Asymmetric Sulfa-Michael Additions

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Abstract: Numerous asymmetric methods have been developed over the past 30 years to effect the Michael reaction of sulfur donors and Michael acceptors. Many of these stoichiometric and catalytic methods are complementary to one another, each having a certain range of substrate tolerance. Organocatalysis has a place at the origin of this field in the discovery of cinchona alkaloid catalyzed sulfa-Michael reactions. At the same time, it is involved in the current state-of-the-art as several elegant tandem processes that employ secondary amine catalysts and involve initial sulfa-Michael additions have been developed.

1 Introduction

Sulfur-containing compounds can be found in all living organisms and, therefore, play an important role in biochemistry (for example, biotin, protein cross-linking agents, ligands in bio-inorganic complexes).1 Biosynthetically, sulfur functionalities are introduced by a variety of chemical processes, including the sulfa-Michael addition: coenzyme M is synthesized in methanogenic bacteria involving an initial reaction of bisulfite (1) and phospho-enolpyruvate (2) to form acid 3 (Scheme 1).2

Synthetically, sulfur–carbon bonds can be introduced by a variety of methods, including thiocarbonylation and insertion of unsaturated compounds into sulfur–sulfur bonds, and this work has been reviewed previously.3,4 Of these methods, the sulfa-Michael addition (SMA), the reaction of a sulfur nucleophile and carbon–carbon multiple bond electrophile activated by an electron-withdrawing group, plays an important role (Scheme 2, route A). This is in part due to the diversity of nucleophilic and electrophilic components available and reactive in this transformation. Furthermore, nitrogen- and oxygen-containing compounds of this type can be easily prepared in Mannich and aldol reactions, respectively (Scheme 2, route B). However, the aldol reactions involving thiocarbonyl electrophiles are of limited synthetic viability because thiocarbonyl compounds can be poor electrophiles, unstable under the aldol reaction conditions, and difficult to synthesize (Scheme 2).5

In similarity to all Michael additions, the SMA has the potential to create two stereogenic centers in one synthetic step when an appropriately substituted Michael acceptor is employed. In addition, sulfur functionality can be readily removed by oxidative or reductive means, or converted into other useful functional groups such as sulfoxides or disulfides, placing further importance on the asymmetric synthesis of sulfur-containing compounds.

Scheme 1

Scheme 2

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The Michael addition of carbon, nitrogen and other nucleophiles has been extensively reviewed. However, only a small body of work is in existence that provides an overview of the sulfa-Michael addition. Moreover, to date, there is no comprehensive review of the asymmetric SMA. Therefore, we attempt in this review to cover the advances in this field from its onset in the 1970s up to the present day.

2 Stoichiometric Reactions

2.1 Chiral Michael Acceptors

In 1989, Effenberger et al. used proline- and prolinol-derived chiral auxiliaries to effect the diastereoselective addition of thiocarboxylic acids to attached methacryloyl substrates (Scheme 3). Proline (X = OH) and N,N-dialkylamide (X = NMe₂) auxiliaries were ineffective (0–8% de), whereas N-alkylamide auxiliaries (X = NHMe, NHEt) produced moderate levels of diastereocontrol (80% de). In the case of the attached N-alkylamide products, the major diastereomer (S,R)-6 could be separated from its diastereomeric impurity (S,S)-6 by fractional dissolution. The authors proposed that, in the stereochemically relevant step, an intramolecular protonation reaction with zwitterion 7 occurred. Notably, the C₂-symmetric (2S,5S)-2,5-bis(dimethylcarboxamido)pyrrolidine was found to control the SMA with excellent levels of asymmetric induction (>99% de) in a few cases.

Using bis(alkyl)pyrrolidine auxiliaries and, Kim et al. utilized an SMA involving thioacetic acid in the synthesis of the ACE inhibitor, captopril (13).

Biographical Sketches

Dieter Enders was born in 1946 in Butzbach, Germany. He studied chemistry at the Justus Liebig University Gießen and received his Dr. rer. nat. under the supervision of Professor D. Seebach in 1974. After postdoctoral studies at Harvard University with Professor E. J. Corey he returned to Gießen, obtaining his habilitation in 1979. In 1980 he moved to the University of Bonn as an associate professor and in 1985 to his present position as Professor of Organic Chemistry at the Rheinisch-Westfälische Technische Hochschule Aachen. His current research interests are asymmetric synthesis, new synthetic methods using organometallics, the stereoselective synthesis of biologically active compounds, and organocatalysis. He has been the recipient of many prizes, among them the Leibniz Prize (Deutsche Forschungsgemeinschaft), the Yamada Prize (Japan), the Max Planck Research Award (Max Planck Gesellschaft and Alexander von Humboldt Foundation) and the Emil Fischer Medal (Gesellschaft Deutscher Chemiker).

Karsten Lüttgen, born in 1978 in Düren (Germany), studied chemistry at the RWTH Aachen and the University of York. He obtained his Dr. rer. nat. in 2006 under the guidance of Prof. D. Enders with a thesis titled ‘Towards the total synthesis of galbonolide A and B’. Since October 2006, he has been working as a process development chemist with DSM in Linz (Austria).

Arun Narine was born in Penticton, BC, Canada in 1977 and began university training at Okanagan University College (B.Sc., 1999). He completed his doctoral studies at Simon Fraser University in the area of synthetic organic chemistry (Ph.D., 2004) under the direction of Prof. Peter D. Wilson. In 2004, he took up a post-doctoral fellowship at SFU with Prof. Andrew J. Bennet in the area of chemical biology, studying an enzyme involved in the lifecycle of the influenza virus, and working on the synthesis of a potential anti-influenza drug. In 2006, he received an Alexander von Humboldt Research Fellowship to conduct research in the group of Prof. Dieter Enders at RWTH Aachen (Germany), where he is currently engaged in the development of new metal-free catalysts and the application of organocatalysis to carbohydrate synthesis and tandem, multicomponent reactions.
The SMA was found to proceed with essentially complete diastereoselection. Harsh conditions (3 M hydrochloric acid, reflux) were required to cleave the amide linkage of the SMA products; however, negligible (3%) racemization was observed. The authors found that the use of proline, which is also a moiety in captopril (13), as a chiral auxiliary led to low levels of diastereoselection. Here, the authors proposed that, in the stereochemically relevant step, an intermolecular protonation reaction of s-cis-amide conformer by thioacetic acid (9) afforded the observed diastereomer 10.

