in the Rh-catalyzed transfer hydrogenation of acetophenone (Scheme 296), providing the product alcohol **1230** with inferior conversion (18% vs 87%) and enantioselectivity (34% vs 43%). Further optimization of the reaction conditions, including additives, transition metal precatalyst, and diamine ligand structure, provided a set of reaction conditions (with a *p*-toluenesulfinyl amine ligand) that allowed this transformation to take place with high enantioselectivity (86% ee).

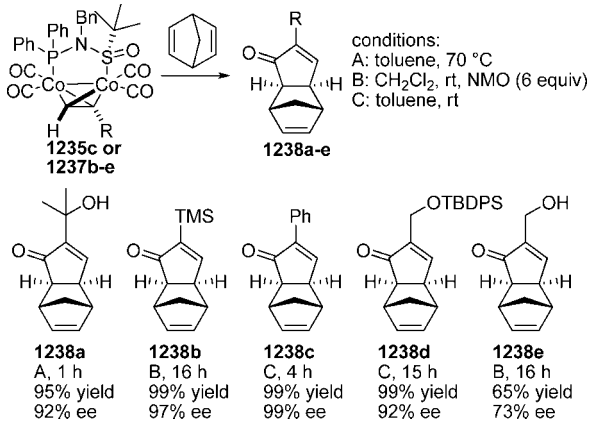
20.1.2. Metal−Ligand Complexes as Stoichiometric Reagents

Riera, Verdaguer, and co-workers have developed a novel class of *N*-phosphino-*tert*-butanesulfinamide (PNSO) ligands **1233** (Scheme 297).[396] The synthesis of these ligands was complicated by the potential for oxygen migration from sulfur to phosphorus. To prevent this, the ligands were isolated as their borane adducts **1232** and then deprotected

Scheme 297. Synthesis of Dicobalt−PNSO Complexes

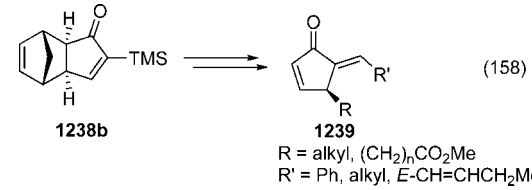


Scheme 298. Pauson−Khand Reaction



and isolated as free ligands. The reaction of these ligands with dicobalt hexacarbonyl-alkyne complex **1234** yielded mixtures of diastereomeric cobalt complexes **1235** and **1236**. The *N*-benzyl derivative **1235c** was obtained with higher diastereoselectivity than the *N*−H and *N*-methyl derivatives **1235a** and **1235b**.

A series of complexes **1237**, all bearing *N*-benzyl substitution, were then prepared analogously for subsequent use in the Pauson−Khand reaction (Scheme 298), and the major diastereomers were isolated in stereochemically pure form by crystallization (**1237e**, R = CH_2OH was isolated as a >20:1 mixture of diastereomers, complete separation was not possible). The Pauson−Khand reaction with norbornadiene gave chiral cyclopentenones **1238** in high yields and with moderate to high enantiomeric purities (73−99% ee) (Scheme 298). In contrast, when similar ligands that incorporated the *p*-toluenesulfinyl group were tested in the Pauson−Khand reaction, lower enantioselectivities (28−94%) were observed.[397] This difference was attributed to the stronger S−Co bond observed in the *p*-toluenesulfinyl complexes, diminishing the required hemilabile character of the ligands. The utility of the Pauson−Khand reaction products was demonstrated in the synthesis of cross-conjugated cyclopentenone derivatives such as **1239** (eq 158), which were evaluated as ligands for the activation of the transcription factor peroxisome proliferator activated receptor-γ (PPAR-γ).[398]



(158)

20.1.3. Noncatalyst Ligand−Metal Complexes

In 1991, Roesky and co-workers reported the synthesis and characterization of a series of eight-membered-ring organometallic complexes **1240**, in which racemic *tert*-butanesulfinamides were used as bidentate ligands via simultaneous N and O coordination to aluminum, indium, or gallium (Figure 19).[399]

An early publication by the Ellman group on sulfinamide-containing chiral ligands detailed the synthesis and crystal structure of an *N*,*S*-bonded *N*,*N*′-bis(*tert*-butanesulfinyl)-amidinate Rh(I) complex (Scheme 299).[81] Acid-catalyzed condensation of *tert*-butanesulfinamide with trimethyl orthoacetate yielded imidate **1241**, which was then reacted with the potassium salt of a second equivalent of *tert*-butanesulfinamide to provide *pseudo*-C_2 symmetric *N*,*N*′-bis(sulfinyl)-amidine ligand **1242**. Treatment of this ligand with base in the presence of $[Rh(cod)Cl]_2$ provided the air-stable Rh(I) complex **1243**, which was characterized by X-ray structural analysis. Interestingly, this amidinate complex displays asymmetric metal binding via the nitrogen and the sulfur of the two sulfinyl groups.

Riera, Verdaguer, and co-workers examined the ability of the PNSO ligands (*vide supra*) to form a variety of cationic Rh(I) complexes (Figure 20).[400] While these ligands act as *P*,*S*-ligands in their interaction with dimeric cobalt species (see Scheme 297), they were found to bind either as *P*,*S* or *P*,*O* ligands to rhodium, depending on the coordination environment. In addition to examining the structures of these complexes, ligand displacement studies were performed to establish the hemilabile nature of these ligands, allowing coordination sites for incoming phosphines. In particular, treatment of complex **1244a** with either 2 equiv of PPh_3 or 1 equiv of the bidentate diphenylphosphinoethane (dppe) allowed displacement of the cyclooctadiene (COD) ligand. However, treatment of **1244b** or **1244c** with 4 equiv of PPh_3 had no effect, demonstrating that the PNSO ligands are more competent ligands than monophosphines. Treatment of **1244b** with 2 equiv of dppe caused complete ligand displacement, while the cyclohexyl analogue **1244c** was unreactive toward dppe.

Bergman and Ruck explored the insertion of *N*-*tert*-butanesulfinyl imine **133** into the zirconium−carbon bond of an azazirconacyclobutene **1245**, providing six-membered metallocycle **1246** (Scheme 300).[401] Formation of the metallocycle occurred at 105 °C, and upon further heating to 135 °C, it underwent a retro-[4 + 2] cycloaddition to afford α,β-unsaturated imine **1248**. However, the novel *N*-*tert*-butanesulfinyl imidozirconocene **1247** was not observed by ^1H NMR or as a precipitate from the reaction mixture. Due to the instability of imine **133** above 115 °C, the authors hypothesize that the sulfinyl group did not survive the

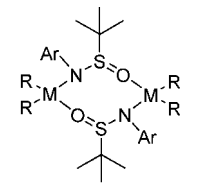


Figure 19. NSO heterocyclic complexes.

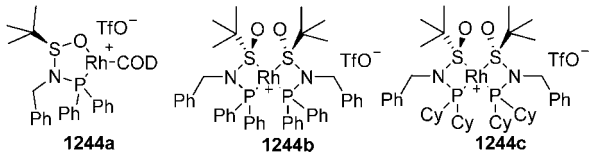
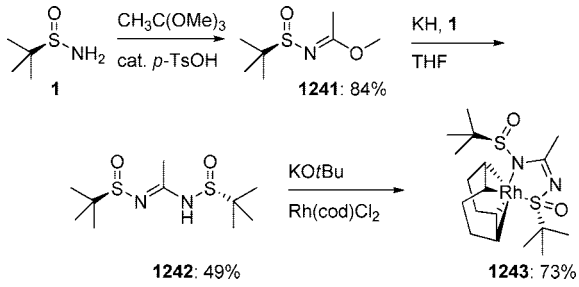
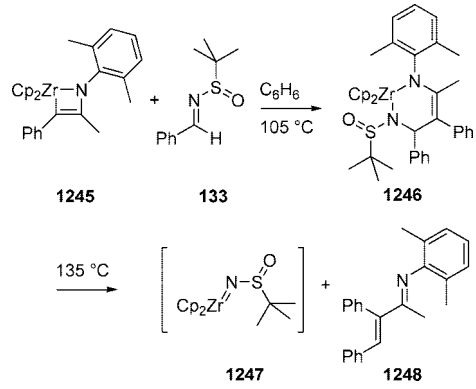


Figure 20. PNSO rhodium complexes.

Scheme 299. Synthesis of Complex 1243



Scheme 300. Reaction of *N-tert*-Butanesulfinyl Imine 133 with Azazirconacyclobutene 1245



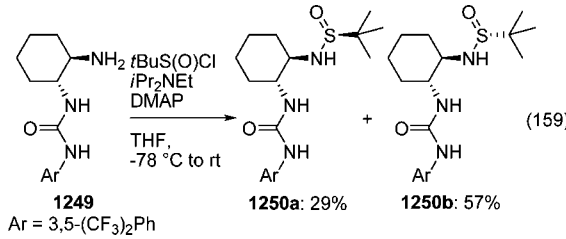
elevated temperatures required for the retro-[4 + 2] cycloaddition.

