

Organocatalytic Carbon–Sulfur Bond-Forming Reactions

Pankaj Chauhan, Suruchi Mahajan, and Dieter Enders*

Institute of Organic Chemistry, RWTH Aachen University Landoltweg 1, 52074 Aachen, Germany



Author Information	BB
Corresponding Author	BB
Notes	BB
Biographies	BB
Acknowledgments	BB
Abbreviations	BB
References	BC
Note Added in Proof	BF

CONTENTS

1. Introduction	A
2. Enantioselective Organocatalytic C–S Bond Formations	C
2.1. Sulfa-Michael Additions	C
2.1.1. Lewis Base–Brønsted Acid or Lewis Base Catalysis	V
2.1.2. Amino Catalysis via Iminium Activation	AB
2.2. Reactions of Sulfur Nucleophiles with Other Acceptors	AB
2.2.1. 1,2-Addition Reactions	AC
2.2.2. 1,6-Addition Reactions	AD
2.2.3. γ -Addition Reactions	AE
2.2.4. Reactions with Morita–Baylis–Hillman Carbonates	AE
2.3. Desymmetrization Reactions	AE
2.3.1. Desymmetrization of Anhydrides	AF
2.3.2. Desymmetrization of Azlactones	AG
2.3.3. Desymmetrization of meso-Aziridines	AJ
2.3.4. Desymmetrization of meso-Epoxides	AJ
2.3.5. Desymmetrization of Oxetanes	AJ
2.4. Sulfenylation Reactions	AJ
2.4.1. Lewis Base–Brønsted Acid or Lewis Base Catalysis	AO
2.4.2. Amino Catalysis via Enamine Activation	AP
2.5. Trifluoromethylsulfonylation Reactions	AP
2.6. Aminosulfonylation Reactions	AR
2.7. Oxsulfonylation Reactions	AR
2.8. Carbosulfonylation Reactions	AR
2.9. Cycloaddition Reactions	AS
2.10. Asymmetric Alkylation of Sulfenate Salts	AT
3. Nonenantioselective Organocatalytic C–S Bond Formations	AT
3.1. Sulfa-Michael Additions	AV
3.2. 1,6-Addition Reactions	AW
3.3. Ring-Opening of Epoxides, Aziridines, and Cyclopropanes	AX
3.4. Sulfenylation Reactions	AY
3.5. Thioesterification Reactions	AZ
3.6. Miscellaneous	BA
4. Summary and Outlook	

1. INTRODUCTION

Carbon–heteroatom bond formations are very important reactions in organic synthesis and have attracted the interest of many synthetic organic chemists, leading them to develop new methodologies for these transformations. Among various carbon–heteroatom bond formations, the carbon–sulfur (C–S) bond formations hold a prominent position in the race for the synthesis of valuable chemical entities, because organosulfur compounds are widely present in nature and various biological systems. The organosulfur compounds such as amino acids [cysteine (**1**) and methionine (**2**)], peptides [glutathione (**3**)], as well as protein cross-linking agents, biotin (**4**), and ligands in bioinorganic complexes **5** and **6**, etc., play an important role in the biochemistry of almost all living organisms (Figure 1).¹ In addition to this, organosulfur compounds are inevitably present in many synthetic drugs and bioactive natural products, for example, **7–16**.² Interestingly, all of the 10 top selling drugs in 2012 were organosulfur compounds.³

The carbon–sulfur bond formations constitute a very important class of reactions in biological processes. For example, the synthesis of coenzyme M (**20**) in methanogenic bacteria is governed by an initial C–S bond formation reaction of bisulfite **17** with phosphoenolpyruvate (**18**) to form the acid **19** [Scheme 1 (1)].⁴ The metabolism of acrylamide, a toxic component of heated food, is also initiated by the sulfa-Michael addition of glutathione (**3**) to the acrylamide double bond [Scheme 1 (2)].⁵ In another example, the defense mechanism of the unicellular polyploidy invasive green alga *Caulerpa taxifolia* against mechanical injury via wound closure also involves a C–S bond formation between oxytoxin **2** (**21**) and cysteine (**1**) in the presence of lysine to form **22** through a sulfa-Michael addition (Figure 2).⁶

Because of the many pharmaceutical applications as well as the biological values of organosulfur compounds, the catalytic C–S bond formations stand at the forefront of investigation and innovation in modern synthetic organic chemistry. To date, significant progress has been achieved for the construction of new C–S bonds, mainly involving addition and substitution strategies (Scheme 2). The addition of various sulfur

Received: April 30, 2014

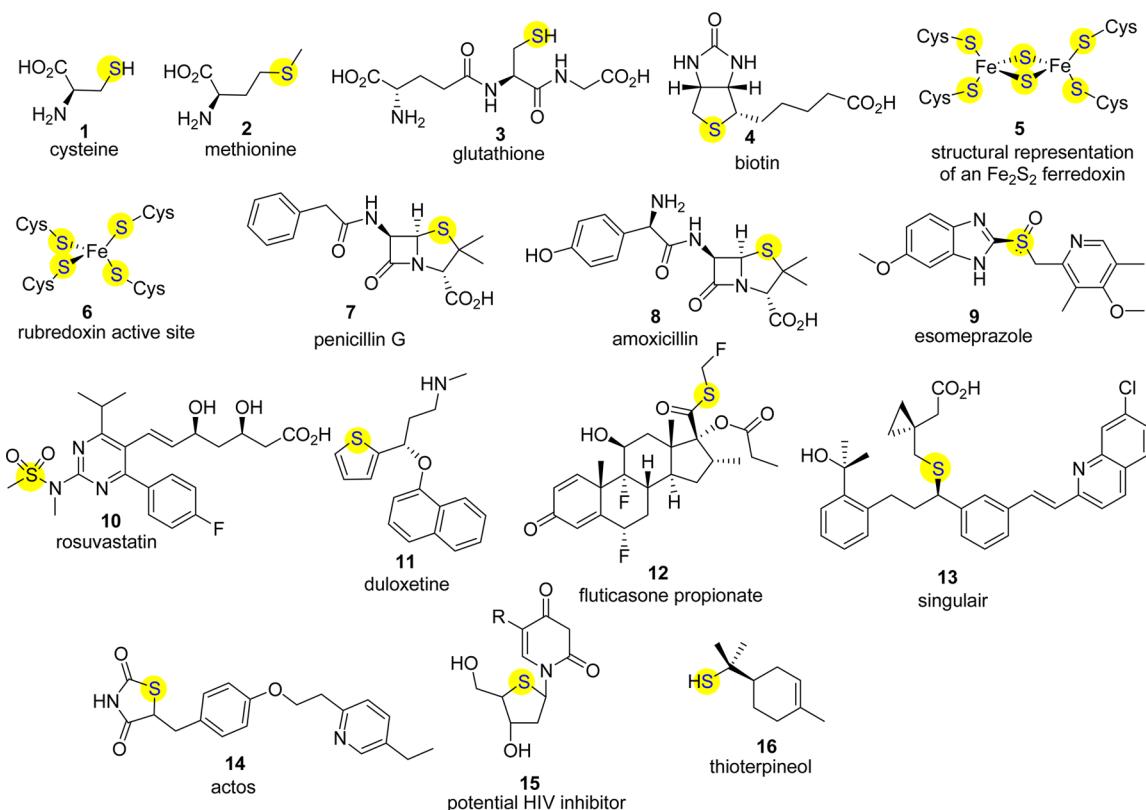
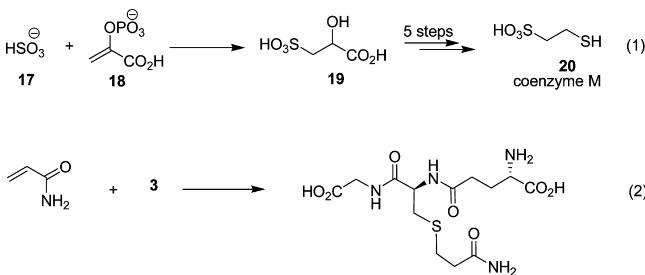


Figure 1. Representative classes of valuable biologically active organosulfur compounds present in nature and organosulfur drugs.

Scheme 1. C–S Bond Formations in Nature: Coenzyme M Synthesis (1) and Metabolism of Acrylamide (2)



Scheme 2. General Strategies for the Catalytic Generation of C–S Bonds

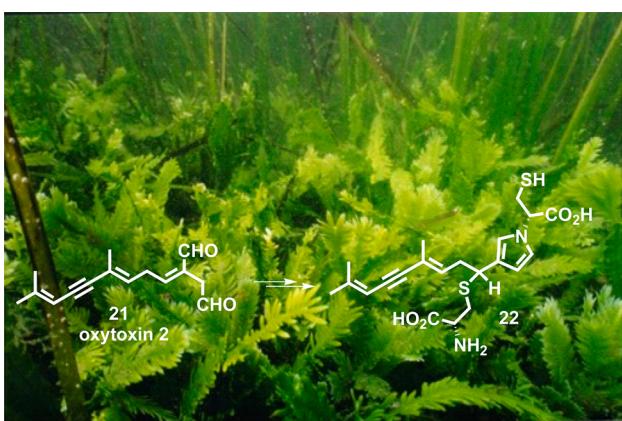
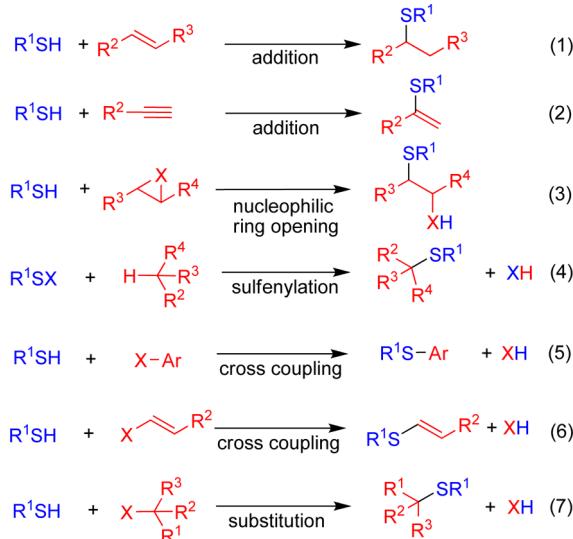
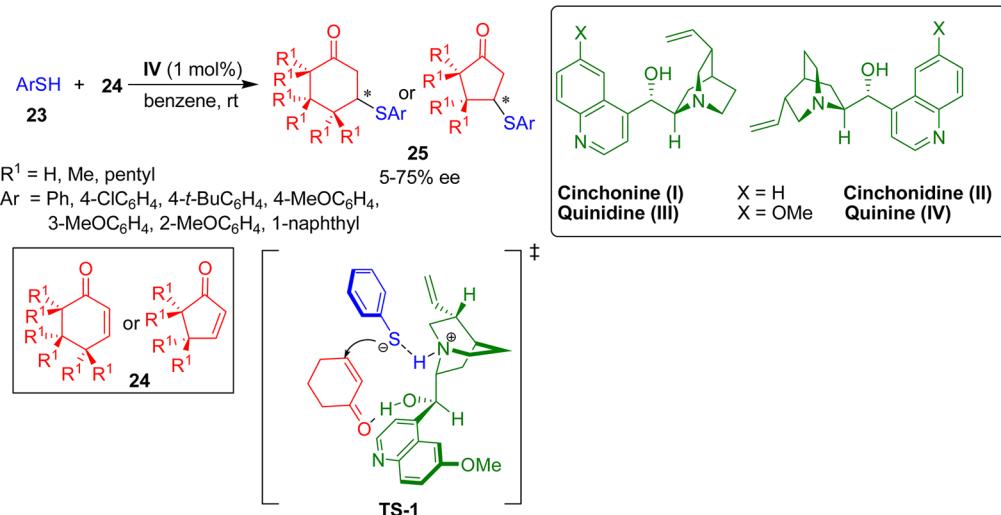


Figure 2. Defense mechanisms via wound closure in the invasive green alga *Caulerpa taxifolia* involving a sulfa-Michael addition.