Under Lewis acid catalysis, the reaction rates for thioacids 5 were faster, but the diastereoselectivities were severely eroded (6–10% de with TiCl4). However, for aliphatic and aromatic thiol SMAs, Lewis acid catalysis was required. For these substrates, when conversions were generally high, the reaction diastereoselectivities varied considerably (50–82% de).

Mechanistically, for thiocarboxylic acids 5, the nucleophile can protonate the enolate intermediate to generate chelate 16 which is then protonated stereoselectively from the more accessible Re-face (Figure 1). Titanium(IV) chloride was suggested to form mixtures of chelates 17 and 18, with and without sulfur coordination, each reacting via their diastereotopic faces and leading to lower observed diastereoselectivities.

Tomioka et al. reported a comparable approach to synthesize β-(phenylthio)carboxylate derivatives 21. After extensive optimization, modifying the nucleophile counterion and Lewis acid catalyst, the SMA to the acceptors 19 using catalytic quantities of lithium thiophenolate (PhSLi) in the presence of stoichiometric magnesium perchlorate and excess thiophenol (20) proceeded with essentially complete diastereocentrol (98% de) (Scheme 6). If either lithium thiophenolate or magnesium perchlorate were omitted, the reaction only proceeded in moderate selectivity (70% de). Interestingly, in the absence of magnesium perchlorate, the SMA became nonselective (4% de) when performed with stoichiometric lithium thiophenolate (2 equiv) was used (30% de). This phenomenon was attributed to formation of either a monometallic syn-chelate 22 or bimetallic anti-chelate 23 as reactive intermediates when catalytic or excess lithium thiophenolate, respectively, was employed.
Under the optimized reactions conditions, various α,β-unsaturated imides 24 were found to react with thiophenol (20) to form the 1,4-adducts 25 in moderate to excellent yields as well as diastereoselectivities (70–98% de) (Scheme 7).

Naito and co-workers developed an SMA whereby two contiguous stereogenic centers could be created. Thus, thiophenol and isomeric E- and Z-imides (E)-26 and (Z)-26 were found to react readily at low temperature and afford the 1,4-adducts 27 and 28 in good yield and diastereoselectivity (Scheme 8). Interestingly, thiophenol added to the isomeric imides (E)-26 and (Z)-26 to give doubly epimeric Michael products 27 and 28. Thus, an Evans oxazolidinone of the same absolute configuration could be used to prepare enantiomeric thioacid products. Mechanistically, the authors suggested that, following the initial Michael addition of imides (E)-26 and (Z)-26 to give the epimeric enolates 29 and 30, the stereoselectivity of the subsequent protonation reaction was controlled by the newly formed β-stereocenter, and not by the oxazolidinone auxiliary.

Naito and co-workers utilized this sulfa-Michael methodology in the formal total synthesis of the calcium-channel blocker, (+)-diltiazem (37) (Scheme 9). A 4-methoxycinnamoyl imide 31 was reacted with a mixture of 2-aminothiophenol (32) and lithium 2-aminothiophenate (33) to afford the Michael adduct 34 in moderate diastereoselectivity (64% de). Exposure of this inseparable diastereomeric mixture 34 to trimethyl aluminum cleaved the auxiliary and the resulting amino acid cyclized spontaneously to the lactam 35, from which its diastereomeric impurity could now be removed. Finally, deprotection with titanium(IV) chloride afforded the alcohol 36, which had previously been transformed into the drug (+)-diltiazem (37).
ical integrity. Derivatives of the Oppolzer auxiliary have also been synthesized for use in the SMA; however, no improvement in diastereoselectivity has been observed.\(^\text{23}\)

In their synthesis of (+)-trans-whisky lactone 46 (R = Bu) and (+)-trans-cognac lactone 46 (R = pentyl), Naito and co-workers utilized an SMA, here with the enantiomeric Oppolzer sultam ent-42, which installed the two stereogenic centers of these simple natural products 46 (Scheme 11).\(^\text{24}\) The methacrylates 43 were reacted with thiophenol in the presence of catalytic amounts of lithium thiophenate to form adduct 44 in 83% yield, ‘in addition to small amounts of unidentified diastereoisomers’. Following auxiliary removal and homologation, the natural product synthesis was completed in an intramolecular carboxylate displacement reaction of a sulfonyl ion 45.

**Scheme 11**

Wu and co-workers performed SMAs of substituted N-enoylsultams 47 and thiols 48 in the presence of several Lewis acids (Scheme 12).\(^\text{25}\) Although boron trifluoride–diethyl etherate and diethylaluminum chloride gave either no conversion or low diastereoselectivity, respectively, titanium(IV) chloride was found to promote the reaction efficiently in certain cases. Sulfur nucleophiles 48 containing additional heterofunctionality provided the highest levels of asymmetric induction. The authors proposed a transition state where coordination of the additional heterofunctionality of these nucleophiles 48 (e.g., thiobenzoic acid) to the metal center of the titanium–Michael acceptor complex directed the nucleophile approach in a highly stereoselective fashion.

The SMA of thiols and cinnamoyl substrates attached to chiro-inositol auxiliaries was reported by Hoberg and co-workers in 2004 (Scheme 13).\(^\text{26}\) Lithium salts of various electron-rich thiophenols and benzylthiol 51 reacted with the enoates 50 in good yield with complete diastereoselection (>98% de). Interestingly, electron-poor thiophenol 51 (R = 4-O\(_2\)NC\(_6\)H\(_4\)) was unreactive and an aliphatic thiol 51 (R = isopentyl) reacted, but in low diastereoselectivity (~50% de). Using an enantiomeric auxiliary, the authors also prepared an enantiomeric product, in one case. Removal of the chiral auxiliary was achieved in a base-promoted hydrolysis reaction, without racemization of the \(\beta\)-thioacid products 53.