20.2. Catalytic Ligands

20.2.1. Catalytic Ligands with Stoichiometric Metal Reagents

Catalyst **1250b** (eq 159), which combines a hydrogen-bonding urea for electrophile activation along with the Lewis basic *tert*-butanesulfinamide group for nucleophile activation, was reported by the Jacobsen group for the indium-mediated allylation of acyl hydrazones (Table 34).[402,403] Diastereomers **1250a** and **1250b** were prepared by treating amine **1249** with *tert*-butanesulfinyl chloride and were separated by silica gel chromatography (eq 159). It is proposed based on the X-ray crystal structure of **1250b** that an internal hydrogen bond between the sulfinyl N−H and the urea oxygen may help to rigidify the catalyst structure and increase the urea acidity. The stereochemistry of the sulfinyl group was found to be critical in the catalytic allylation reaction, as demonstrated by the observation that **1250a** provided allylation product with 26% ee, compared to **1250b**, which provided the desired product with 91% ee under otherwise identical conditions.

In contrast to hydrazones **1251** derived from aryl and heteroaryl aldehydes, which underwent allylation with high selectivity (entries 1−9, Table 34), those derived from alkyl aldehydes exhibited poor selectivity in the allylation reaction (generally <50% ee). This limitation was partially overcome



by increasing the electron-withdrawing character of the hydrazone *N*-acyl protecting group, as demonstrated by entry 10.

The use of substituted allyl bromides **1253** was also investigated (Scheme 301). While high enantioselectivity was achieved (≥85% ee for each product), poor diastereo- and regiocontrol were observed. The similar distribution of products arising from *E* vs *Z* crotyl bromide suggests that the allyl indium species may not be configurationally stable under the reaction conditions.

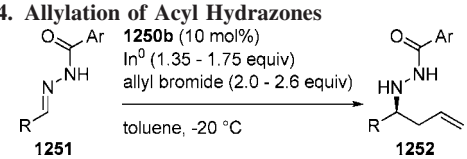
Qin and co-workers explored the use of *tert*-butanesulfinamide-based ligands **1257**−**1259** (Figure 21) as catalysts for the addition of diethylzinc to aldehydes.[404] Synthesis of optimal ligand **1257a** was carried out by condensation of *tert*-butanesulfinamide with salicylaldehyde, followed by $NaBH_4$ reduction of the imine.

The use of **1257a** as a catalyst for addition of diethylzinc to aldehydes was highly enantioselective for aromatic and heteroaromatic aldehyde substrates, yielding alcohols **1261a**−**f**, while moderate selectivity was observed for the addition to alkenyl and alkyl aldehydes to yield alcohols **1261g** and **h** (Scheme 302). A transition state structure was proposed to explain the observed stereochemistry of the product (Figure 22). In this structure, coordination of the phenolic oxygen, the nitrogen, the sulfinyl oxygen, and the carbonyl oxygen to a single zinc ion is expected to provide a highly ordered structure. Delivery of the ethyl group from a second zinc species, which is coordinated to the phenolic oxygen and the carbonyl oxygen, is stereospecific, and the aldehyde facial selectivity is explained by placing the aldehyde R group in the position further away from the bulky *tert*-butanesulfinyl group.

20.2.2. Organocatalysts

The first sulfinamide organocatalyst was reported by Sun and co-workers in 2006 for the enantioselective reduction of *N*-aryl ketimines with trichlorosilane.[142] In initial studies,

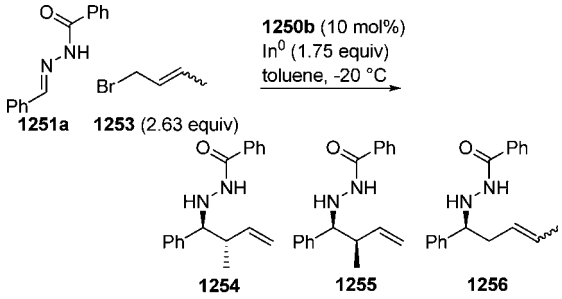
Table 34. Allylation of Acyl Hydrazones



entry	R	Ar	yield (%)	ee (%)
1	Ph	Ph	87	92
2	*p*-Cl-Ph	Ph	83	92
3	2-furyl	Ph	90	87
4	2-thienyl	Ph	82	93
5	*p*-(CO_2Me)-Ph	Ph	92	76
6	*o*-Br-Ph	Ph	78	93
7	*o*-Tol	Ph	89	95
8	1-naphthyl	Ph	89	95
9	*p*-MeO-Ph	Ph	79	93
10[a]	*i*Pr	3,5-(CF_3)$_2$-Ph	55	80

[a] Reaction was run at −40 °C.

Scheme 301. Additions of Crotyl Bromides to Acyl Hydrazones



it was found that *tert*-butanesulfinamide (**1**) was capable of catalyzing the desired transformation (Scheme 303) in 60% yield and with 21% ee. Structure optimization led to the design of catalysts **1265** (Figure 23), which incorporate a proximally placed Brönsted acid in addition to the Lewis basic sulfinyl moiety. This hydroxyl group was found to be important for high enantioselectivity, and modulation of its

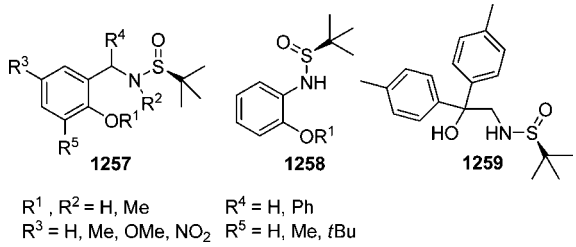


Figure 21. Potential ligands for diethylzinc additions.

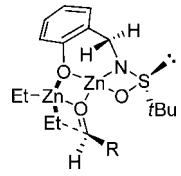
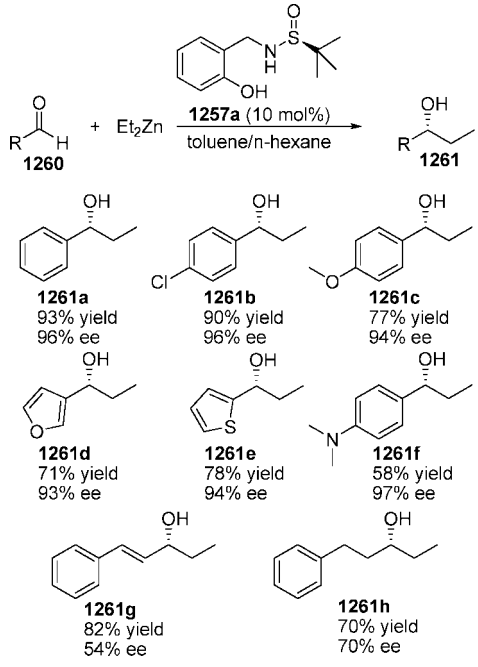
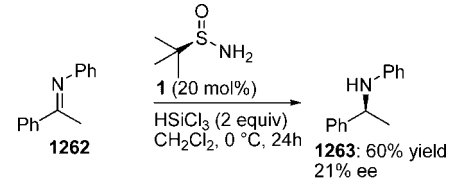


Figure 22. Proposed transition state.

Scheme 302. Addition of Diethylzinc to Aldehydes



Scheme 303. Initial Results for Imine Reduction



acidity by changing the aryl substitution pattern further enhanced the performance of the catalyst, with the best performance obtained (92% yield, 92% ee) by catalyst **1265c**.

After optimization of reaction conditions, the scope of the **1265c**-catalyzed enantioselective reduction of imines was

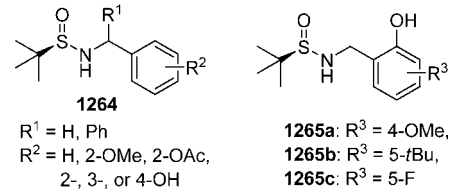
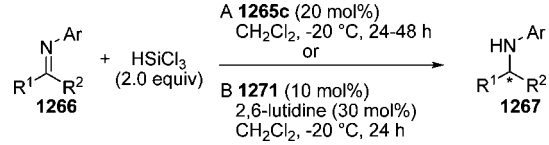


Figure 23. Catalyst structure optimization.

Table 35. Organocatalytic Reduction of *N*-Aryl Imines



entry	R^1	R^2	Ar	conditions	yield (%)	ee (%)
1	Ph	Me	Ph	A	92	92
				B	91	96
2	4-CF_3-Ph	Me	Ph	A	93	92
				B	95	95
3	4-NO_2-Ph	Me	Ph	A	94	90
				B	90	93
4	4-Br-Ph	Me	Ph	A	92	92
				B	92	95
5	4-OMe-Ph	Me	Ph	A	98	93
				B	83	95
6	2-Np	Me	Ph	A	96	90
				B	77	94
7	6-OMe-2-Np	Me	Ph	A	97	91
				B	80	93
8	Cy	Me	Ph	A	78	74
				B	84	75
9	*i*Pr	Me	Ph	A	78	79
				B	87	82
10	Ph	Me	4-Cl-Ph	A	94	92
				B	93	95
11	Ph	Me	4-Me-Ph	A	87	91
				B	88	92
12	Ph	Me	4-OMe-Ph	A	97	91
				B	92	92
13	Ph	Me	2-OMe-Ph	A	73	88
				B	75	72
14	4-CF_3-Ph	Me	4-OMe-Ph	A	80	90
				B	90	83
15	2-Np	Me	4-OMe-Ph	A	86	88
				B	86	91
16	Ph	Et	4-OMe-Ph	A	84	92
				B	84	92
17	Ph	Et	Ph	A	92	93
				B	86	94
18	Ph	*n*Pr	Ph	A	87	91
				B	87	91
19	Ph	*c*Pr	Ph	B	70	93
20	Ph	*n*Bu	Ph	A	94	93
				B	89	91
21	Ph	*i*Bu	Ph	A	82	86
				B	82	93

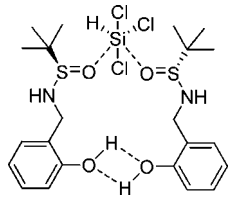


Figure 24. Proposed binding mode for reduction.