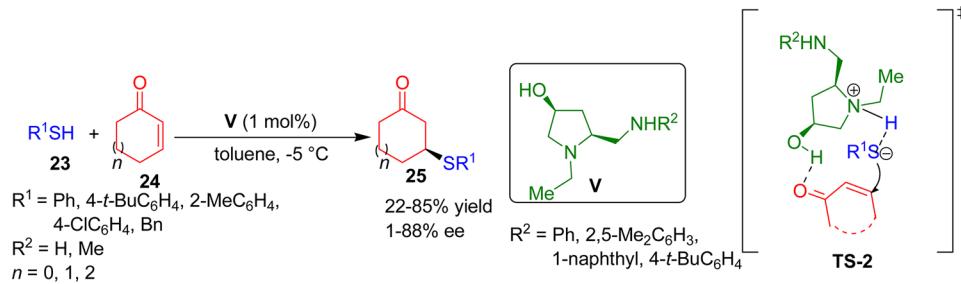
nucleophiles to carbon–carbon double bonds [Scheme 2 (1)] as well as thiolytic cleavage of epoxides, aziridines, anhydride, etc.,

represent the most convenient methods for the formation of new C–S bonds [Scheme 2 (3)]. Recently, metal-catalyzed additions of sulfur nucleophiles to the carbon–carbon triple bond were performed with excellent selectivity to provide useful vinyl sulfides [Scheme 2 (2)].⁷ Another approach for the construction of C–S bonds is the sulfenylation reaction, which employs electrophilic sulfur reagents [Scheme 2 (4)]. The C–S bond formation via substitution involves metal-catalyzed cross-coupling reactions with aryl and vinyl halides [Scheme 2 (5) and (6)] and the direct substitution of leaving groups such as halides, sulfonates, O-phosphonite, etc., by a sulfur nucleophile

Scheme 3. Quinine-Catalyzed SMA to Cyclic Enones



Scheme 4. Enantioselective SMA Catalyzed by Hydroxyproline Derivatives



[Scheme 2 (7)]. There are several reviews and some book chapters on transition metal-catalyzed C–S bond formation reactions.^{8,9} Even though a thorough exploration of organocatalytic methods for the generation of new C–S bonds has been carried out, so far there is no comprehensive review that deals with this important area of research.

Organocatalysis, which uses small organic molecules to catalyze organic transformations, is a relatively new and rapidly growing field within the domain of catalytic asymmetric and nonenantioselective synthesis.^{10,11} The use of small organic molecules as catalysts offers several fundamental advantages over the metal- and biocatalysts, as they can easily be obtained from readily available materials, they are insensitive to air and moisture, they are robust, less toxic, and they can also provide both enantiomers of bioactive compounds such as drugs and natural products, with high enantioselectivity.¹² The organocatalysts not only promote simple C–C, C–N, C–O, C–P, and C–S bond formations, but they also facilitate more complex domino/cascade reactions via multicomponent one-pot protocols. The organocatalytic C–C and carbon–heteroatom bond formations have been reviewed from time to time. Although several examples of organocatalyzed C–S bond formations existed in the literature even before the renaissance of organocatalysis in the year 2000 and a significant growth has been witnessed in recent years, however, this topic has not been reviewed so far in a general way.

2. ENANTIOSELECTIVE ORGANOCATALYTIC C–S BOND FORMATIONS

The majority of useful organosulfur compounds are chiral and optically active, and thus tremendous progress has been made for the asymmetric formation of new C–S bonds. This Review will cover the literature reports on organocatalytic asymmetric C–S bond formations via sulfa-Michael reactions (since 2007), 1,2-, 1,6-, and γ -additions of sulfur nucleophiles, desymmetrization of anhydrides, aziridines, oxetanes, and azlactones, as well as sulfenylation reactions published since the beginning of this century. Nonenantioselective C–S bond formations will also be covered in a separate chapter.

2.1. Sulfa-Michael Additions

The 1,4-addition of sulfur nucleophiles to unsaturated acceptors known as sulfa-Michael addition (SMA) is a very important and common method for the formation of a new C–S bond.¹³ The chiral organocatalysts including Lewis bases, Lewis base–Brønsted acid catalysts, and secondary as well as primary amines are found to promote the sulfa-Michael additions with a high level of enantioselectivity.

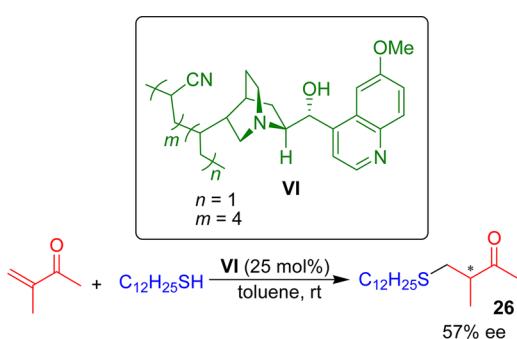
2.1.1. Lewis Base–Brønsted Acid or Lewis Base Catalysts. Chiral bifunctional Lewis base–Brønsted acid¹⁴ and Lewis base catalysts¹⁵ derived from natural products such as cinchona alkaloids and amino acids as well as those derived from synthetic chiral diamines have emerged as powerful catalysts for the sulfa-Michael additions to various acceptors such as α,β -unsaturated carbonyl compounds, nitroalkenes, maleimides, sulfones, and sulfonates.

2.1.1.1. Addition to α,β -Unsaturated Carbonyl Compounds. **2.1.1.1.1. Addition to α,β -Unsaturated Ketones.** In 1977, Wynberg and co-workers exploited the catalytic potential of natural cinchona alkaloids **I–IV** for enantioselective SMAs of aromatic thiols **23** with cyclic enones **24** for the first time (Scheme 3).¹⁶ Quinine **IV** at low catalyst loading promoted the SMA of **23** to various cyclic enones, providing β -thio ketones **25** in low to moderate enantioselectivities (5–75% ee). Wynberg's group also carried out kinetic and experimental studies on the cinchona alkaloid-catalyzed SMAs to establish the mechanism, which revealed the bifunctional nature of the quinidine.¹⁷ The plausible transition state **TS-1** involves a ternary complex consisting of the catalyst, the ammonium thiolate, and the cyclohexenone, in which the thiol is deprotonated by the quinuclidine nitrogen and the enone is activated through hydrogen bonding to the 9-OH of the quinidine. Furthermore, the catalyst conformation and trimolecular complex in the transition state were also confirmed by computational and NOESY experiments.¹⁸ Wynberg and co-workers further investigated the effect of metal and fluoride additives on quinidine-catalyzed SMAs.¹⁹ These additives resulted in good yields ranging from 75% to 94%; however, the level of enantioselectivity was low (<36% ee).

Mukaiyama and co-workers investigated the catalytic potential of hydroxyproline derivatives **V** for the SMA with cyclic enones (Scheme 4).²⁰ The sulfa-Michael products were generally formed in moderate to high enantioselectivities; however, five- and seven-membered unsaturated ketones gave low enantioselectivities (11–38% ee), and benzylthiol was found to be a poor nucleophile providing only 22% yield and 1% ee. These aminoalcohol catalysts **V** were regarded as mimics of natural cinchona alkaloids, because both structures contain β -amino alcohol groups, and almost similar reaction conditions were required to achieve high enantioselectivity of the SMA products. A transition state **TS-2** similar to that for the quinine-catalyzed SMA was proposed involving the dual hydrogen-bonding activation of the enone and the sulfur nucleophile with the hydroxyl group and the tertiary amine, respectively.

One year after the first reports on organocatalytic sulfamichael reactions, Kobayashi and Iwai developed immobilized cinchona alkaloid catalysts via a copolymerization reaction of the C-3 vinyl group of the alkaloids with acrylonitrile (Scheme 5).²¹ Quinine-acrylonitrile (1:4) copolymer VI catalyzed a SMA/protonation of dodecanethiol with 3-methylbut-3-en-2-one to provide the corresponding adduct 26 in enantioselectivity (57% ee) comparable to that of quinine, with 76% conversion after 7 days.

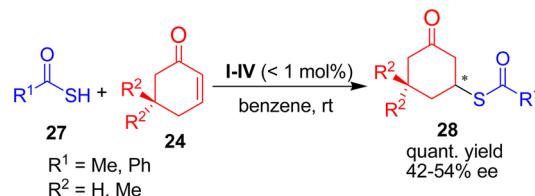
Scheme 5. Quinine-acrylonitrile Copolymer-Catalyzed SMA of Dodecanethiol to 3-Methyl-butenone



Hodge and co-workers immobilized the cinchona alkaloids by linking the cinchona vinyl and the thiol groups of polystyrene thiols via a sulfide linkage.²² The catalytic potential of these cross-linked polymers was explored for the enantioselective SMA of thiophenols and thiobenzoic acid to cyclohexenone. However, the level of asymmetric induction was found to be lower than that of the corresponding free cinchona alkaloids. These polymer bound cinchona alkaloids also led to moderate asymmetric induction in the reaction of benzyl thiol with nitrostyrene.

Gawronski et al. screened the natural cinchona alkaloids I–IV for the enantioselective SMA of thioacids 27 to cyclohexenones 24 (Scheme 6).²³ All four alkaloids I–IV at low loading provided the respective Michael adducts 28 in almost quantitative yield and moderate enantioselectivities (42–54% ee).

Scheme 6. Cinchona Alkaloid-Catalyzed Enantioselective Michael Additions of Thioacids to Cyclohexenones

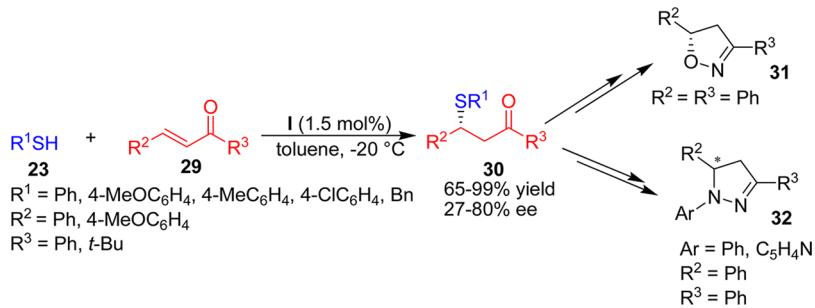
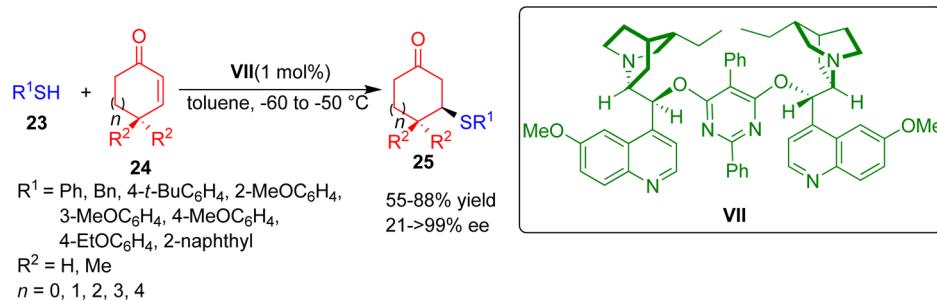
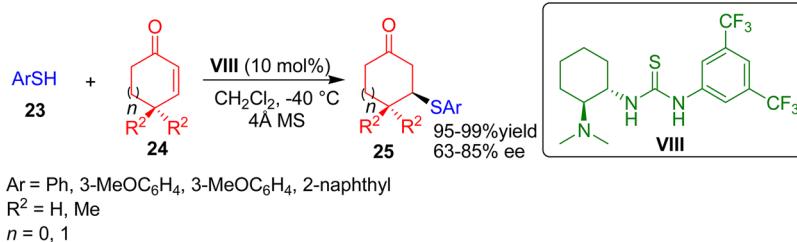


Sera et al. studied the quinine- and quinidine-catalyzed addition of thiols as well as carbon nucleophiles to α,β -unsaturated ketones at elevated pressure.²⁴ The enantiomeric excesses of the sulfa-Michael adducts were lower at high pressure (9000 bar) than at atmospheric pressure by a factor of 1.2–2. Notably, the enantioselectivity decreased to a greater extent for the sterically less demanding thiols and/or α,β -unsaturated ketones.