**Scheme 12**

**Scheme 13**

### 2.2 Chiral Sulfur Donors

Tomioka and co-workers used a protected isoborneol thiol to develop a tandem sulfa-Michael/intramolecular aldol reaction (Scheme 14).\(^\text{27}\) Addition of the lithium salt of thiol 55 to the aldehyde-ester 54 afforded, in both cases, a 4:1 ratio of the cycloadducts 57 and 58 (\(n = 0, 1\)). This ratio represents the diastereoselectivity of the initial SMA, as the subsequent aldol reaction was demonstrated to proceed solely in a syn-stereoselective fashion. Removal of the isoborneol auxiliary was not described, though the cycloalkanes 57 and 58 could be treated with Raney nickel to remove the entire isoborneol thiol group and afford chiral \(\beta\)-hydroxyster products. Of note, the reaction was less efficient when the isoborneol-modified thiol 62 (see Scheme 16) was used, presumably due to quenching of the enolate intermediate 56 by the unprotected hydroxyl substituent of thiol 62.

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(S)-Phosphorodithioate 60 has been used previously in the formal 1,2-addition reaction of hydrogen sulfide and alkenes.28 Recent investigations in our group have demonstrated that (E)-cinnamaldehyde (59) and dithioate 60 react in moderate yield and high diastereoselectivity (Scheme 15).29

Scheme 15

The β-thioalcohol product 61 was obtained in 92% ee following reductive auxiliary removal. The method does not appear to be general, as low diastereoselection (30% de) was observed with aliphatic α,β-unsaturated aldehydes.

Node and co-workers have performed dimethylaluminum chloride promoted SMAs using isoborneol-modified thiol 62 (Scheme 16).30 Adducts 64 were obtained in good to excellent diastereoselectivity (75–96% de) and the SMA tolerated α,β-unsaturated amides and esters 63 with significant variation in α-substitution. The β-thiocarbonyl products 65 were removed from the isoborneol auxiliary (destroyed under reaction conditions) in a boron trifluoride–diethyl etherate promoted Wagner–Meerwein rearrangement (WMR)/thiol-exchange reaction without loss of stereochemical integrity in the products (≥98% ee). Presumably, the reactive vinyl sulfides 66 formed in the initial WMR then reacted with dodecanethiol to release β-thio alcohols 65.

2.3 Tandem Sulfamichael/Meerwein–Ponndorf–Verley Reduction Reactions

In 1996, Node and co-workers reported a novel tandem sulfamichael/reduction reaction whereby α,β-unsaturated ketones could be stereoselectively reduced to chiral alcohols.31 Mechanistically, the reaction sequence involves a Lewis acid promoted SMA of a chiral 1,3-thioalcohol 68 and α,β-unsaturated ketone 67 to form a ten-membered metallocycle intermediate 69 (Scheme 17). Subsequent 1,7-hydride shift within this transient species 69 in a Meerwein–Ponndorf–Verley (MPV) reduction generates the attached chiral alcohol 71 via the intermediacy of a second metallocycle 70. Finally, the chiral allylic, aliphatic or β-thio alcohol product 72, 73 or 74 can, in theory, be liberated by oxidative or reductive desulfurization, or auxiliary cleavage, respectively.

In the first instance, the isoborneol-modified thiol 62 was reacted with a series of α,β-unsaturated ketones 75 in the presence of dimethylaluminum chloride at room temperature to produce the tandem Michael/MPV adducts in good to excellent yield (Scheme 18).31 In most cases, only a single diastereoisomer, 76, was observed by 1H NMR spectroscopic analysis. Reductive desulfurization proceeded in good to excellent yield and the chiral alcohol products 78 were obtained in high enantiomeric purity (89–98% ee) (Scheme 19). Of note, for aliphatic α,β-unsaturated ketones 75, the desulfurization reaction was performed following benzyolation of the alcohol moiety of adduct 76. An oxidative desulfurization protocol was also developed, which efficiently produced allylic alcohols 77 from the tandem Michael/MPV adducts 76.32 In several subsequent reports, Node et al. examined the use of other chiral 1,3-thioalcohols 79 and 80 in the tandem sulfamichael/MPV reaction, and discovered that these chiral scaffolds could also produce high levels of asymmetric induction (Figure 2). The pulegone-derived thiol 79 was briefly examined, and, although able to induce a high level of asymmetric induction, gave a poor yield of the desired tandem sulfa-Michael/MPV product. The camphor-derived thiol 80 was, however, found to be effective in terms of both chemical yield and asymmetric induction.
The products 81 from the tandem sulfa-Michael/MVP reaction with camphor-derived thiol 80 could also be converted into \( \beta \)-thio alcohols 82 (Scheme 20). This was accomplished in a base-catalyzed elimination reaction trapping the reactive enone intermediate 83 with an external sulfur nucleophile. The isoborneol-derived products 76 were unreactive in this process as they lack a \( \beta \)-hydrogen.

More recently, the same group discovered a two-step protocol for the release of \( \beta \)-thio alcohols anti-82 from the isoborneol-derived products 81 (Scheme 21). Ketone 84 was reduced and diol 85 was exposed to boron trifluoride-diethyl etherate to effect a WMR/thiol-exchange reaction (see Scheme 16).

Of importance, the isoborneol- and camphor-derived thiols 71 and 76 are complementary as they produce diastereomeric anti or syn products 83, respectively, in generally good diastereoselectivity and high enantioselectivity.33
Node and co-workers have also developed a one-step protocol for the installation of three contiguous stereogenic centers into $\alpha,\beta$-unsaturated ketones (Scheme 22).35

![Scheme 22](image)

Employment of $\alpha,\beta$-disubstituted chalcones 86 ($R^3 = \text{Ph}$) in the tandem sulfa-Michael/MVP reaction afforded solely the 1,3-$\text{anti}$ products 87 and 88 in generally good yield. Within these products, the $\alpha$-stereocenter was formed highly stereoselectively ($87:88 = 92:8$ to 100:0, 84% de). However, other $\alpha,\beta$-unsaturated ketones ($R^3 = \text{i-Pr}, \text{Et}, \text{c-Hex}$) were found to react under these conditions in low to moderate yields (31–78%) and diastereoselectivities (16–60% de).

To improve reaction efficiency, Brønsted acid additives were screened. Node and co-workers found that pentafluorobenzoic acid (PFBA, $p\text{K}_a \sim 2$) could effectively increase both conversion and stereoselectivity, whereas both more ($p$-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid) and less acidic (benzoic acid, acetic acid, pentafluorophenol) co-catalysts performed less efficiently. Thus, addition of pentafluorobenzoic acid (1.5 equiv) resulted in moderate yields (50–71%) of adducts 87 and 88 in moderate to excellent diastereoselectivity (46–100% de). Of note, although the pentafluorobenzoic acid co-catalyst facilitated a more efficient tandem sulfa-Michael/MVP reaction, small amounts (5–14%) of the diastereomeric syn-1,3 products (syn-87, syn-88) were formed. Mechanistically, the authors speculate that pentafluorobenzoic acid takes part in a ligand-exchange reaction with the remaining methyl substituent on the aluminum center of the metallalcycle 69, with the resultant species being more reactive in the subsequent MVP reduction reaction (see Scheme 17). As before, the $\beta$-thio alcohol products could be revealed by lithium aluminum hydride reduction and Lewis acid promoted WMR/trans-thioetherification (see Scheme 21).