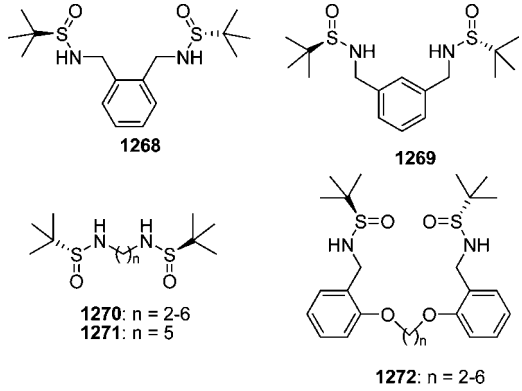


Figure 25. Bis-sulfinyl catalysts for reduction of ketimines.

examined (Table 35, reaction conditions A). The imine *N*-substituent was limited to aryl derivatives, although varying electronic substitution (entries 10−13) was well tolerated, including the use of the *p*-methoxyphenyl (PMP) group (entries 12, 14−16). When the imine R^1 group was aromatic and R^2 was aliphatic, high levels of enantioselectivity were achieved for a variety of aryl groups (entries 1−7) and alkyl groups (entries 17−20). Significantly, high enantioselectivities were even achieved when R^1 and R^2 were branched alkyl groups and methyl, respectively, albeit with slightly lower selectivity (entries 8−9).

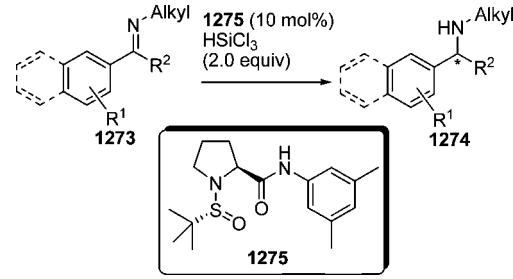
While a rationalization of the transition state leading to enantioselectivity for catalyst **1265c** was not proposed in the initial report, a clear positive nonlinear effect with respect to enantioselectivity was observed, suggesting that more than one catalyst molecule is involved in the stereochemistry-determining step.[142] Subsequent work by the same group expanded further on this observation, with a dimeric binding mode proposed to explain these results (Figure 24).[405] This model also is consistent with the observed importance of the phenolic hydroxyl group, which could provide an organized noncovalent tether between the two catalyst molecules.

Based on this working hypothesis, bis-sulfinyl catalysts **1268**−**1272** (Figure 25) were designed to incorporate a variety of different tethers.[405] Catalyst **1271** was identified from this set as an effective and highly enantioselective catalyst for the reduction of ketimines, in most cases providing superior results to those obtained with the original sulfinyl catalyst (Table 35, conditions B versus A). It was also found that addition of a substoichiometric amount of 3,5-lutidine had a beneficial effect on the enantioselectivity of the reaction (96% ee with 0.3 equiv vs 91% without), although stoichiometric amounts shut down the reaction. Importantly, the enantiomeric purity of bis-sulfinyl catalyst **1271** was found to have a linear correlation with product enantioselectivity, consistent with the expectation that a single molecule of this bidentate catalyst is involved in the stereodetermining step.

While catalysts **1265c** and **1271** were broadly applicable to the reduction of *N*-aryl ketimines, they were not successful for reactions with imines with aliphatic nitrogen substituents. For highly enantioselective reductions of this substrate class, Sun and co-workers recently reported sulfinamide catalyst **1275** (Table 36).[406] The substrate scope for this reaction includes *N*-benzyl (entries 1−12, 24), *N*-allyl (entries 13−20), and saturated unbranched (entry 21) and β-branched *N*-alkyl substitution (entry 22) of aromatic ketimines.

In contrast to the organocatalysts discussed above, which relied on the Lewis basic nature of the sulfinamide oxygen for activation of substrates, Ellman and co-workers have

Table 36. Enantioselective Reduction of Aromatic *N*-Alkyl Ketimines



entry	R^1	R^2	alkyl	solvent	yield (%)	ee (%)
1	H	Me	Bn	toluene	98	96
				CCl_4	90	97
2	4-F	Me	Bn	toluene	80	96
				CCl_4	82	97
3	4-Cl	Me	Bn	toluene	92	95
4	3-Cl	Me	Bn	toluene	98	97
5	4-Br	Me	Bn	toluene	80	96
6	3-Br	Me	Bn	toluene	93	97
7	4-CF_3	Me	Bn	toluene	94	98
				CCl_4	93	96
8	4-NO_2	Me	Bn	toluene	80	>99
				CCl_4	98	94
9	4-Me	Me	Bn	toluene	95	91
10	4-OMe	Me	Bn	toluene	54	78
				CCl_4	90	92
11	2-naphthyl	Me	Bn	toluene	96	96
				CCl_4	83	98
12	6-OMe-2-naphthyl	Me	Bn	toluene	70	82
				CCl_4	89	95
13	H	Me	allyl	toluene	82	92
				CCl_4	80	93
14	4-F	Me	allyl	toluene	88	90
				CCl_4	83	96
15	4-Cl	Me	allyl	toluene	97	89
16	2-Cl	Me	allyl	toluene	75	97
17	4-Br	Me	allyl	toluene	83	93
18	4-CF_3	Me	allyl	toluene	65	97
19	4-NO_2	Me	allyl	toluene	97	96
20	4-Me	Me	allyl	toluene	88	83
				CCl_4	80	85
21	H	Me	nPr	toluene	67	66
				CCl_4	60	90
22	H	Me	iBu	toluene	56	70
				CCl_4	80	87
23	H	Me	4-OMeBn	toluene	85	93
				CCl_4	83	95
24	H	Et	Bn	toluene	80	89

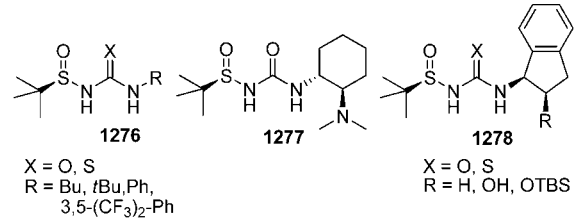
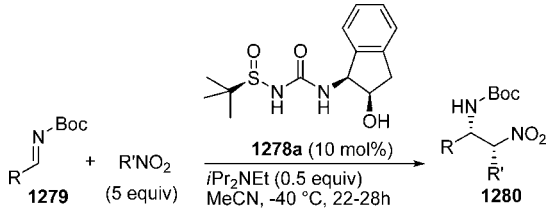


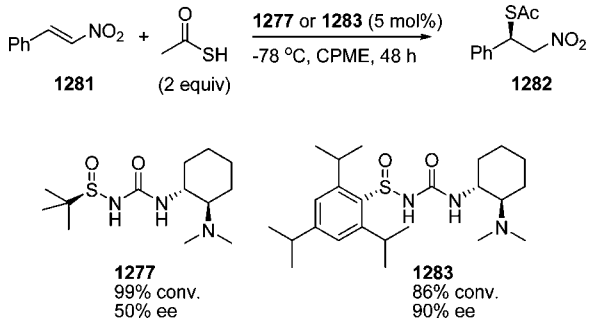
Figure 26. Sulfinyl urea catalysts.

Table 37. Organocatalytic Aza-Henry Reaction

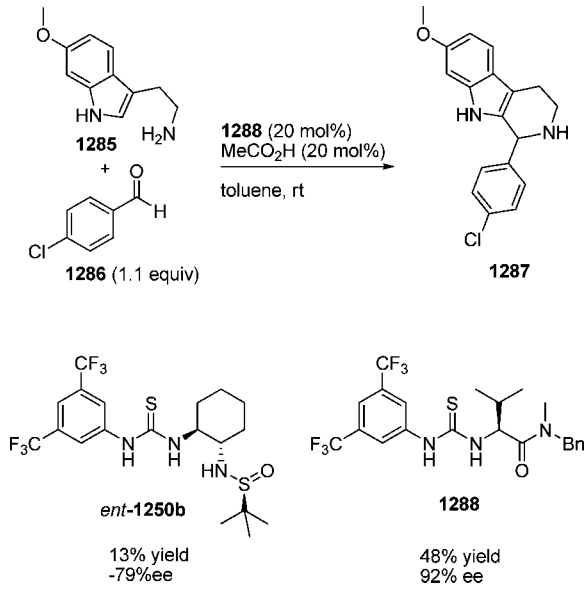


entry	R	R′	major product	yield (%)	d.r.	ee (%)
1	C_6H_5	Me	**1280a**	84	85:15	95
2	*p*-$MeOC_6H_4$	Me	**1280b**	64	90:10	95
3	*p*-MeC_6H_4	Me	**1280c**	68	79:21	95
4	*p*-$CF_3C_6H_4$	Me	**1280d**	92	77:23	92
5	*o*-ClC_6H_4	Me	**1280e**	88	80:10	94
6	2-naphthyl	Me	**1280f**	80	84:16	93
7	Bu	Me	**1280g**	80	92:8	96
8	*i*-Bu	Me	**1280h**	76	93:7	96
9	*i*-Bu	Bn	**1280i**	62	88:12	96
10	*i*-Bu	H	**1280j**	64		95

Scheme 304. Addition of Thioacetic Acid to Nitroalkenes



Scheme 305. Catalyst Screening for the Pictet−Spengler Reaction



disclosed the development of *tert*-butanesulfinyl urea catalysts such as **1276**−**1278** (Figure 26).[407] In these catalysts, the sulfinyl group serves both as a chiral directing group and as an acidifying substituent on the urea, making it a stronger hydrogen-bonding organocatalyst. The application of optimized catalyst **1278a** to the enantioselective aza-Henry reaction is outlined in Table 37, including additions of several different nitroalkanes to both aromatic and aliphatic *N*-Boc aldimines.