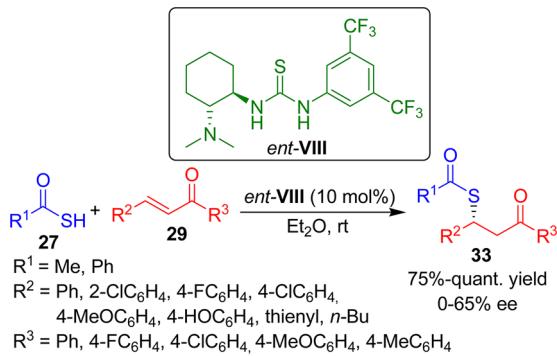
In 2001, Skarzewski et al. reacted acyclic α,β -unsaturated ketones **29** with thiols **23** in the presence of cinchonine as the catalyst to provide sulfa-Michael adducts **30** in moderate to excellent yields (65–99%) and low to good enantioselectivities (27–80% ee) (Scheme 7).²⁵ In some instances, the adducts were recrystallized to reach a nearly enantiomerically pure form (>95% ee). Later, the authors demonstrated that the sulfa-Michael adducts could be used to prepare 4,5-dihydroisoxazoles **31** and 4,5-dihydropyrazoles **32**.²⁶

One year later, Deng's group reported an elegant enantioselective SMA of thiols **23** to cyclic enones **24** using the dimeric cinchona-derived organocatalyst **VII** with no hydrogen donor unit (Scheme 8).²⁷ The screening of different aryl and benzyl thiols with cyclohexenone using a low catalyst loading (1 mol %) of the quinidine-derived dimeric organo-catalyst **VII** revealed that 2-naphthyl mercaptan gives a maximum enantioselectivity. The enantioselective conjugate addition of 2-naphthyl mercaptan to **23** provides corresponding sulfa-Michael adducts **25** in good to excellent yields (55–99%) and moderate to high enantioselectivities (41–99% ee).

In 2005 Chen and co-workers reported an efficient organocatalytic asymmetric SMA of thiols to α,β -unsaturated carbonyl compounds (Scheme 9).²⁸ Takemoto's tertiary amine-thiourea **VIII** was found to be the best catalyst for promoting the 1,4-addition of thiophenols to cyclic enones **24**, which afforded excellent yields (95–99%) and moderate to good enantioselectivities of sulfa-Michael adducts **25** (63–85% ee).

Scheme 7. Cinchonine-Catalyzed Enantioselective SMA of Acyclic α,β -Unsaturated Ketones with Thiols**Scheme 8.** Enantioselective SMA of Cyclic Enones with Thiols Promoted by a Dimeric Quinidine Catalyst**Scheme 9.** Enantioselective SMA of Thiols to Cyclic Enones Employing Takemoto's Thiourea Catalyst

In 2006, W. Wang's group published an enantioselective SMA of thiocarboxylic acids **27** to chalcones **29** catalyzed by a Takemoto's tertiary amine-thiourea *ent*-**VIII** (Scheme 10).²⁹

Scheme 10. Enantioselective SMA of Thiocarboxylic Acids to Chalcones Employing Takemoto's Thiourea Catalyst

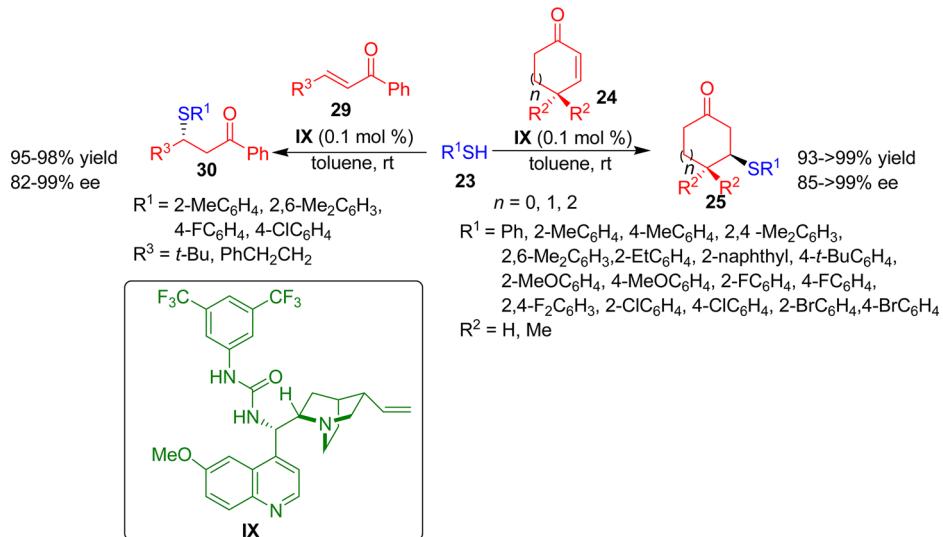
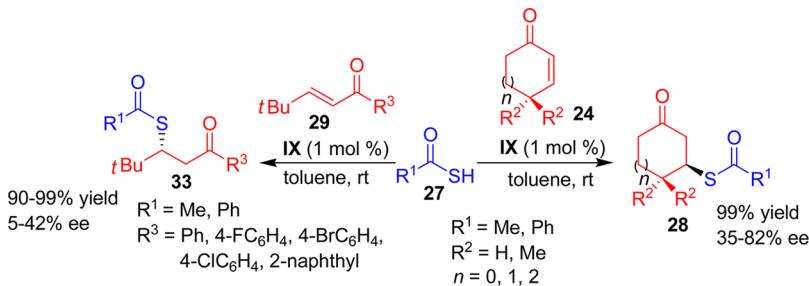
The corresponding products **33** were isolated in good to excellent yields (75%-quant.) and low to moderate enantioselectivities (15–65% ee). However, the enones bearing aliphatic groups gave no asymmetric induction.

In 2010, Singh and co-workers reported a highly efficient SMA of thiols **23** with various α,β -unsaturated ketones **24** and

29 catalyzed by the cinchona-derived tertiary amine-urea **IX** (Scheme 11).³⁰ The catalyst **IX** promoted the enantioselective 1,4-addition of various thiophenols to cyclic enones **24** to provide the SMA products **25** in excellent yields (93–99%) and good to excellent enantioselectivities (85–99% ee) at an extremely low catalyst loading of 0.1 mol %. The low catalyst loading of **IX** also catalyzes the SMA of thiophenols with acyclic enones **29**, giving rise to the Michael adducts **30** in good to excellent yields (95–98%) and enantioselectivities (82–99% ee).

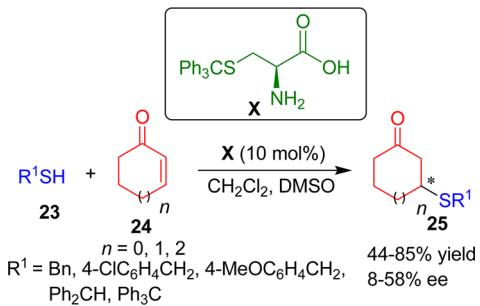
Singh's group also devised an organocatalytic asymmetric SMA of thiocarboxylic acids **27** with enones (Scheme 12).³¹ Only 1 mol % of the cinchona-derived tertiary amine-urea **IX** efficiently catalyzed the sulfa-Michael addition of thioacetic/thiobenzoic acid with six- and seven-membered cyclic enones **24** to furnish the SMA products **28** in excellent yields (99%) and moderate to good enantioselectivities (60–82% ee), whereas cyclopentenone resulted in only a low level of enantioselectivity (35–50%). The amino-urea **IX**-catalyzed additions of thiocarboxylic acids to acyclic enones **29** provide **33** in excellent yields (90–99%) but with rather poor enantioselectivities (5–42% ee).

Hara and co-workers used the commercially available primary amino acid (*S*)-triphenylmethyl L-cysteine (**X**) as an efficient catalyst for promoting the SMA of arylmethyl thiols **23** to cyclic enones **24** (Scheme 13).³² With the amino acid

Scheme 11. SMA of Thiols to Various α,β -Unsaturated Ketones Catalyzed by a Cinchona-Derived Tertiary Amine-ureaScheme 12. SMA of Thiocarboxylic Acids to Various α,β -Unsaturated Ketones Catalyzed by a Cinchona-Derived Tertiary Amine-urea

catalyst X, the addition products **25** were obtained in moderate to good yields (44–85%) and poor to moderate enantioselectivities (8–58% ee).

Scheme 13. SMA Catalyzed by (S)-Triphenylmethyl L-Cysteine



Meciarová and co-workers reported that the addition of thiophenols to chalcone in the presence of different organocatalysts, such as amino acids and their derivatives, cinchona alkaloids, nicotine, and chiral hydroxy acids, in ionic liquids proceeds with excellent yields (76–99%), but very poor enantioselectivities (0–4% ee).³³ In contrast, 16% and 26% ee were observed, when L-proline and cinchonine were used in dichloromethane as solvent instead of ionic liquids.

Kumar and Akanksha screened different amino acids for SMAs of thiophenols to chalcones in methanol.³⁴ Only L-

proline provided a moderate level of enantioselectivities in the range of 24–45% ee with high product yields of 92–98%. However, the L-proline-catalyzed SMA of benzyl mercaptan with chalcones gave nearly racemic products in high yields.

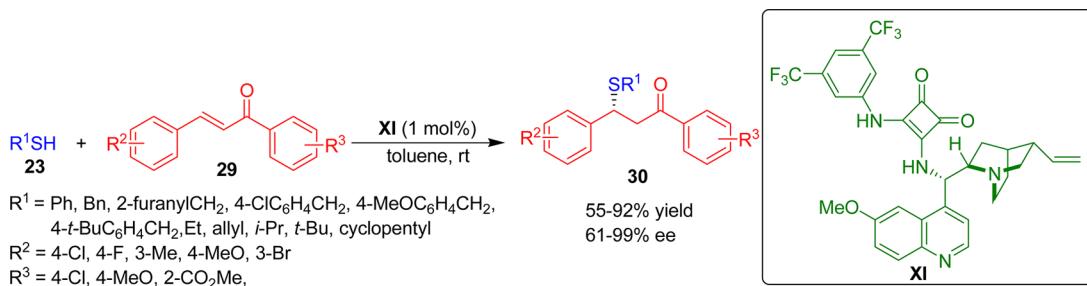
Chen and co-workers described a bifunctional cinchona alkaloid squaramide catalyst XI-promoted asymmetric SMA of thiols **23** to chalcones **29** (Scheme 14).³⁵ The reaction of a series of substituted chalcones with thiophenol and a variety of alkyl and benzyl thiols gave sulfa-Michael adducts **30** in moderate to high yields (55–92%) and moderate to excellent enantioselectivities (61–99% ee) with a low loading of XI.

Adamo's group reported an efficient catalytic enantioselective 1,4-addition of sodium bisulfite to chalcones **29** catalyzed by bifunctional tertiary amine-thiourea organocatalysts (Scheme 15).³⁶ The cinchona-derived amino-thiourea catalysts XII and XIII provided a straightforward access to both enantiomers of the chiral aliphatic sulfonic acid derivatives **34** in high yields (87–97%) and good to excellent enantioselectivities (82–99% ee).

In 2001 Athawale's group prepared the quinine- and quinidine-polymers XIV and XV (Figure 3) by a chemoenzymatic method.³⁷ Both catalysts promoted efficiently the asymmetric SMA of thiophenol with cyclohexenone in good yield (86%) and moderate enantioselectivity (51% ee), the latter being slightly higher than those obtained in the same reaction catalyzed by the parent alkaloids (41% ee).