Node and co-workers have also used this methodology to synthesize whisky and cognac lactones 4636 (see Scheme 11) and conducted several investigations to elucidate the mechanism of the tandem sulfa-Michael/MVP reduction reaction.31,32 Based on equilibration and isotopic crossover experiments, the authors demonstrated that the process involved a dynamic kinetic resolution. The initial Michael products are formed reversibly and in low diastereoselectivity. This mixture is then resolved, as only one diastereomer is reactive in the subsequent highly stereoselective MVP reduction.

### 2.4 Formal Sulfa-Michael Additions by Intramolecular Sulfur Transfer

In 2001, Palomo et al. developed a new strategy to prepare $\beta$-thio alcohols and acids that relies on an intramolecular formal ‘SH’ transfer to $\alpha,\beta$-unsaturated imides.37 Conceptually, the sulfur-transfer reaction relies on a $[3,3]$-electrocyclic rearrangement of the oxazolidine-2-thione metal complex 90 to form the thiazine intermediates 92 (Scheme 23). This step constitutes a formal SMA as sulfur adds to the $\beta$-carbon of the $\alpha,\beta$-unsaturated imide 89. Subsequent hydrolysis of the thiazines 91 and 92 generates an attached $\beta$-thioacid derivative 93. In the first instance, Palomo et al. found that a variety of chiral $\alpha,\beta$-unsaturated imides 94 reacted readily in the presence of a Lewis acid to form, following hydrolysis, the desired products 95 in generally high diastereoselectivity (Scheme 24).37
The reaction tolerated both alkyl- and aryl-substituted substrates. However, whereas alkyl substrates 94 (R = alkyl) reacted with near complete diastereoselectivity, aromatic substrates 94 (R = aryl) were less reactive, necessitating warmer reaction temperatures, and lower levels of diastereoselectivity were observed. Interestingly, all of the chiral auxiliaries screened (96, 97) for the sulfur-transfer reaction gave nearly equally high diastereoselectivity. Reductive or hydrolytic removal of the chiral auxiliary released β-thio alcohol or β-thio acid products, respectively, in good yields. Of note, tin(IV) chloride, boron trifluoride–diethyl etherate, niobium(V) chloride and trimethylsilyl chloride have also been screened as Lewis acid catalysts – all lead to high diastereoselectivities (≥96% de for the same substrate) and niobium(V) chloride appears to give the best yields.38 Using this method, Ortiz et al. have prepared chiral 3-methylthio alcohols.39 Recently, Palomo et al. have found that the sulfur-transfer reaction can also proceed under Brønsted acid catalysis.40 This method is complementary to the Lewis acid promoted reaction, as enantiomeric products are obtained, again, in generally excellent stereoselectivity.

In 2004, Palomo et al. made a significant contribution to the field by extending this concept to the generation of quaternary C–S stereogenic centers (Scheme 25).41 A variety of β,β-disubstituted substrates 98, here under boron trifluoride–diethyl etherate catalysis, reacted in moderate to good yield and generally excellent diastereoselectivity. The authors also showed that both E- and Z-geometrical isomers of substrate 98 afforded product 99 of the same absolute configuration in identical diastereoselectivity. This suggests that the stereochemistry-determining step in this reaction is protonation of the boron enolate intermediate.

Scheme 25

Kataoka and co-workers have developed a tandem sulfa-Michael/aldol reaction that relies on an initial intramolecular ‘SH’ transfer reaction. Treatment of imide 100 and acetal 101 with tin(IV) chloride resulted in the highly diastereoselective formation of the 3-sulfanylpropionamides 102 containing three contiguous stereocenters (Scheme 26).42 The reaction was found to proceed only in the case of acetals 101 derived from aromatic aldehydes. Mechanistically, the authors propose that, following an intramolecular sulfur transfer, the intermediate tin enolate reacts with the oxonium ion 103 generated by Lewis acid promoted extrusion of methanol from acetal 101. Of note, using a less-hindered Evans oxazolidinone, Kataoka and co-workers have performed a similar tandem sulfa-Michael/aldol reaction. In this case, four contiguous stereocenters were produced as the auxiliary carbon–sulfur bond was less labile.41,44

Scheme 26

3 Chiral-Metal-Complex-Catalyzed Reactions

Sundararajan and co-workers have developed the heterobimetallic complex 107 for use in Michael additions.45–47

The ligand, synthesized in a variation of Trost’s original procedure46 from (R)-styrene oxide and benzylamine, was reacted with lithium aluminum hydride to afford the desired metal complex 107, which was used without prior isolation. In the SMA with cyclic enones 104, although yields were excellent (96–97%) and reaction rates extremely fast (1 min), relatively high catalyst loadings (0.3 equiv) were required, and only low to moderate enantioselectivities for product 106 resulted (26–45% ee) (Scheme 27).

Scheme 27

Tomioka and co-workers have developed a chiral tridentate amino ether 110 for use in the SMA of lithium thiophenolates.49 The synthesis of ligand 110 involved an aromatic nucleophilic substitution of the reactive chromium complex 109 with a chiral amino alcohol 108, fol-
Various 2-substituted thiophenols 112 were screened and both tert-butyl and trimethylsilyl substitutions were found to significantly increase the asymmetric induction (88% and 90% ee, respectively) with no decrease in yield. Interestingly, these more sterically demanding nucleophiles reacted more rapidly (1 h vs. 2–3 h). The silyl group of the product 113 (R = TMS) could be readily removed in quantitative yield by treatment with triflic acid, with no loss of stereochemical integrity of the product. Under optimized reaction conditions (–60 °C, 1:1 toluene–hexane), various α,β-unsaturated esters were reacted with 2-(trimethylsilyl)thiophenol (112, R = TMS) to afford the corresponding products in generally excellent yield (99%) and enantiomeric purity (93–97% ee). Exceptions were α,β-unsaturated esters bearing a branched side chain or a phenyl group.