Recently, *tert*-butanesulfinyl urea catalyst **1277** was applied to the addition of thioacetic acid to nitroalkenes, providing the product with 50% ee on initial screening (Scheme 304). Optimization of the catalyst structure revealed that the triisopropylphenylsulfinyl urea **1283** provides excellent enantioselectivity for this transformation.[408]

Catalyst *ent*-**1250b**, developed for indium-mediated allylation of hydrazones (*vide supra*) was screened in the enantioselective one-pot Pictet−Spengler reaction (Scheme 305), providing the product with 79% ee.[409] However, catalyst *ent*-**1250b** provided only 13% yield, while catalyst **1288** provided the product in 48% yield. Further optimization was therefore carried out with catalyst **1288**, which lacks the sulfinamide functionality.

21. Conclusion

The measure of success of any reagent, catalyst, or method must ultimately be based on the extent to which it is used in compound preparation. Many researchers from around the world have contributed innovative and often practically useful methods that have established *tert*-butanesulfinamide as an extremely versatile reagent for the robust and general asymmetric synthesis of diverse classes of amine-containing compounds. Moreover, as demonstrated by the many applications discussed in this review, a rapidly increasingly number of researchers now extensively rely on *tert*-butanesulfinamide in endeavors that range from the total synthesis of natural products, to the preparation of chemical tools for catalysis, materials, and chemical biology research, and particularly, to the development of pharmaceutical agents and agrochemicals. The commercial availability of *tert*-butanesulfinamide in large quantities at low cost, the robustness and generality of many of its methods, and the prominence of amine-containing compounds in drugs, agrochemicals, and naturally occurring materials ensures that *tert*-butanesulfinamide-based methods will continue to be some of the most extensively used methods in synthesis.

22. Acknowledgments

We gratefully acknowledge the researchers who carried out the work described herein. They are individually identified in the references. We also appreciate the care and effort of the reviewers of this manuscript, who provided valuable input. Finally, we thank the National Science Foundation (CHE-0742565) for support of this work.

23. References

(1) For example, Advanced Asymmetrics, Inc. is currently cost competitive for smaller quantities (<1 kg) and Allychem for larger quantities (>1 kg) [The authors do not hold stock or receive personal renumeration from either company].
(2) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.
(3) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
(4) (a) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichim. Acta* **2005**, *38*, 93. (b) Senanayake, C. H.; Han, Z.; Krishnamurthy, D. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; 2008. (c) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.
(5) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.
(6) Caldwell, J. J.; Collins, I. *Synlett* **2006**, 2565.
(7) Nitta, A.; Fujii, H.; Sakami, S.; Nishimura, Y.; Ohyama, T.; Satoh, M.; Nakaki, J.; Satoh, S.; Inada, C.; Kozono, H.; Kumagai, H.; Shimamura, M.; Fukazawa, T.; Kawai, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5435.

(8) Sealy, J. M.; Truong, A. P.; Tso, L.; Probst, G. D.; Aquino, J.; Hom, R. K.; Jagodzinska, B. M.; Dressen, D.; Wone, D. W. G.; Brogley, L.; John, V.; Tung, J. S.; Pleiss, M. A.; Tucker, J. A.; Konradi, A. W.; Dappen, M. S.; Toth, G.; Pan, H.; Ruslim, L.; Miller, J.; Bova, M. P.; Sinha, S.; Quinn, K. P.; Sauer, J.-M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6386.
(9) Shiau, T. P.; Houchin, A.; Nair, S.; Xu, P.; Low, E.; Najafi, R.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1110.
(10) Shao, P. P.; Ye, F.; Weber, A. E.; Li, X.; Lyons, K. A.; Parsons, W. H.; Garcia, M. L.; Priest, B. T.; Smith, M. M.; Felix, J. P.; Williams, B. S.; Kaczorowski, G. J.; McGowan, E.; Abbadie, C.; Martin, W. J.; McMasters, D. R.; Gao, Y.-D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5334.
(11) Low, E.; Nair, S.; Shiau, T.; Belisle, B.; Debabov, D.; Celeri, C.; Zuck, M.; Najafi, R.; Georgopapadakou, N.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 196.
(12) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865.
(13) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645.
(14) Netscher, T.; Prinzbach, H. *Synthesis* **1987**, *1987*, 683.
(15) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.
(16) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.
(17) (a) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed.* **1996**, *34*, 2640. (b) Bolm, C.; Schlingloff, G.; Bienewald, F. *J. Mol. Catal., A: Chem.* **1997**, *117*, 347.
(18) Blum, S. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 150.
(19) Balcells, D.; Maseras, F.; Lledos, A. *J. Org. Chem.* **2003**, *68*, 4265.
(20) Ma, Y.; Wang, X.; Wang, Y.; Feng, Y.; Zang, Y. *Synth. Commun.* **2004**, *34*, 501.
(21) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317.
(22) Weix, D. J.; Ellman, J. A.; Wang, X.; Curran, D. P. *Org. Synth.* **2005**, *82*, 157.
(23) Colonna, S.; Gaggero, N.; Carrea, G.; Pasta, P.; Alphand, V.; Furstoss, R. *Chirality* **2001**, *13*, 40.
(24) Dzyuba, S. V.; Klibanov, A. M. *Biotechnol. Lett.* **2003**, *25*, 1961.
(25) Colonna, S.; Pironti, V.; Drabowicz, J.; Brebion, F.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2005**, 1727.
(26) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
(27) Khiar, N.; Mallouk, S.; Valdivia, V.; Bougrin, K.; Soufiaoui, M.; Fernandez, I. *Org. Lett.* **2007**, *9*, 1255.
(28) Basak, A.; Barlan, A. U.; Yamamoto, H. *Tetrahedron: Asymmetry* **2006**, *17*, 508.
(29) Liao, J.; Sun, X.; Cui, X.; Yu, K.; Zhu, J.; Deng, J. *Chem.—Eur. J.* **2003**, *9*, 2611.
(30) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651.
(31) Khiar, N.; Fernández, I.; Alcudia, F. *Tetrahedron Lett.* **1994**, *35*, 5719.
(32) Garcia Ruano, J. L.; Fernandez, I.; del Prado Catalina, M.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.
(33) (a) Wudl, F.; Lee, T. B. K. *J. Chem. Soc., Chem. Commun.* **1972**, 61. (b) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349.
(34) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885.
(35) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991.
(36) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880.
(37) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Su, X.; Wilkinson, H. S.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Tetrahedron* **2005**, *61*, 6386.
(38) Qin, Y.; Wang, C.; Huang, Z.; Xiao, X.; Jiang, Y. *J. Org. Chem.* **2004**, *69*, 8533.
(39) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.
(40) Lu, B. Z.; Jin, F.; Zhang, Y.; Wu, X.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 1465.
(41) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.
(42) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.
(43) Peltier, H. M.; Evans, J. W.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 1733.
(44) Shibata, N.; Matsunaga, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Synlett* **2005**, 1699.
(45) Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646.
(46) Aggarwal, V. K.; Barbero, N.; McGarrigle, E. M.; Mickle, G.; Navas, R.; Suarez, J. R.; Unthank, M. G.; Yar, M. *Tetrahedron Lett.* **2009**, *50*, 3482.
(47) Drabowicz, J.; Bujnicki, B.; Biscarini, P.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3177.
(48) (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229. (b) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.
(49) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268.
(50) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
(51) Higashibayashi, S.; Tohmiya, H.; Mori, T.; Hashimoto, K.; Nakata, M. *Synlett* **2004**, 457.
(52) Huang, Z.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005**, 1334.
(53) Jiang, Z.-Y.; Chan, W. H.; Lee, A. W. M. *J. Org. Chem.* **2005**, *70*, 1081.
(54) Ardej-Jakubisiak, M.; Kawecki, R.; Swietlinska, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2507.
(55) Fan, R.; Pu, D.; Wen, F.; Ye, Y.; Wang, X. *J. Org. Chem.* **2008**, *73*, 3623.
(56) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847.
(57) Ardej-Jakubisiak, M.; Kawecki, R. *Tetrahedron: Asymmetry* **2008**, *19*, 2645.
(58) Chen, S.; Zhao, Y.; Wang, J. *Synthesis* **2006**, 1705.
(59) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537.
(60) Colyer, J. T.; Andersen, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. *J. Org. Chem.* **2006**, *71*, 6859.
(61) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 5393.
(62) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.
(63) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772.
(64) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948.
(65) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538.
(66) Ando, M.; Sato, N.; Nagase, T.; Nagai, K.; Ishikawa, S.; Takahashi, H.; Ohtake, N.; Ito, J.; Hirayama, M.; Mitobe, Y.; Iwaasa, H.; Gomori, A.; Matsushita, H.; Tadano, K.; Fujino, N.; Tanaka, S.; Ohe, T.; Ishihara, A.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem.* **2009**, *17*, 6106.
(67) Denolf, B.; Mangelinckx, S.; Toernroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129.
(68) Denolf, B.; Mangelinckx, S.; Toernroos, K. W.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 187.
(69) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396.
(70) Jayathilaka, L. P.; Deb, M.; Standaert, R. F. *Org. Lett.* **2004**, *6*, 3659.
(71) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304.
(72) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594.
(73) (a) Saaby, S.; Bayon, P.; Aburel, P. S.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352. (b) Münster, P.; Steglich, W. *Synthesis* **1987**, *1987*, 223.
(74) Kuduk, S. D.; Marco, C. N. D.; Pitzenberger, S. M.; Tsou, N. *Tetrahedron Lett.* **2006**, *47*, 2377.
(75) Truong, V. L.; Menard, M. S.; Dion, I. *Org. Lett.* **2007**, *9*, 683.
(76) Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379.
(77) Liu, Z.-J.; Liu, J.-T. *Chem. Commun.* **2008**, 5233.
(78) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 3792.
(79) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.
(80) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3.
(81) Souers, A. J.; Owens, T. D.; Oliver, A. G.; Hollander, F. J.; Ellman, J. A. *Inorg. Chem.* **2001**, *40*, 5299.
(82) Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539.
(83) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518.
(84) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.
(85) Liu, Z.-J.; Mei, Y.-Q.; Liu, J.-T. *Tetrahedron* **2006**, *63*, 855.
(86) Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 7342.
(87) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 3621.
(88) Bian, X.; Zhang, D.; Huang, Z.; Qin, Y. *Synlett* **2006**, 3419.
(89) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905.
(90) Zhao, C.-H.; Liu, L.; Wang, D.; Chen, Y.-J. *Eur. J. Org. Chem.* **2006**, 2977.
(91) Dessole, G.; Bernardi, L.; Bonini, B. F.; Capito, E.; Fochi, M.; Herrera, R. P.; Ricci, A.; Cahiez, G. *J. Org. Chem.* **2004**, *69*, 8525.
(92) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.
(93) Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923.
(94) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303.
(95) For the application of a Grignard addition to a phenylacetaldimine for the asymmetric synthesis of Pavine and Isopavine alkaloids using a support-bound sulfinamide, see: Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127.
(96) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th ed.; O'Neil, M. J., Heckelman, P. E., Koch, C. B., Roman, K. J., Eds.; Merck & Co.: Whitehouse Station, NJ, 2006.