Hansen et al. developed an immobilized cinchona-derived organocatalyst XVI using thiol–ene chemistry involving thiol

Scheme 14. SMA of Thiols with Chalcones Catalyzed by a Cinchona Alkaloid Squaramide



Scheme 15. SMA of Sodium Bisulfite with Enones Catalyzed by Cinchona-Derived Amino-thioureas

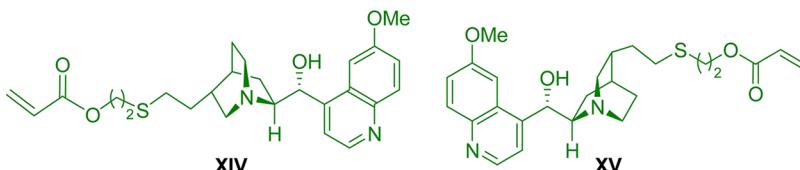
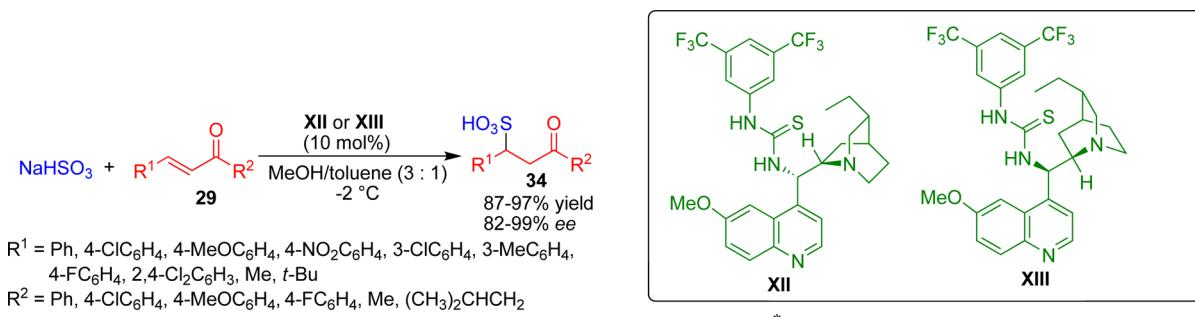
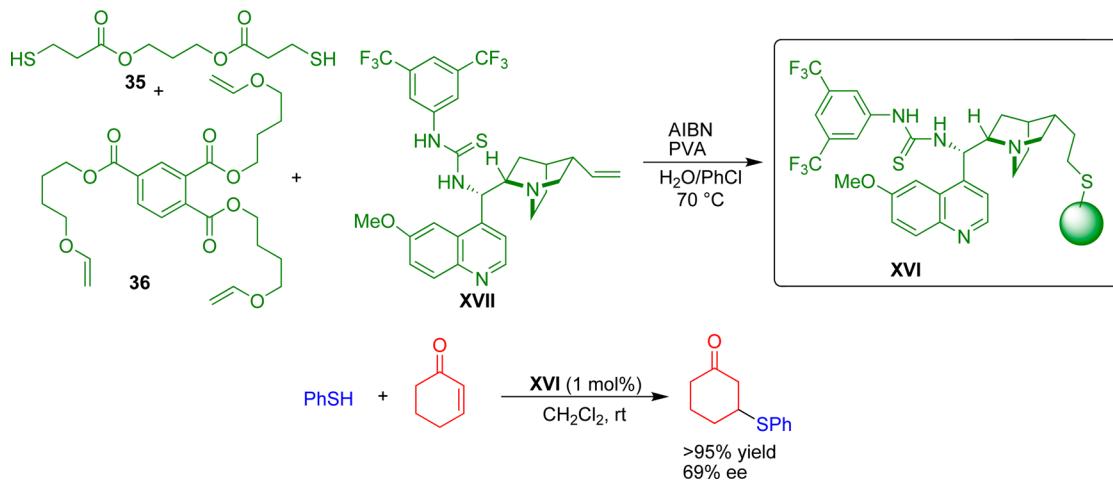


Figure 3. Structures of polymer-supported cinchona alkaloids.

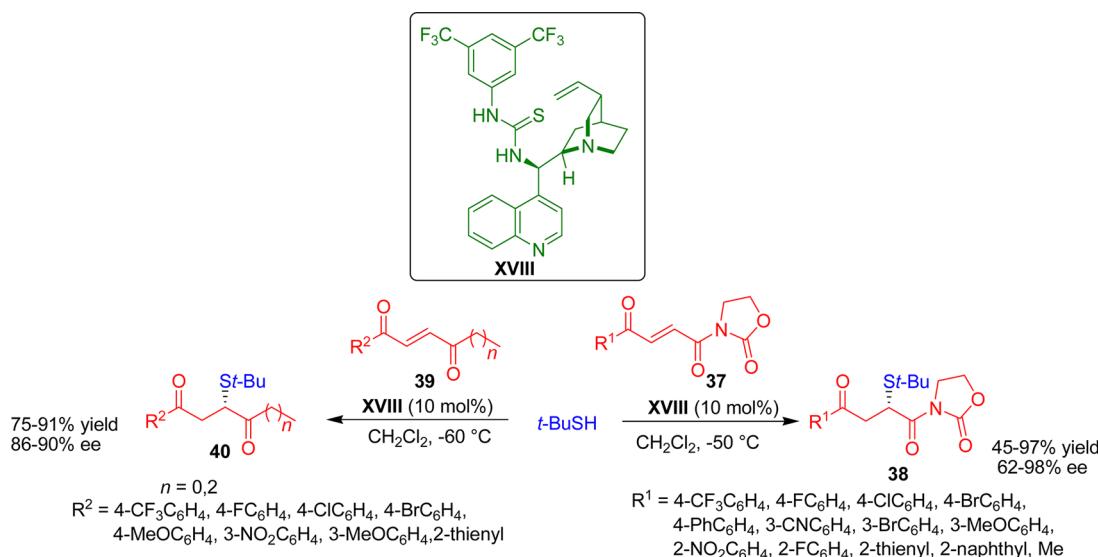
Scheme 16. SMA of Thiophenol to Cyclohexenone Promoted by the Supported Thiourea Catalyst XVI



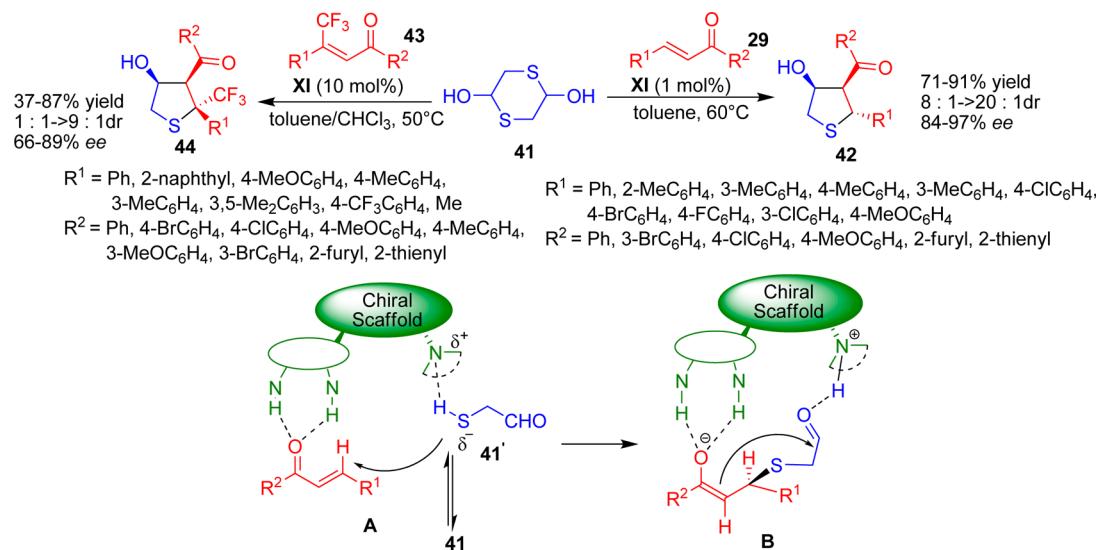
35, polyfunctional alkenes 36, and the unmodified thiourea XVII, in which the catalyst immobilization and the bead polymerization are combined in a single step (Scheme 16).³⁸ The resulting spherical and gel-type polymer beads of XVI were evaluated as organocatalysts in asymmetric Michael reactions. The supported thiourea organocatalyst XVI catalyzed efficiently the asymmetric SMA of cyclohexenone with thiophenol to provide the sulfa-Michael adduct in >95% yield and 69% ee. However, the supported organocatalyst gave lower enantioselectivity than the corresponding unsupported thiourea.

Jiang and co-workers have developed a highly enantio- and regioselective organocatalytic SMA of *tert*-butyl mercaptan with (*E*)-4-oxo-4-arylbutenamides 37 catalyzed by cinchona-derived tertiary amine-thiourea organocatalyst XVIII (Scheme 17).³⁹ Several chiral sulfur-containing imides 38 were synthesized in 75–97% yield and 62–98% ee. However, (*E*)-4-oxo-4-methylbutenamide provided the corresponding Michael adduct in only moderate yield (45%) and 62% ee. In addition, XVIII catalyzed the SMA of *tert*-butyl mercaptan to (*E*)-4-oxo-4-

Scheme 17. Enantioselective SMA of *tert*-Butyl Mercaptan with (*E*)-4-Oxo-4-aryl/alkyl-butenamides and (*E*)-4-Oxo-4-arylbutenones



Scheme 18. Cinchona Squaramide-Catalyzed Domino Sulfa-Michael/Aldol Reaction between 1,4-Dithiane-2,5-diol and Chalcones



arylbutenones **39**, allowing an easy access to sulfur containing ketones **40** in 75–91% yields and 86–90% ee.

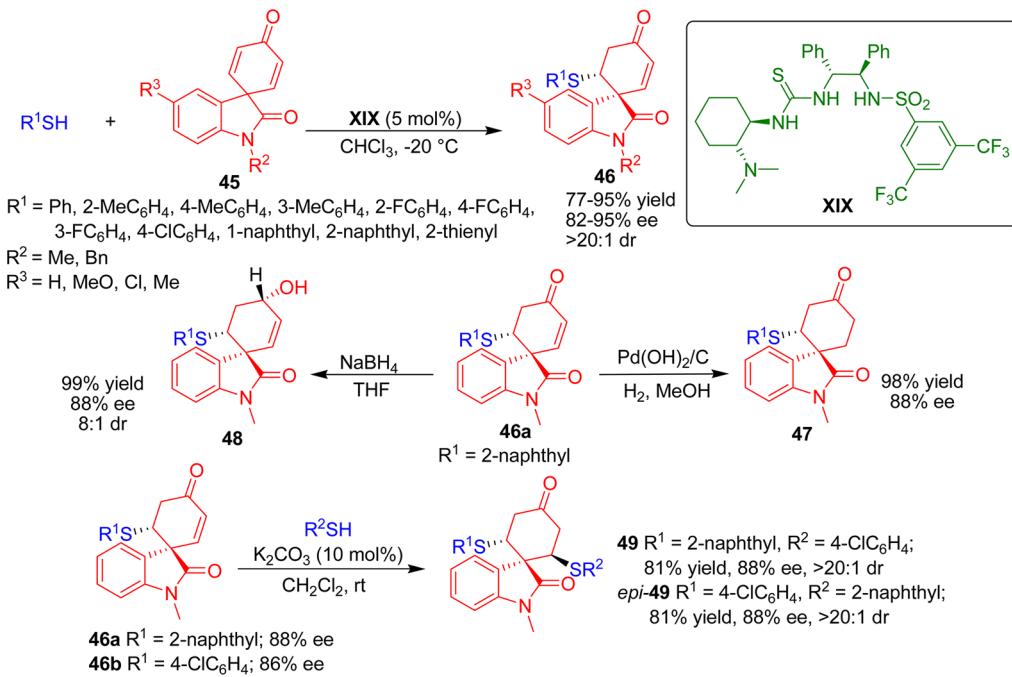
Xu and co-workers reported an efficient synthesis of enantioenriched trisubstituted tetrahydrothiophenes **42** via a bifunctional amino-squaramide **XI**-catalyzed domino sulfa-Michael/aldol reaction between 1,4-dithiane-2,5-diol (**41**) and chalcones **29** (Scheme 18).⁴⁰ The cinchona-derived amino-squaramide **XI** at low catalyst loading provided access to trisubstituted tetrahydrothiophenes **42** bearing three contiguous stereogenic centers in good yields (71–91%) and high stereoselectivities (8:1–20:1 dr and 84–97% ee). A remarkable temperature effect on the reaction efficiency was observed, and a synthetically potential gram-scale synthesis was also conducted successfully. A plausible mechanism for this cascade reaction involves the initiation of the reaction via a synergistic activation of both mercaptoacetaldehyde **41'** (generated from **41**) and the enone by catalyst **XI** to form the transition state **A**, which initiates an intramolecular SMA to provide the

intermediate complex **B**. The subsequent intramolecular aldol reaction resulted in the desired product.