In subsequent reports, Tomioka and co-workers evaluated ligands of modified structure, revealing the important structural features required for catalysis,52 and then extended the method to α,β-unsaturated ketones53 and the synthesis of several biologically relevant molecules.52 Furthermore, the metal-catalyzed SMA could be coupled with a substrate-directed enantioselective protonation reaction (Scheme 30).53 Following rate-determining sulfamido-Michael addition, unreacted thiophenol 116 rapidly protonated the intermediate enolate to afford the chiral α-alkyl esters 117 in moderate to high enantioselectivity.

Shibasaki and co-workers found that chiral heterobimetallic complexes, used previously in asymmetric Michael reactions involving malonates and organometallic reagents, could also catalyze the reaction of α,β-unsaturated carbonyl compounds and aromatic thiols.54 Under optimized reaction conditions, LaNa 3tris(binaphthoxide) (121) catalyzed the reaction of aromatic thiols 119 and cyclohex-2-en-1-one 118 (R1 = H, n = 2) rapidly (20 min) in moderate to good enantioselectivity (68–84% ee) (Scheme 31). Five- and seven-membered α,β-unsaturated ketones 118 could also be utilized. Although the seven-membered substrates 118 (n = 3) reacted with good levels of asymmetric induction (83% ee), extended reaction times (43 h) were required. β-Substitution of the ketone 118 (R1 = Me) was also detrimental to reaction rate.

In enantioselective protonation reactions, α-substituted α,β-unsaturated acrylates (R2 = OEt) and thioacrylates 122 (R2 = SEt) reacted with 4-(tert-butyl)thiophenol (123) in moderate to excellent yields and stereoselectivities (Scheme 32). Mechanistically, the authors proposed a bifunctional role of the metal complex 121 – both activating the α,β-unsaturated substrate by coordination to the central lanthanum atom, and directing nucleophilic attack via a sodium–thiophenolate interaction.
Shibasaki and co-workers have also used the heterobimetallic complex 121 in catalytic asymmetric sulfa-Michael/protonation reactions whereby racemic 5-methylbicyclo[3.3.0]oct-1-ene was kinetically resolved, and in the total synthesis of epothilones A and B.

Another type of tridentate chiral ligand, 4,6-dibenzo-furandiyl-2,2'-bis(4-phenyloxazoline) (DBFOX/Ph), has been developed by Kanemasa and co-workers for use in various cycloaddition reactions. Transition-metal perchlorate aqua complexes of this ligand are air-stable and highly active catalysts in the SMA. Imide 127 was reacted with thiols to afford the adducts in varying yield and generally high enantioselectivity (Scheme 33).

Magnesium perchlorate, zinc perchlorate hexahydrate, zinc trifluoromethanesulfonate and zinc iodide complexes prepared from the DBFOX/Ph ligand showed satisfactory catalytic activity but low enantioselectivity. Interestingly, performance of the reaction under anhydrous conditions (4 Å MS), or with a non-aqua complex, resulted in completely racemic product. The reaction efficiency was also highly dependent on solvent, temperature and additives. For example, in dichloromethane–methanol (1:1) and dichloromethane–ammonium chloride (aq) (10:1), under otherwise identical conditions, the magnitude of asymmetric induction changed from 82% ee to 27% ee, in favor of the opposite enantiomer. Furthermore, the presence of an amine co-catalyst [1,8-bis(dimethylamino)naphthalene] was found to increase both reaction rates and enantioselectivities (as the reaction could be performed at lower temperature). The authors propose that the amine co-catalyst increases the nucleophilicity of the thiol nucleophile.

The chiral $C_2$-symmetric N-oxide ligand 130, developed initially by Nakajima and co-workers for the catalytic enantioselective alkylation of aldehydes with allylitricho-roslanes, has also proved effective in the metal-catalyzed SMA (Scheme 34).

Among the various metal halides surveyed, cadmium iodide complexes promoted the reaction in good yield and moderate enantioselectivity (57% ee). Under optimized conditions (0.01 equiv complex, toluene, r.t.), a variety of cyclic and acyclic $\alpha,\beta$-unsaturated ketones and aldehydes and thiols were reacted to form $\beta$-thiocarbonyl compounds in generally good yield and up to 78% ee. However, from these studies, no clear structure–enantioselectivity relationship emerged. A brief mechanistic study revealed a slight positive nonlinear effect, indicating possible aggregation of the cadmium–ligand complex.

Kobayashi et al. have examined the use of bidentate proline derivatives 132 in the metal-catalyzed SMA (Figure 3).

Initial screening experiments revealed hafnium trifluoromethanesulfonate in combination with ligand 132 ($R^1 = CO-t$-Bu, $R^2 = Ph$, $R^3 = Me$) could catalyze the SMA of benzyliothiol 133 ($R = Bn$) and imide 134.
Variation of the \( \alpha,\beta \)-unsaturated substrate 134 and thiol 133 revealed that the enantioselectivity: (i) decreased as the steric demand of the Michael acceptor 134 increased, and (ii) was invariant to thiol 133 variation. The authors also showed that in a few cases, the more sterically demanding ligand 132 (\( R_1 = \text{CO-adamantyl}, R_2 = \text{Ph}, R_3 = \text{Me} \) vs. \( R_1 = \text{CO-t-Bu} \)) could increase the levels of asymmetric induction by up to 23%.

Katsuki and co-workers have explored the use of hafnium complex 139 in the SMA (Figure 4). Using 0.05 equivalent of the complex 139, thiophenol 136 (\( R = \text{Ph} \)) and imide 127 (see Scheme 36) reacted under the optimized reaction conditions in good to excellent yield (\( \geq 81\% \)) and excellent enantioselectivity (\( \leq 93\% \) ee). The authors observed a correlation between the purity of the catalyst 139 and reaction efficiency, and speculated that lithium salt impurities were the cause of observed detrimental effects in certain cases.

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4 Organocatalyzed Reactions

4.1 Cinchona Alkaloid Catalysts

In 1977, Pracejus and co-workers reported the first catalytic asymmetric SMA. In this seminal study, which built upon Wynberg’s earlier study of cinchona alkaloid catalyzed Michael reactions involving nitrosulfone nucleophiles, benzylthiol 131, \( \alpha \)-phthalimidomethacrylate 140 and catalytic quantities of various optically active amines 143–150 were reacted to afford cysteine derivatives 142 in low to moderate enantioselectivity (4–54% ee) (Figure 5, Scheme 37). Of the various alkaloids 143–150 screened, cinchonas 143–146 were found to give the highest levels of asymmetric induction.