(97) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195.
(98) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590.
(99) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641.
(100) Dirscherl, G.; Rooshenas, P.; Schreiner, P. R.; Lamaty, F.; Koenig, B. *Tetrahedron* **2008**, *64*, 3005.
(101) Hashmi, A. S. K.; Schaefer, S.; Bats, J. W.; Frey, W.; Rominger, F. *Eur. J. Org. Chem.* **2008**, 4891.
(102) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599.
(103) Schultz-Fademrecht, C.; Kinzel, O.; Markó, I. E.; Pospisil, T.; Pesci, S.; Rowley, M.; Jones, P. *Tetrahedron* **2009**, *65*, 9487.
(104) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193.
(105) Kosciolowicz, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1444.
(106) Grajewska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 557.
(107) (a) Kuduk, S. D.; Di Marco, C. N.; Chang, R. K.; Wood, M. R.; Schirripa, K. M.; Kim, J. J.; Wai, J. M. C.; DiPardo, R. M.; Murphy, K. L.; Ransom, R. W.; Harrell, C. M.; Reiss, D. R.; Holahan, M. A.; Cook, J.; Hess, J. F.; Sain, N.; Urban, M. O.; Tang, C.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G. *J. Med. Chem.* **2007**, *50*, 272. (b) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Di Marco, C. N.; Murphy, K. L.; Ransom, R. W.; Reiss, D. R.; Tang, C.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3608. (c) Feng, D.-M.; DiPardo, R. M.; Wai, J. M.; Chang, R. K.; Di Marco, C. N.; Murphy, K. L.; Ransom, R. W.; Reiss, D. R.; Tang, C.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G.; Kuduk, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 682.
(108) Donald, A.; McHardy, T.; Rowlands, M. G.; Hunter, L.-J. K.; Davies, T. G.; Berdini, V.; Boyle, R. G.; Aherne, G. W.; Garrett, M. D.; Collins, I. *J. Med. Chem.* **2007**, *50*, 2289.
(109) Fustero, S.; Jimenez, D.; Sanchez-Rosello, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700.
(110) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109.
(111) Marriner, G. A.; Kerwin, S. M. *J. Org. Chem.* **2009**, *74*, 2891.
(112) Reddy, L. R.; Prashad, M. *Chem. Commun.* **2010**, *46*, 222.
(113) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452.
(114) Yamaguchi, K.; Kazuta, Y.; Hirano, K.; Yamada, S.; Matsuda, A.; Shuto, S. *Bioorg. Med. Chem.* **2008**, *16*, 8875.
(115) Fei, Z.; Wu, Q.; Zhang, F.; Cao, Y.; Liu, C.; Shieh, W.-C.; Xue, S.; McKenna, J.; Prasad, K.; Prashad, M.; Baeschlin, D.; Namoto, K. *J. Org. Chem.* **2008**, *73*, 9016.
(116) Han, Z.; Krishnamurthy, D.; Pflum, D.; Grover, P.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2002**, *4*, 4025.
(117) Jiang, W.; Chen, C.; Marinkovic, D.; Tran, J. A.; Chen, C. W.; Arellano, L. M.; White, N. S.; Tucci, F. C. *J. Org. Chem.* **2005**, *70*, 8924.
(118) Jiang, W.; Tran, J. A.; Tucci, F. C.; Fleck, B. A.; Hoare, S. R.; Markison, S.; Wen, J.; Chen, C. W.; Marinkovic, D.; Arellano, M.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6546.
(119) Chen, C.; Tucci, F. C.; Jiang, W.; Tran, J. A.; Fleck, B. A.; Hoare, S. R.; Wen, J.; Chen, T.; Johns, M.; Markison, S.; Foster, A. C.; Marinkovic, D.; Chen, C. W.; Arellano, M.; Harman, J.; Saunders, J.; Bozigian, H.; Marks, D. *Bioorg. Med. Chem.* **2008**, *16*, 5606.
(120) (a) Tucci, F. C.; Tran, J. A.; Jiang, W.; Pontillo, J.; Marinkovic, D.; White, N. S.; Arellano, M.; Fleck, B. A.; Wen, J.; Saunders, J.; Foster, A. C.; Chen, C. *Lett. Drug Des. Discovery* **2006**, *3*, 311. (b) Jiang, W.; Tucci, F. C.; Chen, C. W.; Arellano, M.; Tran, J. A.; White, N. S.; Marinkovic, D.; Pontillo, J.; Fleck, B. A.; Wen, J.; Saunders, J.; Madan, A.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4674. (c) Tran, J. A.; Tucci, F. C.; Jiang, W.; Marinkovic, D.; Chen, C. W.; Arellano, M.; Markison, S.; Fleck, B. A.; Wen, J.; White, N. S.; Pontillo, J.; Saunders, J.; Marks, D.; Hoare, S. R.; Madan, A.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem.* **2007**, *15*, 5166. (d) Tran, J. A.; Tucci, F. C.; Arellano, M.; Jiang, W.; Chen, C. W.; Marinkovic, D.; Fleck, B. A.; Wen, J.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1931.
(121) (a) Chen, C. W.; Tran, J. A.; Jiang, W.; Tucci, F. C.; Arellano, M.; Wen, J.; Fleck, B. A.; Marinkovic, D.; White, N. S.; Pontillo, J.; Saunders, J.; Madan, A.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4800. (b) Tran, J. A.; Jiang, W.; Tucci, F. C.; Fleck, B. A.; Wen, J.; Sai, Y.; Madan, A.; Chen, T. K.; Markison, S.; Foster, A. C.; Hoare, S. R.; Marks, D.; Harman, J.; Chen, C. W.; Arellano, M.; Marinkovic, D.; Bozigian, H.; Saunders, J.; Chen, C. *J. Med. Chem.* **2007**, *50*, 6356. (c) Tran, J. A.; Chen, C. W.; Jiang, W.; Tucci, F. C.; Fleck, B. A.; Marinkovic, D.; Arellano, M.; Chen, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5165.
(122) (a) Chen, C.; Jiang, W.; Tran, J. A.; Tucci, F. C.; Fleck, B. A.; Markison, S.; Wen, J.; Madan, A.; Hoare, S. R.; Foster, A. C.; Marinkovic, D.; Chen, C. W.; Arellano, M.; Saunders, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 129. (b) Tran, J. A.; Chen, C. W.; Tucci, F. C.; Jiang, W.; Fleck, B. A.; Chen, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1124.
(123) Rajapakse, H. A.; Young, M. B.; Zhu, H.; Charlton, S.; Tsou, N. N. *Tetrahedron Lett.* **2005**, *46*, 8909.
(124) Grajewska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2008**, *18*, 2910.
(125) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627.
(126) Cheng, L.; Liu, L.; Sui, Y.; Wang, D.; Chen, Y.-J. *Tetrahedron: Asymmetry* **2007**, *18*, 1833.
(127) Qiu, X.-L.; Zhu, J.; Wu, G.; Lee, W.-H.; Chamberlin, A. R. *J. Org. Chem.* **2009**, *74*, 2018.
(128) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484.
(129) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 603.
(130) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 3198.
(131) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 4188.
(132) Garcia, D.; Moreno, B.; Soler, T.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 4710.
(133) Zhang, W.-X.; Ding, C.-H.; Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. *Tetrahedron Lett.* **2006**, *47*, 8391.
(134) Zhang, W. X.; Hou, X. L. *Chin. Chem. Lett.* **2006**, *17*, 1037.
(135) (a) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, 1637. (b) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (c) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976.
(136) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092.
(137) Recently, the catalytic enantioselective addition of arylboronic acids to aliphatic *N*-toluenesulfonyl and *N*-diphenylphosphinyl imines has been reported: Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623.
(138) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481.
(139) Weix, D. J.; Ellman, J. A. Unpublished results, 2005.
(140) Boebel, T. A.; Hartwig, J. F. *Tetrahedron* **2008**, *64*, 6824.
(141) Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709.
(142) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913.
(143) Tanuwidjaja, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626.
(144) Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3163.
(145) Han, Z.; Koenig, S. G.; Zhao, H.; Su, X.; Singh, S. P.; Bakale, R. P. *Org. Process Res. Dev.* **2007**, *11*, 726.
(146) Watzke, A.; Wilson, R. M.; O'Malley, S. J.; Bergman, R. G.; Ellman, J. A. *Synlett* **2007**, 2383.
(147) Chung, J.-U.; Kim, S. Y.; Lim, J.-O.; Choi, H.-K.; Kang, S.-U.; Yoon, H.-S.; Ryu, H.; Kang, D. W.; Lee, J.; Kang, B.; Choi, S.; Toth, A.; Pearce, L. V.; Pavlyukovets, V. A.; Lundberg, D. J.; Blumberg, P. M. *Bioorg. Med. Chem.* **2007**, *15*, 6043.
(148) Reddy, A. V.; Rao, S. U. B.; Narasimha, G. L.; Dubey, P. K. *Synth. Commun.* **2009**, *39*, 1451.
(149) Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, *8*, 139.
(150) Guijarro, D.; Pablo, O.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 5386.
(151) Reingruber, R.; Vanderheiden, S.; Wagner, A.; Nieger, M.; Muller, T.; Es-Sayed, M.; Braese, S. *Eur. J. Org. Chem.* **2008**, 3314.
(152) Reingruber, R.; Vanderheiden, S.; Muller, T.; Nieger, M.; Es-Sayed, M.; Braese, S. *Tetrahedron Lett.* **2009**, *50*, 3439.
(153) Shaw, A. W.; deSolms, S. J. *Tetrahedron Lett.* **2001**, *42*, 7173.
(154) de Solms, S. J.; Ciccarone, T. M.; MacTough, S. C.; Shaw, A. W.; Buser, C. A.; Ellis-Hutchings, M.; Fernandes, C.; Hamilton, K. A.; Huber, H. E.; Kohl, N. E.; Lobell, R. B.; Robinson, R. G.; Tsou, N. N.; Walsh, E. S.; Graham, S. L.; Beese, L. S.; Taylor, J. S. *J. Med. Chem.* **2003**, *46*, 2973.
(155) Asoh, K.; Kohchi, M.; Hyoudoh, I.; Ohtsuka, T.; Masubuchi, M.; Kawasaki, K.; Ebiike, H.; Shiratori, Y.; Fukami, T. A.; Kondoh, O.; Tsukaguchi, T.; Ishii, N.; Aoki, Y.; Shimma, N.; Sakaitani, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1753.
(156) Zhao, Y.-B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1849.
(157) Garcia Ruano, J. L.; Aleman, J.; Parra, A. *J. Am. Chem. Soc.* **2005**, *127*, 13048.
(158) Lee, A.; Ellman, J. A. *Org. Lett.* **2001**, *3*, 3707.
(159) (a) Higashibayashi, S.; Kohno, M.; Goto, T.; Suzuki, K.; Mori, T.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2004**, *45*, 3707. (b) Mori, T.; Higashibayashi, S.; Goto, T.; Kohno, M.; Satouchi, Y.;