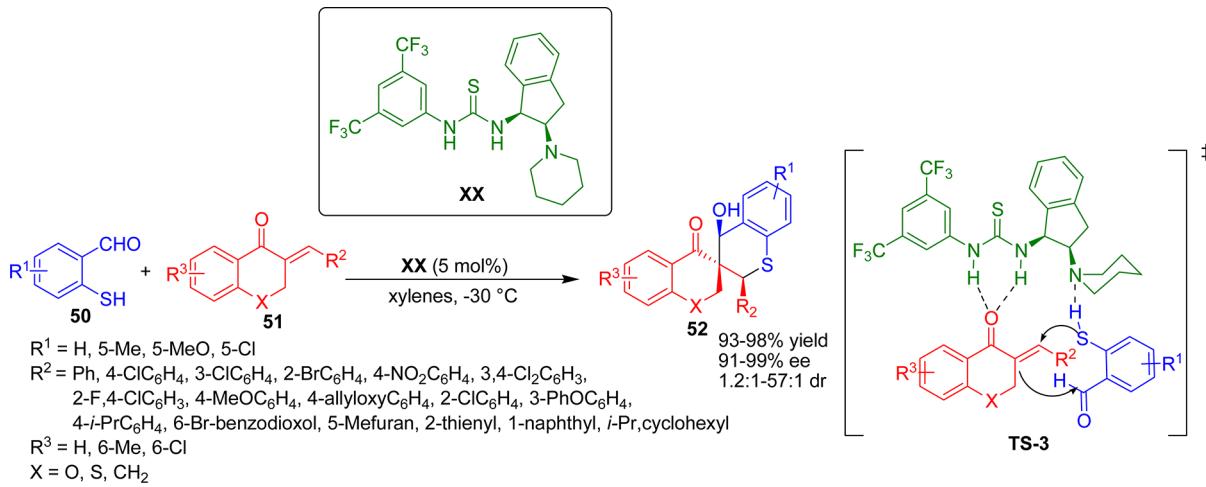
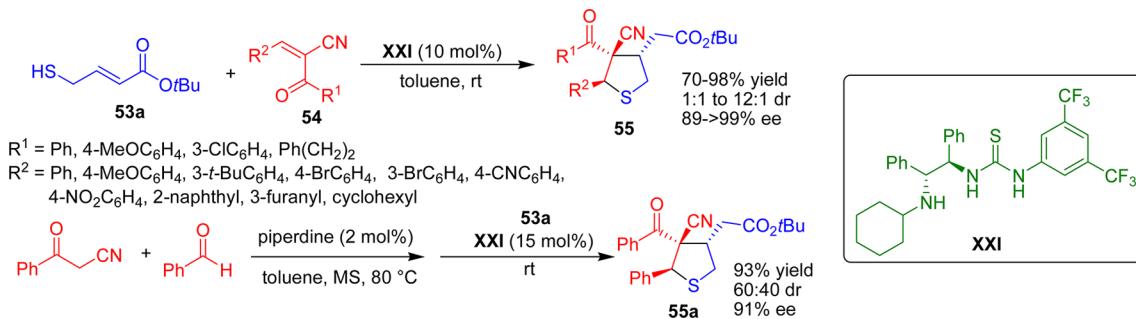
Very recently, a similar organocatalytic domino reaction was reported by Xu and co-workers for the synthesis of functionalized tetrahydrothiophenes **44** with three continuous stereocenters including a trifluoromethylated tetrasubstituted carbon (Scheme 18).⁴¹ The bifunctional tertiary amine-squaramide catalyst **XI** promoted the domino sulfa-Michael/aldol reaction of mercaptoacetaldehyde **41** with β -aryl- β -trifluoromethylated enones **43** to afford the corresponding tetrahydrothiophenes **44** in moderate to good yields and good to high enantioselectivities.

Very recently, C.-J. Wang and co-workers devised an excellent approach for the catalytic asymmetric synthesis of spirocyclic oxindoles **46** bearing an all-carbon quaternary and an adjacent tertiary stereogenic center via an organocatalyzed enantioselective sulfa-Michael/desymmetrization reaction of thiols with oxindoles **45** (Scheme 19).⁴² The tertiary amine-

Scheme 19. Enantioselective Sulfa-Michael/Desymmetrization Catalyzed by a Tertiary Amine-thiourea-sulfonamide



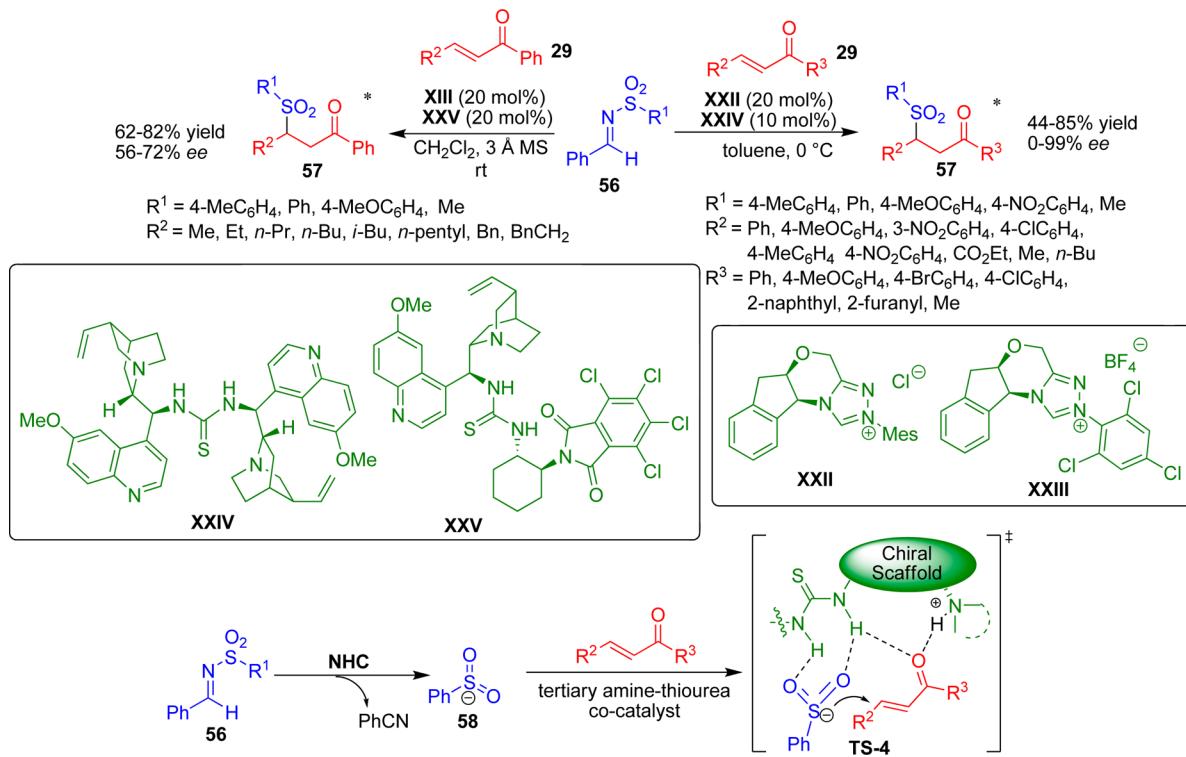
Scheme 20. Stereoselective Domino Reaction of Benzylidenechroman-4-ones with 2-Mercaptobenzaldehydes

Scheme 21. Secondary Amine-thiourea-Catalyzed Domino Sulfa-Michael/Michael Reaction of α -Cyano- α,β -Unsaturated Ketones

thiourea-sulfonamide catalyst XIX exhibits high reactivity and provided spirocyclic oxindoles 46 in excellent diastereoselectivities (>20:1) and very good enantioselectivities (82–95% ee) with a broad range of oxindole substrates. Direct hydrogenation

of the spirocyclic adduct 46a with Pd(OH)₂/C provided the cyclohexanone 47 without loss of diastereomeric and enantiomeric excess. Treatment of the spirocyclic oxindole with NaBH₄ at room temperature afforded the corresponding

Scheme 22. SMA of in Situ Generated Sulfinic Anion to Enones



alcohol **48** containing one quaternary and two tertiary stereogenic centers in high yield and acceptable diastereoselectivity. An achiral base-catalyzed SMA was also successfully implemented, which provided the epimeric *2,6-trans*-configured products **49** and *epi*-**49** by simply switching the addition sequence of the two different sulfur nucleophiles.

In 2010, J. Wang et al. described a highly stereoselective domino reaction of various benzylidenechroman-4-ones **51** with 2-mercaptopbenzaldehydes **50** (Scheme 20).⁴³ A new chiral bifunctional tertiary amine-thiourea catalyst **XX** promoted this asymmetric domino sulfa-Michael/aldol reaction to allow an efficient access to chiral spiro-chromanone-thiochromans **52** in high yields (93–98%) and excellent enantioselectivities (91–99% ee) with moderate to excellent diastereoselectivities (1.2:1–57:1 dr). In the transition state **TS-3**, the catalyst simultaneously activates the benzylidenechroman-4-one and the 2-mercaptopbenzaldehyde with the thiourea and tertiary amine moiety through hydrogen bonding, respectively.

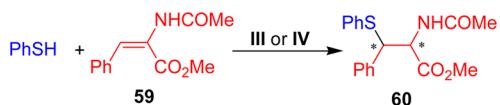
In 2013, the research group of Lattanzi reported a stereoselective synthesis of highly functionalized tetrahydrothiophenes **55** bearing three contiguous stereocenters, one of which is quaternary via an organocatalytic domino sulfa-Michael/Michael reaction involving a dynamic kinetic resolution (DKR) (Scheme 21).⁴⁴ A readily available secondary amine-thiourea **XXI** catalyzed efficiently the domino reaction between (*E*)-*tert*-butyl 4-mercaptop-2-butenoate (**53a**) and (*E*)- α -cyano- α,β -unsaturated ketones **54** to provide the tetrahydrothiophene derivatives **55** in high yields (70–98%), poor to good diastereoselectivities (1:1–12:1 dr), and excellent enantioselectivities (89–99% ee). A one-pot sequential Knoevenagel/double Michael reaction involving benzaldehyde, benzoyl acetonitrile, and the 4-mercaptop-2-butenoate **53a** was also developed successfully, which gave the corresponding tetrahydrothiophene **55a** in 93% yield, 60:40 dr, and 91% ee.

Very recently, Chi and coauthors reported a cocatalytic system of a tertiary amine-thiourea and *N*-heterocyclic carbene (NHC) for the enantioselective addition of the sulfinic anion to enones (Scheme 22).⁴⁵ The combination of an NHC generated from **XXII** and tertiary amine-thiourea **XXIV** efficiently promoted the SMA of the sulfinic anion generated from *N*-sulfonylimine to aryl substituted enones to provide the corresponding β -sulfonyl ketones **57** in low to good enantioselectivities. Under the optimized reaction conditions, the enones bearing alkyl substituents at the β -position resulted in poor enantiodifferentiation; however, the other catalytic combination of NHC precatalyst **XXIII** and thiourea **XXV** under different reaction conditions gave moderate enantioselectivities. The working hypothesis of this transformation is the generation of the sulfinic anion **58** from the sulfonyl imines by the NHC, followed by the activation of the corresponding anion with the thiourea moiety of **XXIV** and simultaneous activation of the enone with the protonated quinuclidine moiety as well as with the thiourea NH through hydrogen bonding as shown in **TS-4**.

2.1.1.2. Addition to α,β -Unsaturated Esters. In 1977, Pracejus and co-workers screened different chiral amines, for example, cinchona alkaloids **I–IV**, strychnine, brucine, (–)-*N*-methyllephedrine, and *N,N*-dimethylphenylethylamine for the enantioselective sulfa-Michael/protonation reaction of benzylthiol with α -phthalimidomethacrylate to provide the corresponding 1,4-adduct with a moderate level of enantioselectivity (4–54% ee).⁴⁶ Among the different chiral amines, the cinchona alkaloids provided maximum enantioselectivity.

Keniya and co-workers reported a SMA of thiophenol to unsaturated acceptor **59** catalyzed by quinidine **III** or quinine **IV** to provide the sulfa-Michael adduct **60** in 40% ee (Scheme 23).⁴⁷ The reductive desulfurization of the sulfa-Michael adduct afforded an enantiomerically enriched phenylalanine derivative.

Scheme 23. Quinine- or Quinidine-Catalyzed Enantioselective SMA of Thiophenol to 59



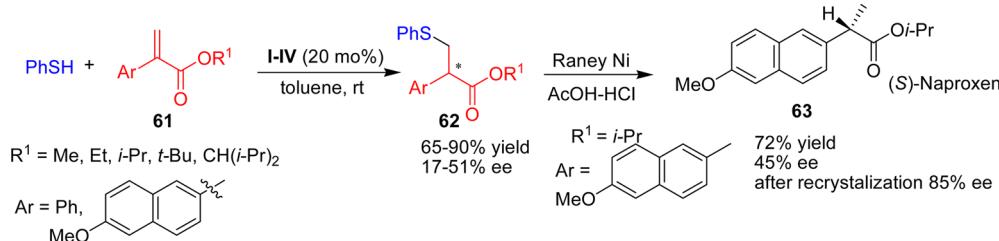
In the early 1990s, Dike and co-workers used natural cinchona alkaloids **I–IV** for the domino sulfa-Michael/protonation of thiophenol with α -phenyl acrylates **61** (Scheme 24).⁴⁸ The corresponding adducts **62** were obtained in 65–90% yield and low to moderate level of enantioselectivities (17–51% ee). The synthetic utility of the quinine-catalyzed domino sulfa-Michael/protonation reaction was explored for the synthesis of enantiomerically enriched (*S*)-naproxen **63** in 45% ee; however, the enantiomeric excess was enriched to 85% after crystallization.