The SMA of benzylthiol and tritylthiol to \( \beta \)-nitrostyrenes 151 was also examined (Scheme 38). Here, brucine 148 was found to be the best catalyst, affording modest enantioselectivities as determined by optical rotation measurements (27% ee).

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At the same time, Wynberg and co-workers described an SMA involving cyclohex-2-en-1-one and various aromatic thiols under quinine (143) catalysis. The β-thioketone products were obtained in good to excellent yield (82–95%) and low to moderate enantioselectivity (6–46% ee). Under the optimized reaction conditions, the authors found that various thiophenols could be added to five- and six-membered enones 154 and 155 in up to 75% ee (Scheme 39).

Investigations of quinine-catalyzed SMAs in the presence of metal and fluoride additives have also been conducted. Although appreciable conversions (75–94% yield) were possible, the levels of asymmetric induction remained low (≤36% ee).

Sera et al. performed a study on the quinine- and quinidine-catalyzed addition of thiols (and carbon nucleophiles) to α,β-unsaturated ketones at elevated pressure. The SMAs proceeded by a factor of 1.2 to 2 lower in enantioselectivity at high pressure (9000 bar) than at atmospheric pressure. Notably, the enantioselectivity decreased to a greater extent for the less sterically demanding thiols and/or α,β-unsaturated ketones.

Kobayashi et al. made an interesting discovery while studying the addition of thioglycolic acid (159) to β-nitrostyrene (160): the level and sense of asymmetric induction was dependent on the amount of catalyst employed (Scheme 40). With 0.01 equivalent quinine (143), the reaction rate was low (88% yield after 114 h) and the (−)-adduct 161 was obtained in 15% ee, while with 0.27 equivalent quinine loading, adduct 161 was produced as a racemate (1% ee). As the catalyst loading was further increased toward 1 equivalent, the ee increased to 35% in favor of the enantiomeric (+)-adduct 161, which was produced rapidly (96% yield after 30 min). Furthermore, under more dilute conditions ([159] = 0.05 M), the reaction efficiency could be maintained (86% yield, 15 min) while significantly increasing the enantioselectivity of the process (58% vs. 35% ee with 1.09 equiv quinine).
the ammonium salt and quinine compete, resulting in catalysis of the reaction with no observable asymmetric induction. On the other hand, at high catalyst loading, quinine (143) is a good catalyst (as indicated by the highly reduced reaction times), yielding the opposite enantiomer of the product and a higher enantioselectivity. Yamashita et al. have examined the SMA of various maleates 162 and thiophenol (20) catalyzed by several cinchona alkaloids (Scheme 41). Generally, the reaction proceeded in excellent yield (>95%) and the highest levels of asymmetric induction were observed with cinchonine (144) catalysis and maleates 162 derived from secondary alcohols. The enantioselectivity was higher in nonpolar solvents and was dependent on the reaction concentration: more dilute solutions led to significantly higher enantioselectivities, and here, so at the expense of yield.

Scheme 41

Keniya et al. developed an asymmetric synthesis of (R)- and (S)-phenylalanine utilizing an SMA (Scheme 42). The enantiomeric Michael adducts 165 could be prepared under quinine (143) or quinidine (145) catalysis; however, in both cases only low levels of asymmetric induction were observed (40% ee). Reductive desulfurization afforded enantiomerically enriched phenylalanine 166.

Scheme 42

Enantiomerically enriched (S)-naproxen has also been synthesized using a quinine-catalyzed SMA (Scheme 43). Although only moderate enantioselectivities (46% ee) were obtained, low catalyst loading was possible (0.002 equiv).

Scheme 43

could be recrystallized to near enantiomerically pure form (>95% ee). More recent investigations by Skarżewski et al. demonstrated that the Michael adducts 172 could be used to prepare 4,5-dihydroisoxazoles and 4,5-dihydropyrazoles.

Scheme 44

To date, the most effective cinchona-based catalyst for SMAs of cyclic α,β-unsaturated ketones is pyrimidine 173 (Figure 7). At room temperature, pyrimidine 173 catalyzed the reaction of 2-thionaphthol and six- to nine-membered cyclic α,β-unsaturated ketones and various substituted cyclohex-2-en-1-ones in >88% yield and 92–99% ee. Although moderate enantioselectivity was obtained with cyclopent-2-en-1-one (41% ee), highly enantioselective conjugate addition was accomplished with 4,4-dimethylcyclopent-2-en-1-one (92% ee).

4.2 Tertiary Amino Alcohol Catalysts

Starting in 1981, Mukaiyama and co-workers published several studies involving hydroxyproline derivatives 177 in the SMA of cyclic α,β-unsaturated ketones (Scheme 45). The sulfa-Michael products 176 were
generally formed in moderate to high enantioselectivity. Five- and seven-membered ketones $174$ ($n = 0, 2$) reacted in low stereoselectivity (11–38% ee) and benzylthiol was not a good nucleophile (22% yield, 1% ee).

[Scheme 46]

These catalysts $177$ can be regarded as simplified cinchona alkaloids ($143$–$146$), as both structure types contain $\beta$-amino alcohol groups and, as such, similar reaction conditions were required to achieve high enantioselectivity. Thus, nonpolar solvents and low substrate concentration were both necessary for high asymmetric induction. In addition, and in analogy to quinine-catalyzed reactions, the enantioselectivity was relatively insensitive to temperature. Furthermore, deletion of the hydroxyl substituent resulted in a completely ineffective catalyst (3% ee). Based on these observations, the authors proposed a transition state similar to that for quinine-catalyzed SMAs (see Figure 6), involving nucleophilic attack of the thiphenoate–ammonium complex on the hydrogen-bond-activated $\alpha,\beta$-unsaturated ketone. The authors also examined the use of cycloalk-2-en-1-ones $178$ and found these to react in excellent yield ($\geq 95\%$) and generally good enantioselectivity (63–85% ee) (Scheme 46).

[Scheme 46]

4.3 Secondary Amine Catalysts

A variety of secondary amine catalysts have been examined for use in the asymmetric SMA (Figure 8).