Shinko, K.; Suzuki, K.; Suzuki, S.; Tohmiya, H.; Hashimoto, K.; Nakata, M. *Chem. Asian J.* **2008**, *3*, 984.
(160) Yoshida, K.; Yamaguchi, K.; Sone, T.; Unno, Y.; Asai, A.; Yokosawa, H.; Matsuda, A.; Arisawa, M.; Shuto, S. *Org. Lett.* **2008**, *10*, 3571.
(161) Yoshida, K.; Yamaguchi, K.; Mizuno, A.; Unno, Y.; Asai, A.; Sone, T.; Yokosawa, H.; Matsuda, A.; Arisawa, M.; Shuto, S. *Org. Biomol. Chem.* **2009**, *7*, 1868.
(162) Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850.
(163) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49.
(164) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.
(165) Wipf, P.; Pierce, J. G. *Org. Lett.* **2006**, *8*, 3375.
(166) Fuller, A. A.; Du, D.; Liu, F.; Davoren, J. E.; Bhabha, G.; Kroon, G.; Case, D. A.; Dyson, H. J.; Powers, E. T.; Wipf, P.; Gruebele, M.; Kelly, J. W. *Proc. Natl. Acad. Sci.* **2009**, *106*, 11067.
(167) Yin, C.; Hui, X.-P.; Xu, P.-F.; Niu, L.-F.; Chen, Y.-F.; Wang, B. *Adv. Synth. Catal.* **2009**, *351*, 357.
(168) Schomaker, J. M.; Toste, F. D.; Bergman, R. G. *Org. Lett.* **2009**, *11*, 3698.
(169) Dougherty, A. M.; McDonald, F. E.; Liotta, D. C.; Moody, S. J.; Pallas, D. C.; Pack, C. D.; Merrill, A. H. *Org. Lett.* **2006**, *8*, 649.
(170) Dong, Z.; Pyne, S. G. *Sulfur Lett.* **2002**, *25*, 37.
(171) (a) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349. (b) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.
(172) Wang, X.-Z.; Burke, T. R., Jr. *Synlett* **2004**, 469.
(173) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353.
(174) Grainger, R. S.; Welsh, E. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377.
(175) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608.
(176) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382.
(177) Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Thornton-Pett, M.; Sridharan, V. *Chem. Commun.* **2002**, 1372.
(178) Cooper, I. R.; Grigg, R.; Hardie, M. J.; MacLachlan, W. S.; Sridharan, V.; Thomas, W. A. *Tetrahedron Lett.* **2003**, *44*, 2283.
(179) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
(180) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777.
(181) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.
(182) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979.
(183) During the preparation of this manuscript, a study on the analogous α-benzoyloxyallylation was reported: Liu, M.; Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Chem.—Eur. J.* **2009**, *15*, 10217.
(184) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537.
(185) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291.
(186) Maji, M. S.; Frohlich, R.; Studer, A. *Org. Lett.* **2008**, *10*, 1847.
(187) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Org. Lett.* **2008**, *10*, 3109.
(188) Lettan, R. B., II; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227.
(189) Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *Synlett* **2006**, 1272.
(190) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941.
(191) Patterson, A. W.; Ellman, J. A. *J. Org. Chem.* **2006**, *71*, 7110.
(192) Patterson, A. W.; Wood, W. J. L.; Hornsby, M.; Lesley, S.; Spraggon, G.; Ellman, J. A. *J. Med. Chem.* **2006**, *49*, 6298.
(193) Alkynyl tertiary carbinamines **458** have also been utilized in the synthesis of potent inhibitors of the *T. cruzi* protease cruzain implicated as a target for the treatment of Chagas disease: Brak, K.; Doyle, P. S.; McKerrow, J. H.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6404.
(194) Chen, X.-Y.; Qiu, X.-L.; Qing, F.-L. *Tetrahedron* **2008**, *64*, 2301.
(195) Grigg, R.; McCaffrey, S.; Sridharan, V.; Fishwick, C. W. G.; Kilner, C.; Korn, S.; Bailey, K.; Blacker, J. *Tetrahedron* **2006**, *62*, 12159.
(196) Jacobsen, M. F.; Skrydstrup, T. *J. Org. Chem.* **2003**, *68*, 7112.
(197) Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.* **2005**, *105*, 425.
(198) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
(199) Herbert, J. M.; Frehel, D.; Vallee, E.; Kieffer, G.; Gouy, D.; Berger, Y.; Necciari, J.; Defreyn, G.; Maffrand, J. P. *Cardiovasc. Drug Rev.* **1993**, *11*, 180.
(200) Follmann, M.; Graul, F.; Schaefer, T.; Kopec, S.; Hamley, P. *Synlett* **2005**, 1009.
(201) Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077.
(202) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
(203) Andreassen, T.; Hansen, L.-K.; Gautun, O. R. *Eur. J. Org. Chem.* **2008**, 4871.
(204) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269.
(205) (a) Andreassen, T.; Haaland, T.; Hansen, L. K.; Gautun, O. R. *Tetrahedron Lett.* **2007**, *48*, 8413. (b) Andreassen, T.; Lorentzen, M.; Hansen, L.-K.; Gautun, O. R. *Tetrahedron* **2009**, *65*, 2806.
(206) Gu, C.-L.; Liu, L.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 5754.
(207) Shibasaki, M.; Kanai, M.; Mita, T. *Org. React.* **2008**, *70*, 1.
(208) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-h. *J. Org. Chem.* **1996**, *61*, 440.
(209) (a) Davis, F. A.; Srirajan, V. *J. Org. Chem.* **2000**, *65*, 3248. (b) Portonovo, P.; Liang, B.; Joullie, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 1451.
(210) Mabic, S.; Cordi, A. A. *Tetrahedron* **2001**, *57*, 8861.
(211) Plant, A.; Thompson, P.; Williams, D. M. *J. Org. Chem.* **2008**, *73*, 3714.
(212) Luo, Y.-C.; Zhang, H.-H.; Xu, P.-F. *Synlett* **2009**, 833.
(213) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704.
(214) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Synthesis* **2005**, 575.
(215) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433.
(216) Luo, Y.-C.; Zhang, H.-H.; Liu, Y.-Z.; Cheng, R.-L.; Xu, P.-F. *Tetrahedron: Asymmetry* **2009**, *20*, 1174.
(217) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; 2000.
(218) Chen, Q.; Yuan, C. *Synthesis* **2007**, 3779.
(219) During the preparation of this manuscript, the analogous addition of diethyl thiophosphonate to *N-tert*-butanesulfinyl aldimines and ketimines was also disclosed: Chen, Z.; Li, J.; Yuan, C. *Synthesis* **2009**, 3930.
(220) Chen, Q.; Li, J.; Yuan, C. *Synthesis* **2008**, 2986.
(221) Zhang, D.; Yuan, C. *Chem.—Eur. J.* **2008**, *14*, 6049.
(222) Borissenko, L.; Groll, M. *Chem. Rev.* **2007**, *107*, 687.
(223) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910.
(224) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036.
(225) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.
(226) For early reports on acetate enolate additions to *p*-toluenesulfinyl aldimines, see::(a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037–7039. (b) Fujusawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881–3884.
(227) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.
(228) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932.
(229) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276.
(230) Brinner, K.; Doughan, B.; Poon, D. J. *Synlett* **2009**, 991.
(231) During the preparation of this manuscipt, the highly diastereoselective addition of a samarium enolate (derived from the corresponding α-chloroester) to an *N-tert*-butanesulfinyl imine was reported: Concellon, J. M.; Rodriguez-Solla, H.; Simal, C. *Adv. Synth. Catal.* **2009**, *351*, 1238.
(232) Girgis, M. J.; Liang, J. K.; Du, Z.; Slade, J.; Prasad, K. *Org. Process Res. Dev.* **2009**, *13*, 1094.
(233) Davis, F. A.; Qiu, H.; Song, M.; Gaddiraju, N. V. *J. Org. Chem.* **2009**, *74*, 2798.
(234) Grigg, R.; Blacker, J.; Kilner, C.; McCaffrey, S.; Savic, V.; Sridharan, V. *Tetrahedron* **2008**, *64*, 8177.
(235) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577.
(236) Tjoeng, F. S.; Toth, M. V.; McMackins, D. E.; Adams, S. P. U.S. Patent 5314902, 1994.
(237) Lee, Y.; Silverman, R. B. *Org. Lett.* **2000**, *2*, 303.
(238) Backes, B. J.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 2322.
(239) (a) Lee, K.; Zhang, M.; Yang, D.; Burke, T. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3399. (b) Lee, K.; Zhang, M.; Liu, H.; Yang, D.; Burke, T. R., Jr. *J. Med. Chem.* **2003**, *46*, 2621.
(240) (a) Gao, Y.; Voigt, J.; Wu, J. X.; Yang, D.; Burke, T. R., Jr. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1889. (b) Wei, C.-Q.; Gao, Y.; Lee, K.; Guo, R.; Li, B.; Zhang, M.; Yang, D.; Burke, T. R. *J. Med. Chem.* **2002**, *46*, 244.
(241) Wen, S.; Carey, K. L.; Nakao, Y.; Fusetani, N.; Packham, G.; Ganesan, A. *Org. Lett.* **2007**, *9*, 1105.
(242) Edmondson, S. D.; Wei, L.; Xu, J.; Shang, J.; Xu, S.; Pang, J.; Chaudhary, A.; Dean, D. C.; He, H.; Leiting, B.; Lyons, K. A.; Patel, R. A.; Patel, S. B.; Scapin, G.; Wu, J. K.; Beconi, M. G.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2409.
(243) Thomas, E. J.; Vickers, C. F. *Tetrahedron: Asymmetry* **2009**, *20*, 970.
(244) Shimamura, H.; Gouda, H.; Nagai, K.; Hirose, T.; Ichioka, M.; Furuya, Y.; Kobayashi, Y.; Hirono, S.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 914.
(245) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **1984**, *23*, 556. (b) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed.* **1983**, *22*, 989.
(246) Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841.