In 2008, Tan et al. reported an improved method for the domino sulfa-Michael/protonation reaction of α -phthalimido-methacrylates using the chiral bicyclic guanidine **XXVI** as organocatalyst (Scheme 25).⁴⁹ The guanidine-catalyzed SMA/protonation reaction of various thiols **23** with *tert*-butyl 2-phthalimidoacrylates **64** afforded the desired adducts **65** in excellent yields (92–99%) and very good enantioselectivities (84–94% ee). In this transformation, the guanidine serves as a Lewis base by abstracting a proton from the thiol (Scheme 26). The corresponding thiolate **A** then undergoes the addition to the β -position of *tert*-butyl 2-phthalimidoacrylate to form an enolate, to which the guanidine delivers a proton from one preferred enantioface giving rise to the asymmetric induction in the desired product, as shown in TS-5. On the basis of DFT calculations, Wong and co-workers suggested an unconventional bifunctional mode of activation by guanidine **XXVI** in the sulfa-Michael/protonation reaction of thiophenol with *tert*-butyl 2-phthalimidoacrylate.⁵⁰ In this transformation, the guanidinium cation acts as a Lewis acid via the electrophilic central carbon, as well as a Brønsted acid.

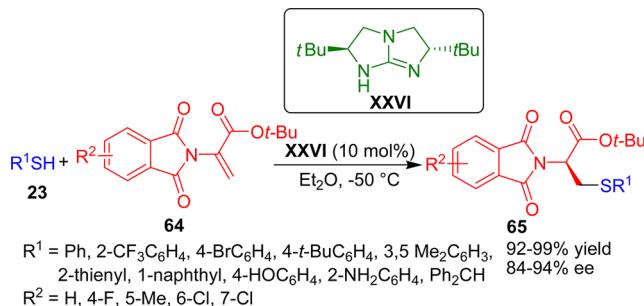
Mukaiyama and Yamashita studied the SMA of maleates with thiophenol promoted by the natural cinchona alkaloids I–IV (Scheme 27).⁵¹ The reaction proceeded with excellent yields (>95%) and low to good levels of asymmetric induction to form the adducts 67. The enantioselectivity of the product was higher in nonpolar solvents. Furthermore, the enantioselectivity of the products depended on the reaction concentration; that is, more dilute solutions led to significantly higher enantioselectivities, but the yield deteriorated.

C.-J. Wang and co-workers reported a multifunctional tertiary amine-thiourea-sulfonamide **XIX**-catalyzed highly enantioselective SMA of thiols to the 4,4,4-trifluorocrotonate **68** (Scheme 28).⁵² The reactions of **68** with aryl thiols catalyzed by 1 mol % of **XIX** afforded the corresponding Michael adducts **69**

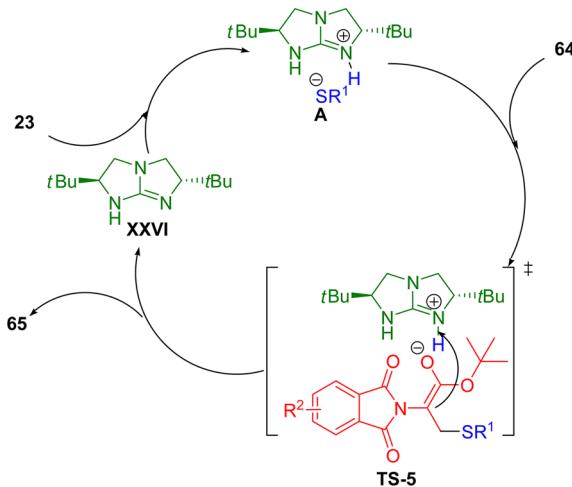
Scheme 24. Domino Sulfa-Michael/Protonation of Thiophenol with α -Phenylacrylates



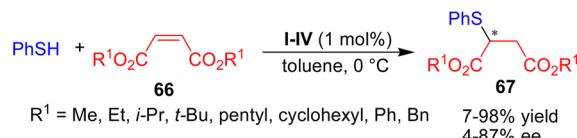
Scheme 25. Chiral Bicyclic Guanidine-Catalyzed Sulfa-Michael/Protonation Reaction



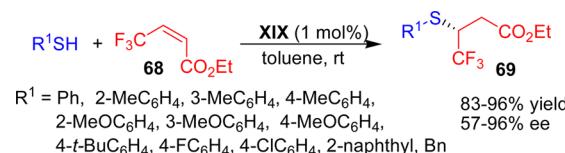
Scheme 26. Catalytic Cycle for the Bicyclic Guanidine-Catalyzed Domino Sulfa-Michael/Protonation Reaction

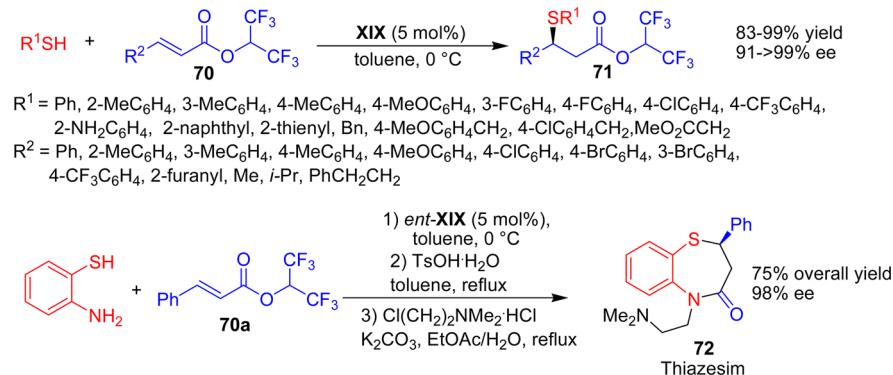
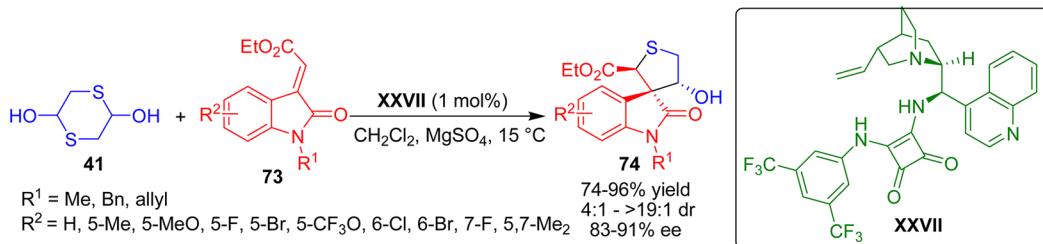
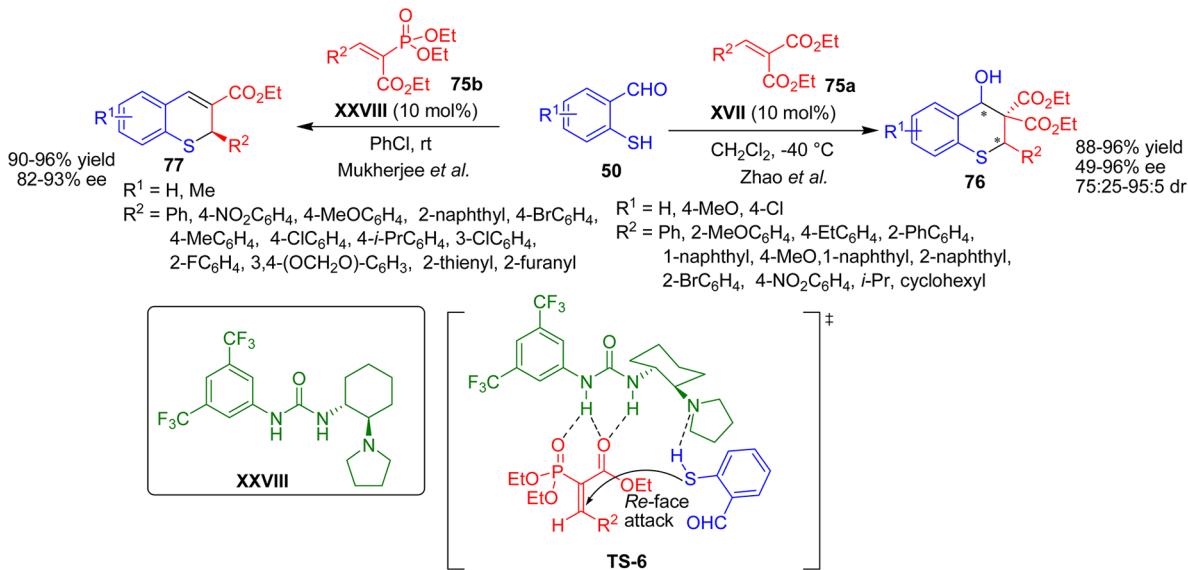


Scheme 27. Cinchona Alkaloid-Catalyzed SMA of Thiophenol with Maleates



Scheme 28. SMA of Thiols with 4,4,4-Trifluorocrotonates



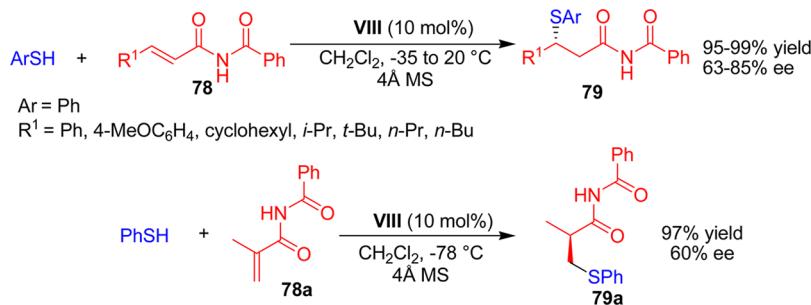
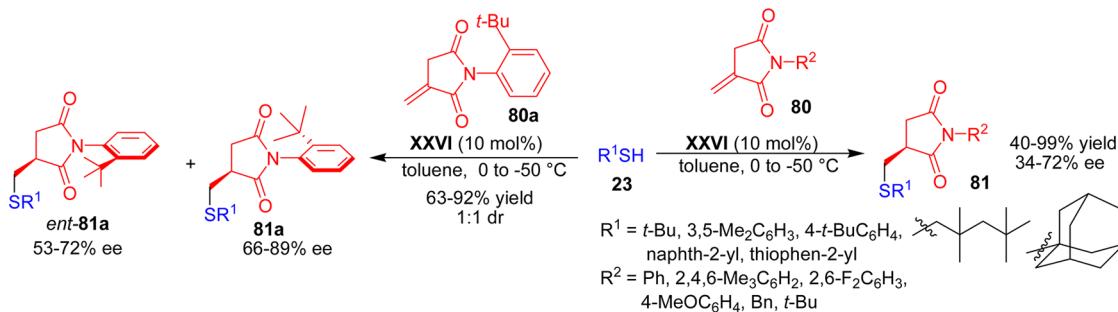
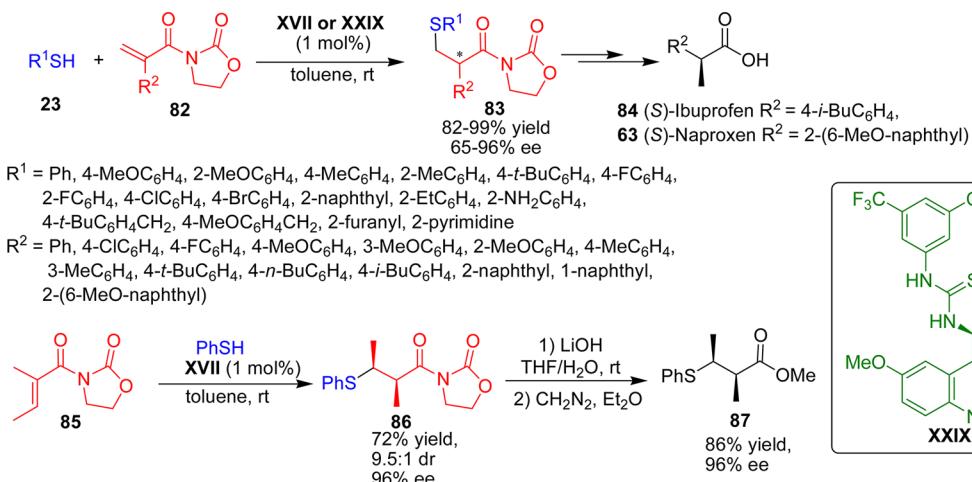
Scheme 29. SMA of Thiols with Hexafluoroisopropyl α,β -Unsaturated Esters**Scheme 30. Domino Sulfa-Michael/Aldol Reaction of 3-Ylideneoxindoles with 1,4-Dithiane-2,5-diol****Scheme 31. Domino Reactions of 2-Mercatobenzaldehydes with Benzylidenemalonates and Vinylphosphonates**

bearing a trifluoromethylated stereogenic center and a sulfur atom in high yields (83–96%) and moderate to excellent enantioselectivities (57–96% ee). However, when benzyl thiol was used only, a moderate level of enantioselectivity was obtained.