In 2005, Jørgensen and co-workers developed an iminium ion promoted SMA of $\alpha,\beta$-unsaturated aldehydes under catalysis by trimethylsilyl ether $185$ (Scheme 47). $185$ Aliphatic and aromatic aldehydes $187$ reacted with several thiols in good yields and excellent enantioselectivities, both determined following reduction of the less stable and first-formed aldehyde products $188$ to the $\beta$-thioalcohols $189$. At room temperature, the Michael adducts $188$ were found to rapidly racemize. However, by performing the reactions at low temperature, racemization could be suppressed, but addition of an acid co-catalyst was required, presumably to catalyze iminium ion formation, and synthetically useful reaction rates were maintained.

In the same study, Jørgensen and co-workers incorporated this SMA into a multicomponent ‘domino’ reaction. $185$ Thus, a mixture of $\alpha,\beta$-unsaturated aldehyde $187$, thiol $190$ and azodicarboxylate $191$ in the presence of trimethylsilyl ether $185$ reacted to form products $192$ with an $\alpha$-hydrazino-$\beta$-thiocarbonyl function (Scheme 48). The initial aldehydic products $192$ were not isolated, but instead reduced and cyclized to form the stable chiral oxazolidinones $193$ in moderate to good overall yield, good to excellent diastereoselectivity, and with near complete enantiocontrol.

Mechanistically, this tandem reaction relies on both iminium ion and enamine catalysis: following nucleophilic attack of the thiol $190$ on the iminium ion activated aldehyde $194$, the resultant enamine intermediate reacts with the azodicarboxylate electrophile ($E^+$) (Scheme 49).

More recently, Jørgensen and co-workers have developed a tandem sulfa-Michael/aldol reaction whereby tetrahdrothiophenes could be synthesized. $189$ A variety of $\alpha,\beta$-unsaturated aldehydes $198$ and 2-thioacetoephone (199)}
were found to react in moderate yield and excellent enantioselectivity (Scheme 50). Mechanistically, the tandem reaction involved an initial SMA reaction of the iminium ion activated aldehyde \( R^2 \) followed by an intramolecular aldol reaction between the resultant enamine intermediate \( R^1 \) and ketone function (E+) of the nucleophile (see Scheme 49).

Recently, Wang et al. developed an organocatalytic method to prepare chiral thiochromenes \( R^6 \) from \( \alpha,\beta \)-unsaturated aldehydes \( R^5 \) and 2-thiosalicylaldehydes \( R^4 \) using a tandem sulfa-Michael/intramolecular aldol reaction (Scheme 52).90 L-Proline and pyrrolidine diamines were catalytically active; however, trimethylsilyl ether \( R^3 \) gave high enantioselectivities in the model reaction between cinnamaldehyde and 2-thiosalicylaldehyde. After 'extensive optimization' of the reaction conditions, the best results were obtained by performing the reaction in toluene in the presence of benzoic acid. Interestingly, molecular sieves were also added to the reaction, although the authors did not comment on their role. The reaction showed \( \alpha,\beta \)-unsaturated substrate generality and the thiochromene products \( R^6 \) were obtained in good to excellent yield and enantioselectivity. Cordova and co-workers have also performed a similar study, and observed comparable results.91

Cordova and co-workers have extended this tandem sulfa-Michael/intramolecular aldol reaction to \( \alpha,\beta \)-unsaturated cyclic ketones (Scheme 53).92 In the model reaction of aldehyde \( R^7 \) and cyclohex-2-en-1-one (208; \( R = H, n = 1 \),...
l-proline (30% ee) and amide 180 (39% ee) each led to low yields and enantioselectivity, while tetrazole 182 and diphenylprolinol 184 were catalytically inactive (see Figure 8). However, prolinol 181 and diamine 183 were more active catalysts. At lower temperature, alkenes 210, formed following silica gel induced elimination of water from the initial aldol products 209, could be obtained in moderate enantioselectivity. Five- and six-membered α,β-unsaturated ketones 208 afforded the alkenes 210 in moderate to good yield and enantioselectivity. Of note, rapid chromatographic purification allowed for the isolation of approximately equal amounts of both the initial aldol products 209 and alkenes 210.

Scheme 53

4.4 Urea-Based Catalysts

Chen and co-workers96 have used the bifunctional thiourea 212, previously described by Takemoto and co-workers for use in Michael reactions of malonates and nitroalkanes,93–95 in the asymmetric SMA. In a model reaction of thiophenol (20) and imide 211 (R = Ph) at room temperature, nonpolar solvents resulted in higher enantioselectivities (60% ee) where polar solvent lowered (THF, 4% ee) or reversed (MeOH, −25% ee) the sense of asymmetric induction (Scheme 54). Addition of molecular sieves was noted to improve the reproducibility of the reactions. A panel of thiophenols was subjected to the SMA; all reacted in excellent yield (90–98%) and in moderate to good enantioselectivity (55–77% ee).

In the same report, Chen and co-workers subjected five-and six-membered α,β-unsaturated ketones to the thiourea 212-catalyzed SMA with various aromatic thiols. Adducts were obtained in excellent yield (95–99%) and moderate to good enantioselectivity (63–85% ee).

Wang and co-workers evaluated several cinchona alkaloids and thiourea 212 as catalysts in the SMA between thiourea 212 and thiourea 212-catalyzed SMA with various aromatic thiols. Adducts were obtained in excellent yield (95–99%) and moderate to good enantioselectivity (63–85% ee).

Wang et al. have also performed a similar study of the SMA of thiourea 212 and α,β-unsaturated ketones 217 catalyzed by cinchona alkaloids or thiourea 212 (Scheme 56).98 Again, thiourea 212 was the optimal catalyst and the reactions proceeded readily at room temperature (3–24 h), although more slowly than the same reaction for β-nitrostyrenes (see Scheme 54). Interestingly, in the model reaction involving trans-chalcone 217 (R1 = R2 = Ph), the enantioselectivity decreased (58% to 44% ee) when the reaction temperature was lowered to 0 °C. Increasing aliphatic substitution of ketone 217 further lowered the enantioselectivity of the reaction (15% ee, R1 = Ph, R2 = Me; 0% ee, R1 = Bu, R2 = Me).