(247) Wang, Y.; He, Q.-F.; Wang, H.-W.; Zhou, X.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588.
(248) Ke, B.; Qin, Y.; Zhao, F.; Qu, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4783.
(249) Burnett, C. M.; Williams, R. M. *Tetrahedron Lett.* **2009**, *50*, 5449.
(250) Guerrini, A.; Varchi, G.; Daniele, R.; Samori, C.; Battaglia, A. *Tetrahedron* **2007**, *63*, 7949.
(251) Guerrini, A.; Varchi, G.; Battaglia, A. *J. Org. Chem.* **2006**, *71*, 6785.
(252) Guerrini, A.; Varchi, G.; Samori, C.; Daniele, R.; Arturo, B. *Tetrahedron Lett.* **2007**, *48*, 5081.
(253) Guerrini, A.; Varchi, G.; Samori, C.; Battaglia, A. *Eur. J. Org. Chem.* **2008**, 3834.
(254) Huang, H.; Guo, X.; Hu, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337.
(255) Chen, Q.; Yuan, C. *Synthesis* **2008**, 1085.
(256) Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 5227.
(257) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2008**, *49*, 2343.
(258) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 2547.
(259) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.
(260) Arefalk, A.; Wannberg, J.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2006**, *71*, 1265.
(261) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184.
(262) Davis, F. A.; Gaspari, P. M.; Nolt, B.; Xu, P. *J. Org. Chem.* **2008**, *73*, 9619.
(263) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413.
(264) Mukaiyama, T.; Michida, M. *Chem. Lett.* **2007**, *36*, 1244.
(265) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **2002**, *55*, 4515.
(266) Nemoto, H.; Moriguchi, H.; Ma, R.; Kawamura, T.; Kamiya, M.; Shibuya, M. *Tetrahedron: Asymmetry* **2007**, *18*, 383.
(267) Zhang, D.; Yuan, C. *Chem.—Eur. J.* **2009**, *15*, 4088.
(268) Harried, S. S.; Croghan, M. D.; Kaller, M. R.; Lopez, P.; Zhong, W.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2009**, *74*, 5975.
(269) Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007**, *9*, 149.
(270) The analogous *N*-acetylthiazolidinethione was also synthesized from an α-chloro-*N*-*tert*-butanesulfinyl imine.
(271) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; Lo Grasso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 490.
(272) Yendapally, R.; Lee, R. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1607.
(273) Konno, T.; Moriyasu, K.; Ishihara, T. *Synthesis* **2009**, 1087.
(274) Xiao, D.; Wang, C.; Palani, A.; Reichard, G.; Aslanian, R.; Shih, N.-Y.; Buevich, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2596.
(275) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445.
(276) Jung, P. M. J.; Beaudegnies, R.; De Mesmaeker, A.; Wendeborn, S. *Tetrahedron Lett.* **2003**, *44*, 293.
(277) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495.
(278) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7317.
(279) Raunkjr, M.; El Oualid, F.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Org. Lett.* **2004**, *6*, 3167.
(280) Risseeuw, M. D. P.; Mazurek, J.; Van Langenvelde, A.; Van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Org. Biomol. Chem.* **2007**, *5*, 2311.
(281) Ko, C. H.; Jung, D. Y.; Kim, M. K.; Kim, Y. H. *Synlett* **2005**, 304.
(282) Chemla, F.; Ferreira, F. *Synlett* **2006**, 2613.
(283) Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235.
(284) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358.
(285) Voituriez, A.; Ferreira, F.; Perez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705.
(286) Seguin, C.; Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *J. Org. Chem.* **2009**, *74*, 6986.
(287) Voituriez, A.; Perez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Org. Lett.* **2009**, *11*, 931.
(288) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *J. Org. Chem.* **2009**, *74*, 2238.
(289) Palais, L.; Chemla, F.; Ferreira, F. *Synlett* **2006**, 1039.
(290) Concellon, J. M.; Riego, E.; Rivero, I. A.; Ochoa, A. *J. Org. Chem.* **2004**, *69*, 6244.
(291) Hodgson, D. M.; Hughes, S. P.; Thompson, A. L.; Heightman, T. D. *Org. Lett.* **2008**, *10*, 3453.
(292) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956.
(293) Lin, X.; Bentley, P. A.; Xie, H. *Tetrahedron Lett.* **2005**, *46*, 7849.
(294) (a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126. (b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.-i.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.
(295) Wang, B.; Wang, Y.-J. *Org. Lett.* **2009**, *11*, 3410.
(296) Ianni, J. C.; Annamalai, V.; Phuan, P.-W.; Panda, M.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 5502.
(297) Liu, R.-H.; Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2008**, *73*, 3307.
(298) Liu, R.-C.; Wei, J.-H.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 2731.
(299) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215.
(300) Wang, R.; Fang, K.; Sun, B.-F.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2009**, 2301.
(301) Wang, B.; Liu, R.-H. *Eur. J. Org. Chem.* **2009**, 2845.
(302) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446.
(303) Liu, J.; Li, Y.; Hu, J. *J. Org. Chem.* **2007**, *72*, 3119.
(304) Sun, X.; Wang, S.; Sun, S.; Zhu, J.; Deng, J. *Synlett* **2005**, 2776.
(305) Sun, X.; Hu, Y.; Fan, C.; Xiao, W. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2009**, *E65*, o172.
(306) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747.
(307) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953.
(308) Masson, G.; Py, S.; Vallee, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772.
(309) (a) Masson, G.; Cividino, P.; Py, S.; Vallee, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265. (b) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229.
(310) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289.
(311) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **2002**, *55*, 5190.
(312) Peltier, H. M.; McMahon, J. P.; Patterson, A. W.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 16018.
(313) Patterson, A. W.; Peltier, H. M.; Sasse, F.; Ellman, J. A. *Chem.—Eur. J.* **2007**, *13*, 9534.
(314) Patterson, A. W.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 4362.
(315) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.
(316) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Synthesis* **2009**, 2083.
(317) Kato, T.; Marubayashi, K.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3693.
(318) (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Kirk, K. L. *Curr. Top. Med. Chem.* **2006**, *6*, 1445.
(319) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589.
(320) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77.
(321) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.
(322) Estivill, C.; Mendizabal, J.; Virgili, A.; Monteagudo, E.; Flor, T.; Sanchez-Ferrando, F.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron* **2008**, *65*, 171.
(323) Truong, V. L.; Pfeiffer, J. Y. *Tetrahedron Lett.* **2009**, *50*, 1633.
(324) (a) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216. (b) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457. (c) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5203. (d) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315. (e) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Eur. J. Org. Chem.* **2005**, 2218.
(325) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882.
(326) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693.
(327) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273.
(328) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489.
(329) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913.
(330) Liu, J.; Zhang, L.; Hu, J. *Org. Lett.* **2008**, *10*, 5377.
(331) (a) Montavon, T. J.; Christianson, C. V.; Festin, G. M.; Shen, B.; Bruner, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3099. (b) Christianson, C. V.; Montavon, T. J.; Festin, G. M.; Cooke, H. A.; Shen, B.; Bruner, S. D. *J. Am. Chem. Soc.* **2007**, *129*, 15744.
(332) Pierry, C.; Zoute, L.; Jubault, P.; Pfund, E.; Lequeux, T.; Cahard, D.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron Lett.* **2009**, *50*, 264.
(333) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 1290.
(334) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707.
(335) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215.
(336) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666.
(337) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403.
(338) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035.
(339) Sieburth, S. M.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311.