C.-J. Wang and co-workers also reported that an electron-withdrawing group, that is, hexafluoroisopropyl, was crucial for the enhancement of the electrophilicity of unsaturated esters and developed a highly efficient asymmetric SMA of a broad range of thiols with various hexafluoroisopropyl α,β -unsaturated esters **70** catalyzed by the amine-thiourea-sulfonamide catalyst **XIX** (Scheme 29).⁵³ With 5 mol % of **XIX**, the corresponding adducts **71** were synthesized in high yields (83–99%) and excellent enantioselectivities (91–99% ee). The

synthetic importance of this methodology was demonstrated by the one-pot three-step synthesis of the antidepressant agent (*R*)-thiazesim **72** in good overall yield and high enantioselectivity.

In 2012, Xiao et al. reported the asymmetric synthesis of spirocyclic oxindole derivatives **74** fused with tetrahydrothiophene via an organocatalytic stereoselective domino sulfa-Michael/aldol reaction (Scheme 30).⁵⁴ The aminosquaramide organocatalyst **XXVII** catalyzed efficiently the domino sulfa-Michael/aldol reaction of 3-ylideneoxindoles **73** with 1,4-dithiane-2,5-diol **41** to provide an efficient access to a new family of tetrahydrothiophene fused spirooxindoles **74** bearing three consecutive stereogenic centers in good to high yields (74–96%) and good to high stereoselectivities (4:1–19:1 dr

Scheme 32. SMA of Thiophenols to α,β -Unsaturated Imides Employing Takemoto's Tertiary Amine-thiourea Catalyst**Scheme 33.** Guanidine-Catalyzed SMA of Thiols with N-Arylitaconimides**Scheme 34.** SMA of Thiols with N-Acryloyloxazolidin-2-ones

and 83–91% ee). A domino Michael/Michael reaction of 3-ylideneoxindoles **73** with (*E*)-methyl 4-mercaptop-2-butenoate catalyzed by a cinchona-derived amino-thiourea afforded tetrahydrothiophene fused spirocyclic oxindole derivatives in 94–98% yields, 88–93% ee, and 84:16–94:6 dr.⁵⁵

In 2008, Zhao and co-workers reported the synthesis of enantioenriched tetrasubstituted thiochromanes via a domino sulfa-Michael/aldol type reaction between 2-mercaptopbenzaldehydes **50** and benzylidene malonates **75a** (Scheme 31).⁵⁶ Using 9-*epi*-aminoquinine thiourea **XVII** as catalyst, a series of chiral tetrasubstituted thiochroman-4-ols **76** were obtained in moderate to high enantioselectivities (49–96% ee) and diastereoselectivities (75:25–95:5 dr). It was observed that the *ortho*-substituents on the phenyl ring of the benzylidene moiety increase the diastereoselectivity of the corresponding products, while the enantioselectivity decreases if the phenyl ring is substituted with an electron-withdrawing group.

Very recently, Choudhury and Mukherjee developed an efficient organocatalytic enantioselective domino sulfa-Michael/Horner–Wadsworth–Emmons (HWR) reaction of 2-mercaptopbenzaldehydes **50** with vinylphosphonates **75b** (Scheme 31).⁵⁷ The chiral bifunctional tertiary amine-urea **XXVIII** promoted the domino reaction between **50** and **75b** to furnish a variety of aryl and heteroaryl-substituted thiochromanes **77** in excellent yields (90–96%) with a high level of enantioselectivities (82–93% ee). The authors have highlighted that the role of the phosphonate moiety is not only limited to enhancing the electrophilicity of the acceptor, but also to participate as a traceless binding site in the transition state TS-6, where the urea forms hydrogen bonds with both carboxylate and phosphonate oxygen atoms. The tertiary amine of the catalyst enhances the nucleophilicity of sulfur nucleophile for the *Re*-face addition at the unsaturated acceptor. Subsequent HWE reaction gave the observed (*R*)-enantiomer of the desired product. The dual role of the phosphonate functionality was

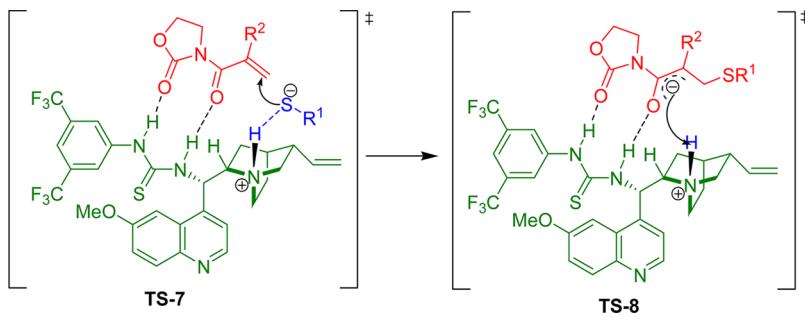


Figure 4. Proposed transition states for the thiourea-catalyzed sulfa-Michael/protonation reaction.

proved by the failure of the reaction of 2-mercaptopbenzaldehyde with ethyl cinnamate under the optimized reaction conditions. However, the phosphonate moiety alone was found to be ineffective to activate the olefin for the Michael addition as is apparent from the inertness of the vinylphosphonate without the ester moiety toward 2-mercaptopbenzaldehyde.

2.1.1.3. Addition to α,β -Unsaturated Amides and Imides. Chen et al. used Takemoto's tertiary amine-thiourea catalyst **VIII** to promote the conjugate addition of thiophenols to α,β -unsaturated imides **78**, leading to the adducts **79** in high yields and moderate enantioselectivities (Scheme 32).²⁸ The amine-thiourea **VIII**-catalyzed domino SMA/protonation of thiophenol to the methacrylic imide **78a** provided the chiral Michael adduct **79a** in 97% yield and 60% ee. The squaramide **XI**-catalyzed similar SMA/protonation reactions of α -substituted acrylimides with alkyl and benzylthiols furnished the corresponding products in good yields (76–95%) and low to good enantioselectivities (13–92% ee).⁵⁸

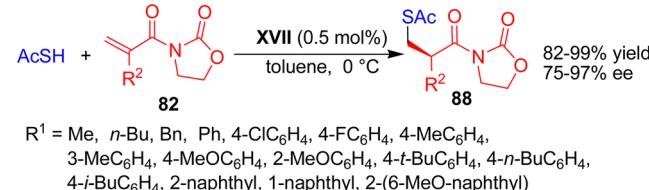
The bicyclic guanidine **XXVI**-catalyzed SMA of N-substituted itaconimides **80** with thiols reported by Tan and co-workers delivered the desired products **81** in 40–99% yields and 34–72% ee (Scheme 33).⁵⁹ The corresponding SMA of thiols with *N*-aryltaconimide **80a** bearing a large *ortho*-*tert*-butyl group led to a diastereomeric mixture of **81a** and *ent*-**81a** in 1:1 ratio with 75–92% yields and 53–89% ee for both diastereomers. The experimental and computational study of the rotational barrier of the C–N axis of *N*-2-*tert*-butyl phenyltaconimide revealed that the experimental ΔG^\ddagger of 32.4 kcal mol^{−1} correlates well with the computational DFT value of ΔG^\ddagger , that is, 30.9 kcal mol^{−1}. Such high energy barriers may provide a useful means for chirality transfer.

Singh and co-workers published an efficient SMA of thiols with α -substituted *N*-acryloyloxazolidin-2-ones **82** catalyzed by the cinchona-derived tertiary amine-thiourea **XVII** (Scheme 34).⁶⁰ The corresponding sulfa-Michael adducts **83** were easily obtained by using only 1 mol % of thiourea in a moderate to high level of enantioselectivity (65–96% ee) from a variety of thiols and α -prochiral imides **82**. Using the pseudoenantiomeric catalyst **XXIX**, the opposite enantiomer of the sulfa-Michael adduct was synthesized with an identical level of enantioselectivity. The synthetic utility of this sulfa-Michael/protonation reaction was further explored by transforming the products obtained with catalyst **XXIX** to biologically active molecules, such as (*S*)-Ibuprofen (**84**) and (*S*)-Naproxen (**63**). Furthermore, the α,β -disubstituted *N*-acryloyloxazolidin-2-one **85** also undergoes a SMA with thiophenol under the catalytic influence of **XVII** to provide the desired adduct **86** in 72% yield, 9.5:1 dr, and 96% ee. The Michael adduct **86** was transformed successfully into the corresponding methyl ester **87** without any epimerization.

The proposed transition state **TS-7** for the tertiary amine-thiourea **XVII**-catalyzed sulfa-Michael/protonation involves the activation of the α -prochiral imide by the thiourea moiety through double hydrogen bonding, while the thiol gets activated by the tertiary nitrogen of the quinuclidine moiety (Figure 4). The Michael addition of thiolate to imide generates a transient ion pair in **TS-8**. Subsequent delivery of the proton from the quinuclidine nitrogen to the *Si*-face of the generated prochiral enolate leads to the formation of the major stereoisomer.

Singh and co-workers further extended the substrate scope of the organocatalytic domino sulfa-Michael/protonation by using thioacetic acid as the nucleophile (Scheme 35).⁶¹ Cinchona-

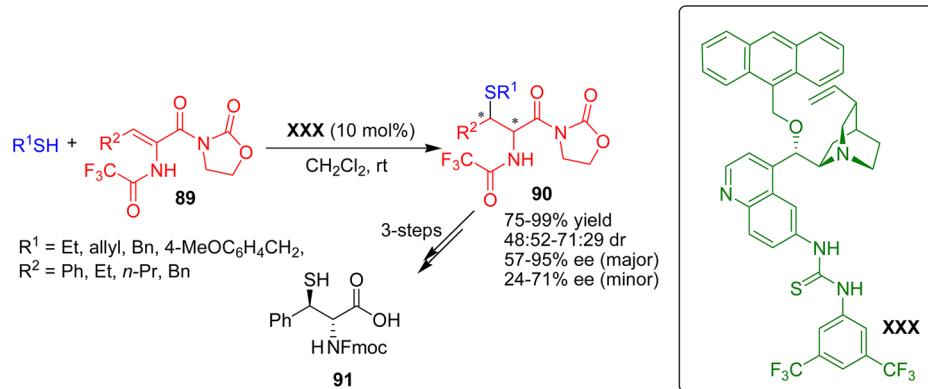
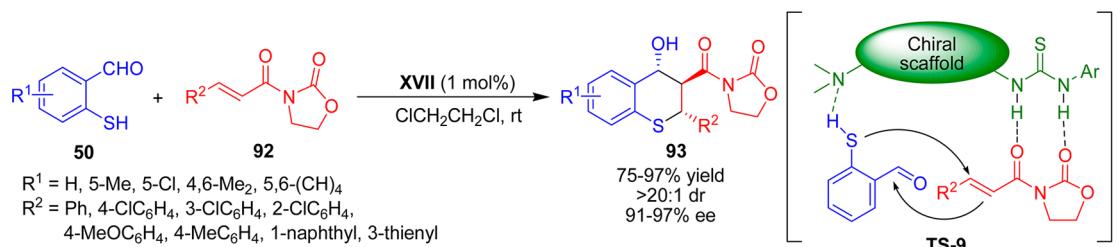
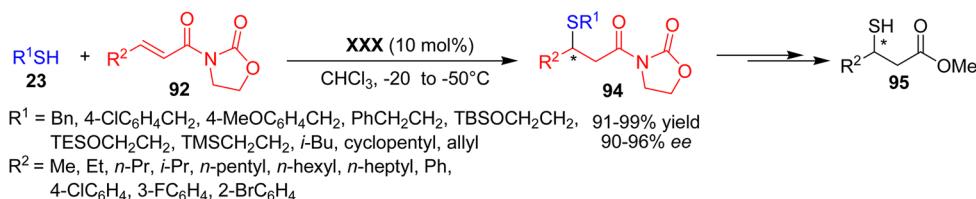
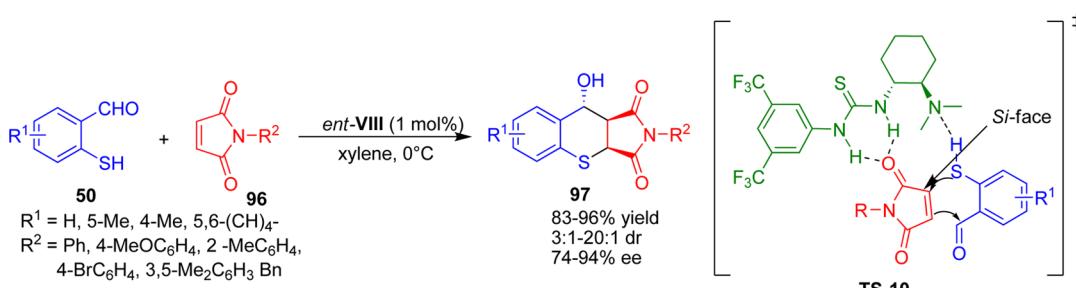
Scheme 35. Sulfa-Michael/Protonation Reaction of Thioacetic Acid with α -Substituted *N*-Acryloyloxazolidin-2-ones