5 Polymer-Catalyzed Reactions

Shortly after the first reports on catalytic SMAs, Kobayashi et al. developed immobilized catalysts. Thus, cinchona alkaloids 143–146, which contain a vinyl side chain, were found to be suitable monomers in the alkene
co-polymerization reaction with acrylonitrile (219) (Scheme 57).\textsuperscript{99} Variation of the stoichiometry of the co-polymerization reaction from quinine/acrylonitrile (1:20 to 1:3), lowered the isolated polymer yield (51% to 11%); however, the quinine content could be increased (0.03 to 0.12 equiv). Of note, the co-polymers were soluble in polar aprotic solvents (N,N-dimethylformamide, dimethylsulfoxide) and insoluble in nonpolar solvents (e.g., toluene).

Scheme 57

The quinine–acrylonitrile (1:4) co-polymer (0.25 equiv quinine) catalyzed an SMA of dodecanethiol (222) and ketone 221 in moderate enantioselectivity (57% ee) and 76% conversion after seven days (Scheme 58). The observed enantioselection was comparable to that obtained in the same reaction catalyzed by free quinine or quinidine (41% ee).

Scheme 58

Hodge et al. have also immobilized cinchona alkaloids in co-polymers of polystyrene thiol, linking the cinchona vinyl and thiol groups via a sulfide linkage.\textsuperscript{100} However, in all examples of their use in SMA, these co-polymers gave lower levels of asymmetric induction than the corresponding free cinchona alkaloid catalysts.

More recently, Athawale et al. have developed a chemoenzymatic method to immobilize cinchona alkaloids for use in the SMA.\textsuperscript{101} This involved lipase-catalyzed reaction of the acrylate donor 225 and the modified cinchona alkaloid 224 prior to radical-initiated polymerization (Scheme 59). Both the quinine- and quinidine-polymers catalyzed the SMA of thiophenol and cyclohex-2-en-1-one in good yield (86%) and moderate enantioselectivity (51% ee), slightly higher than that obtained in the same reaction catalyzed by free quinine or quinidine (41% ee).

Scheme 59

Sundararajan et al. modified their homogeneous heterobimetallic catalyst 107, used previously in SMAs (see Scheme 27), by incorporating it into a polymeric backbone.\textsuperscript{102} The polymer 230 was synthesized by free-radical co-polymerization of the corresponding chiral monomer 229 with styrene and 1,4-divinylbenzene, as a cross-linking reagent (Scheme 60). Catalyst 231 preparation involved treatment of polymer 230 with lithium aluminum hydride. Inductively coupled plasma mass spectrometric analysis of catalyst 232 showed a 1:1 incorporation of lithium and aluminum. In the SMA of thiols and α,β-unsaturated ketones, the Michael adducts were obtained rapidly, in excellent yield and in moderate enantioselectivity (Scheme 61). Furthermore, the levels of asymmetric induction were generally higher than those obtained in the same reaction catalyzed by the nonpolymeric catalyst 107.

Kobayashi et al., having previously demonstrated that hafnium complexes of proline-derived ligands could be used effectively in the SMA (see Scheme 35), immobilized similar ligands on Merrifield resin (Scheme 62). In the reaction of allylthiol (234) and imide 127, the polymer catalyst 235 performed similarly to the unbound catalyst 132 (R\textsubscript{1} = CO-\textit{t}-Bu, R\textsubscript{2} = Ph, R\textsubscript{3} = Me) (91% vs. 94% ee).

6 Miscellaneous Methods

In 1993, Toda and co-workers performed SMAs using chiral inclusion complexes. A 1:1 benzene–hexane solution of cyclohex-2-en-1-one (129) and dioxa[5.4]decan (241) (1:1) was allowed to stand at room temperature for 12 hours, after which time a 1:1 inclusion complex of the two components crystallized (Scheme 63). The pow-
dered, crystalline inclusion complex was treated with aqueous solutions of various thiopyridines or thiopyrimidines under basic conditions and with initial sonication of the reaction mixture. Following dissolution of the resultant product-containing inclusion complex and chromatographic purification, the Michael adducts were obtained in moderate yield and good enantioselectivity. In the case of thiophenol, no asymmetric induction was observed. Therefore, the authors proposed that an additional and rigidifying electrostatic interaction in complex between the base counterion and nitrogen atom of the nucleophile is requisite for enantioselection. Of note, acyclic \( \alpha, \beta \)-unsaturated ketones could also be employed with a similar outcome.

Sakuraba et al. have also carried out SMAs using chiral inclusion complexes; here, of aromatic thiols and \( \beta \)-cyclohexadextrin (CD). In the best example, an aqueous suspension of the 1:1 complex of CD–thiophenol reacted with cyclohex-2-en-1-one in excellent yield (93\%) and low enantioselectivity (30\% ee) after seven days at room temperature.

In the realm of supramolecular chemistry, Scheeren and co-workers prepared the multifunctional aza-crown ethers for use as enantioselective catalysts in the SMA (Scheme 64). These structures allow for the possibility of electrostatic, hydrogen-bonding and \( \pi \)-\( \pi \) substrate–catalyst interactions. This chiral template was, however, ineffective in the asymmetric SMA.

Enzyme-catalyzed SMAs have also been briefly examined. In the presence of several lipases, propenoates and reacted with thiols in moderate yield and enantioselectivity (Scheme 65). The reaction was found to be more enantioselective in nonpolar media. No mechanistic rationale was given, but a recent report on a

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**Scheme 60**

\[
\begin{align*}
\text{Scheme 61} & \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \\
\text{R} & \quad \begin{array}{c}
\text{X} \\
\text{R}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{X} \\
\text{R}
\end{array}
\text{THF, 30 min}
\end{align*}
\]

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**Scheme 62**

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**Scheme 63**

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lipase-catalyzed Michael reaction suggested that an enzyme active site hydrogen-bond activation of the Michael acceptor was operative in that case.\textsuperscript{108}

7 Conclusions and Outlook

Significant advances in the field of asymmetric sulfahydroxy carbon–sulfur stereogenic centers in high stereoselectivity, organocatalysis allows for thiol additions to unsaturated substrates activated by, for example, nitro and aldehyde groups. Future work in the field will likely be focused on the development of methods to employ a range \(\beta,\beta\)-disubstituted Michael acceptors, as these electrophiles have been found to react efficiently in only a limited number of cases. In addition, the discovery of a single set of reaction conditions whereby a diverse set of thiol donors (e.g. alkyl, aryl, and acyl thiols) react in high yield and stereoselectivity has so far remained elusive.

References