(340) Nielsen, L.; Skrydstrup, T. *J. Am. Chem. Soc.* **2008**, *130*, 13145.
(341) Fernandez, I.; Valdivia, V.; Gori, B.; Alcudia, F.; Alvarez, E.; Khiar, N. *Org. Lett.* **2005**, *7*, 1307.
(342) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Synlett* **2003**, 1985.
(343) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Chem. Commun.* **2006**, 1833.
(344) Hannam, J.; Harrison, T.; Heath, F.; Madin, A.; Merchant, K. *Synlett* **2006**, 833.
(345) Forbes, D. C.; Bettigeri, S. V.; Amin, S. R.; Bean, C. J.; Law, A. M.; Stockman, R. A. *Synth. Commun.* **2009**, *39*, 2405.
(346) Forbes, D. C.; Bettigeri, S. V.; Pischek, S. C. *Chem. Commun.* **2009**, 1882.
(347) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Org. Lett.* **2004**, *6*, 2377.
(348) Chigboh, K.; Morton, D.; Nadin, A.; Stockman, R. A. *Tetrahedron Lett.* **2008**, *49*, 4768.
(349) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066.
(350) Kokotos, C. G.; Aggarwal, V. K. *Org. Lett.* **2007**, *9*, 2099.
(351) Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2005**, *127*, 12222.
(352) Zheng, J.-C.; Liao, W.-W.; Sun, X.-X.; Sun, X.-L.; Tang, Y.; Dai, L.-X.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5789.
(353) (a) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410. (b) Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894.
(354) Luisi, R.; Capriati, V.; Florio, S.; Di Cunto, P.; Musio, B. *Tetrahedron* **2005**, *61*, 3251.
(355) Chemla, F.; Ferreira, F. *Synlett* **2004**, 983.
(356) (a) Chemla, F.; Ferreira, F.; Hebbe, V.; Stercklen, E. *Eur. J. Org. Chem.* **2002**, 1385. (b) Chemla, F.; Hebbe, V.; Normant, J. F. *Tetrahedron Lett.* **1999**, *40*, 8093.
(357) Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244.
(358) Ferreira, F.; Audouin, M.; Chemla, F. *Chem.—Eur. J.* **2005**, *11*, 5269.
(359) Hodgson, D. M.; Kloesges, J.; Evans, B. *Org. Lett.* **2008**, *10*, 2781.
(360) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 3211.
(361) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 5662.
(362) Backes, B. J.; Dragoli, D. R.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 5472.
(363) (a) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309. (b) Scott, M. E.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 8154.
(364) Kawecki, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1420.
(365) Davis, F. A.; Qu, J.; Srirajan, V.; Joseph, R.; Titus, D. D. *Heterocycles* **2002**, *58*, 251.
(366) (a) Coulomb, J.; Certal, V.; Fensterbank, L.; Lacote, E.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 633. (b) Coulomb, J.; Certal, V.; Larraufie, M.-H.; Ollivier, C.; Corbet, J.-P.; Mignani, G.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem.—Eur. J.* **2009**, *15*, 10225.
(367) Dondas, H. A.; De Kimpe, N. *Tetrahedron Lett.* **2005**, *46*, 4179.
(368) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751.
(369) Brak, K.; Barrett, K. T.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 3606.
(370) Li, B. F.; Yuan, K.; Dai, L. X.; Hou, X. L. *Synlett* **2005**, 535.
(371) Schenkel, L. B. Ph. D. Thesis, University of California, Berkeley, 2005.
(372) Leemans, E.; Mangelinckx, S.; De Kimpe, N. *Synlett* **2009**, 1265.
(373) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604.
(374) Richey, H. G., Jr.; Farkas, J., Jr. *J. Org. Chem.* **1987**, *52*, 479.
(375) Leca, D.; Song, K.; Amatore, M.; Fensterbank, L.; Lacote, E.; Malacria, M. *Chem.—Eur. J.* **2004**, *10*, 906.
(376) Ruano, J. L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008**, 311.
(377) (a) Ruano, J. L. G.; Aleman, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, *7*, 179. (b) Ruano, J. L. G.; Aleman, J.; Parra, A.; Cid, M. B. *Org. Synth.* **2007**, *84*, 129.
(378) Ruano, J. L. G.; Aleman, J.; Fajardo, C.; Parra, A. *Org. Lett.* **2005**, *7*, 5493.
(379) Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234.
(380) Hodgson, D. M.; Kloesges, J.; Evans, B. *Synthesis* **2009**, 1923.
(381) (a) Hodgson, D. M.; Miles, T. J.; Witherington, J. *Synlett* **2002**, 310. (b) Hodgson, D. M.; Miles, T. J.; Witherington, J. *Tetrahedron* **2003**, *59*, 9729. (c) Hodgson, D. M.; Maxwell, C. R.; Miles, T. J.; Paruch, E.; Matthews, I. R.; Witherington, J. *Tetrahedron* **2004**, *60*, 3611.
(382) (a) Medjahdi, M.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Heterocycles* **2008**, *76*, 569. (b) Medjahdi, M.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 7859.
(383) Tanuwidjaja, J.; Peltier, H. M.; Lewis, J. C.; Schenkel, L. B.; Ellman, J. A. *Synthesis* **2007**, 3385.
(384) Zhu, C.; Shi, Y.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1243.
(385) (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (b) Worch, C.; Mayer, A. C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; 2008.
(386) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
(387) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Editors Comprehensive Asymmetric Catalysis*; Springer: New York, 1999.
(388) Kagan, H. B. *Synlett* **2001**; 0888.
(389) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. *Synlett* **2002**; 0399.
(390) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
(391) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545.
(392) Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800.
(393) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897.
(394) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283.
(395) Zani, L.; Eriksson, L.; Adolfsson, H. *Eur. J. Org. Chem.* **2008**, 4655.
(396) (a) Sola, J.; Reves, M.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 5020. (b) Ji, Y.; Riera, A.; Verdaguer, X. *Org. Lett.* **2009**, *11*, 4346.
(397) Reves, M.; Achard, T.; Sola, J.; Riera, A.; Verdaguer, X. *J. Org. Chem.* **2008**, *73*, 7080.
(398) Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledo, A.; Verdaguer, X.; Riera, A. *Org. Biomol. Chem.* **2008**, *6*, 4649.
(399) Dembowski, U.; Noltemeyer, M.; Gilje, J. W.; Roesky, H. W. *Chem. Ber.* **1991**, *124*, 1917.
(400) Achard, T.; Benet-Buchholz, J.; Riera, A.; Verdaguer, X. *Organometallics* **2009**, *28*, 480.
(401) Ruck, R. T.; Bergman, R. G. *Organometallics* **2004**, *23*, 2231.
(402) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315.
(403) Very recently, the use of sulfinamide derived Lewis basic catalysts containing diverse sulfinyl groups, including *tert*-butyl, for addition of allylsilanes to aldehydes and hydrazones was also reported: Fulton, J. R.; Kamara, L. M.; Morton, S. C.; Rowlands, G. J. *Tetrahedron* **2009**, *65*, 9134.
(404) Huang, Z.; Lai, H.; Qin, Y. *J. Org. Chem.* **2007**, *72*, 1373.
(405) Pei, D.; Zhang, Y.; Wei, S.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, *350*, 619.
(406) Wang, C.; Wu, X.; Zhou, L.; Sun, J. *Chem.—Eur. J.* **2008**, *14*, 8789.
(407) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.
(408) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754.
(409) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.

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