derived tertiary amine-thiourea **XVII** at low catalyst loading promoted the sulfa-Michael/protonation reaction of the thioacetic acid with a series of α -substituted *N*-acryloyloxazolidin-2-ones **82** to afford the addition adducts **88** in 75–97% ee with very good yields (82–99%). The tertiary amine-thiourea **XVII** also catalyzed the 1,4-addition/protonation reaction between a 2-phthalimidoacrylate derivative and thioacetic acid to provide the corresponding adduct in 90% yield and 71% ee.

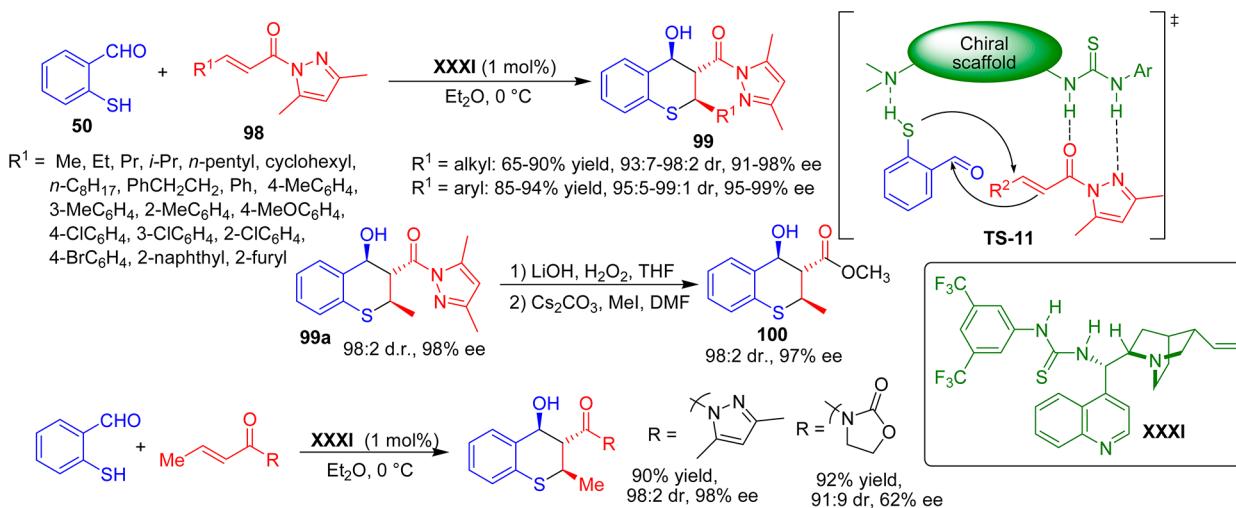
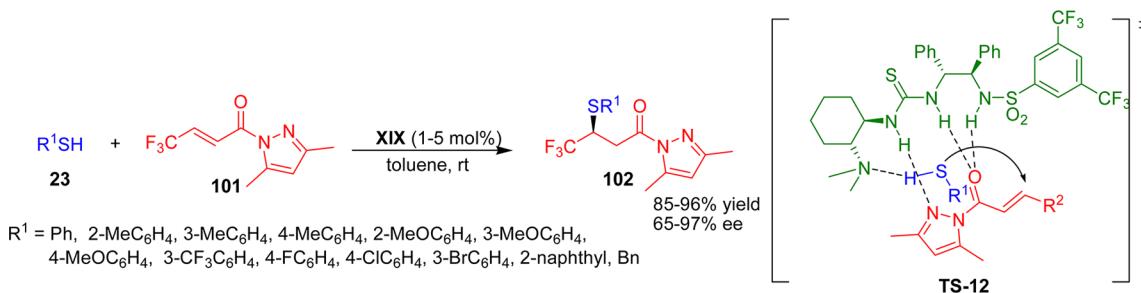
In 2012, Hiemstra and co-workers prepared a new class of substrates **89** based on α,β -unsaturated amino acids for asymmetric organocatalyzed SMAs (Scheme 36).⁶² The cinchona-derived thiourea **XXX** catalyzed the sulfa-Michael/protonation reaction of these new Michael acceptors **89** with aromatic as well as aliphatic thiols proceeding smoothly to provide the 1,4-adducts **90** in good to high yields (75–99%), poor to excellent enantioselectivities (24–95% ee), and low to moderate diastereoselectivities (48:52–71:29 dr). The sulfa-Michael product of this transformation was converted into the β -thiol-substituted amino acid **91** in good overall yield.

In 2007, W. Wang and co-workers developed a highly stereoselective organocatalytic domino sulfa-Michael/aldol reaction for the asymmetric synthesis of synthetically useful thiochromanes (Scheme 37).⁶³ The cinchona-derived thiourea

Scheme 36. Cinchona-Derived Thiourea-Catalyzed SMA of α,β -Unsaturated Amides with Aromatic and Aliphatic Thiols**Scheme 37.** Domino Sulfa-Michael/Aldol Reaction of 2-Mercaptobenzaldehydes with α,β -Unsaturated Oxazolidinones**Scheme 38.** Enantioselective SMA of Alkyl Thiols to α,β -Unsaturated N-Acylated Oxazolidin-2-ones**Scheme 39.** Domino Aulfa-Michael/Aldol Reaction of 2-Mercaptobenzaldehydes with Maleimides Catalyzed by Takemoto's Catalyst

catalyst XVII at low loading (1 mol %) efficiently promoted the domino Michael/aldol reactions of 2-mercaptopbenzaldehydes **50** with α,β -unsaturated oxazolidinones **92** to provide the optically active thiochromane derivatives **93** in good to high yields (75–99%), high diastereoselectivity (>20:1 dr), and excellent enantioselectivities (91–98% ee). This reaction was assumed to proceed via transition state **TS-9**, in which the tertiary amine-thiourea catalyst behaves as a bifunctional catalyst, by providing simultaneous hydrogen-bonding activation to both the 2-mercaptopbenzaldehyde and the α,β -unsaturated oxazolidinones through the quinuclidine nitrogen and thiourea moiety, respectively.

In 2009, Deng et al. reported a new enantioselective SMA of alkyl thiols **23** to α,β -unsaturated *N*-acylated oxazolidin-2-ones **92** (Scheme 38).⁶⁴ The quinidine derived C6'-thiourea **XXX** was found to be the best catalyst to promote the addition of various alkyl thiols **23** to Michael acceptors **92**, giving rise to the 1,4-adducts **94** in excellent yields (91–99%) and high enantioselectivities (90–96%). The products of this transformation served as a precursor for the synthesis of optically active β -mercaptoesters **95**. The quinine and quinidine-derived amino-squaramide-catalyzed SMA of various thiols to β -substituted- β -trifluoromethyl oxazolidinone enoates provided both enantiomers of trifluoromethylated tertiary thioethers in 71–99% yields and 39–99% ee.⁶⁵

Scheme 40. Domino Sulfa-Michael/Aldol Reaction of 2-Mercaptobenzaldehyde with α,β -Unsaturated *N*-Acyl Imides**Scheme 41.** SMA of Thiols to (*E*)-4,4,4-Trifluorocrotonamide

In 2007, W. Wang and co-workers reported an organocatalytic enantioselective domino sulfa-Michael/aldol reaction of 2-mercaptobenzaldehydes **50** with maleimides **96** (Scheme 39).⁶⁶ Low catalyst loading of Takemoto's catalyst *ent*-VIII afforded the succinimide derivatives **97** containing benzothiopyran with three vicinal stereogenic centers in 83–96% yield, 3:1–20:1 dr, and 74–94% ee. The proposed transition state **TS-10** involves the activation of the maleimide with the thiourea moiety of the catalyst and simultaneous activation and orientation of 2-mercaptobenzaldehyde by the tertiary amine functionality of the catalyst through hydrogen bonding for *Si*-face attack to the maleimide. Subsequently, the aldol type addition to the formyl group generates the product with the observed *cis*-(2*S*,3*S*) configuration. One of the limitations of this methodology is the need to use *N*-arylmaleimides, because *N*-alkylmaleimides resulted in a decreased diastereoselectivity. An organocatalytic domino sulfa-Michael/Mannich reaction of 2-mercaptopquinoline-3-carbaldimines with maleimides catalyzed by *ent*-VIII gave rise to the corresponding multifunctionalized tetracyclic quinolines in 85–95% yield, 90–99% ee, and >99:1 dr.⁶⁷

In 2012, C.-J. Wang's group used the low loading of the cinchona-derived thiourea **XXXI** for an efficient domino sulfa-Michael/aldol reaction of 2-mercaptobenzaldehyde **50** with α,β -unsaturated *N*-acyl imides **98** bearing a β -aryl and alkyl substituent to give a direct access to bioactive thiochromanones **99** in 65–94% yield, 93:7–99:1 dr, and 91–99% ee (Scheme 40).⁶⁸ The corresponding optically active adduct **99a** containing three trisubstituted stereogenic centers was readily transformed into a synthetically useful β -hydroxy carboxylic acid ester **100** without losing its stereochemical integrity via

cleavage of the pyrazole moiety followed by esterification. The role of the pyrazole motif for a high asymmetric induction was demonstrated by replacing the pyrazole with the oxazolidinone group in the unsaturated acceptor. The α,β -unsaturated oxazolidinones led to an inferior level of enantio- and diastereoselectivity with the same level of diastereoselectivity, which revealed that introducing the pyrazole moiety into the crotonamide plays a significant role in providing hydrogen-bond acceptor sites for better organization and chelation as shown in **TS-11** and hence delivering higher enantioselectivity as compared to that when using oxazolidinone as an amide moiety.

C.-J. Wang's group further reported an efficient organocatalytic SMA of thiols **23** to *trans*-4,4,4-trifluorocrotonamide **101** catalyzed by the multifunctional tertiary amine-thiourea-sulfonamide catalyst **XIX** (Scheme 41).⁶⁹ A low catalyst loading of **XIX** provided a rapid access to the sulfa-Michael adducts **102** bearing a trifluoromethyl group in 85–96% yield and 65–97% ee. A slow reaction rate and a poor asymmetric induction in the case of an α,β -unsaturated ester suggests the importance of the pyrazole moiety for achieving high enantioselectivity by facilitating the hydrogen-bonding of the substrate with the thiourea moiety. In the transition state **TS-12**, the (*E*)-4,4,4-trifluorocrotonamide gets activated by the thiourea and sulfonamide moiety through multiple hydrogen bonding, thereby increasing its electrophilicity for the *Si*-face attack of the sulfur nucleophile, which in turn is activated by the tertiary amine of the catalyst.

2.1.1.2. Addition to Nitroalkenes. Nitroalkenes are very powerful acceptors for various nucleophiles in asymmetric and nonasymmetric transformations.⁷⁰ The asymmetric Michael

addition of various nucleophiles to nitroalkenes represents a direct and most appealing approach to chiral nitroalkanes, which can then be transformed into other valuable molecules.⁷¹

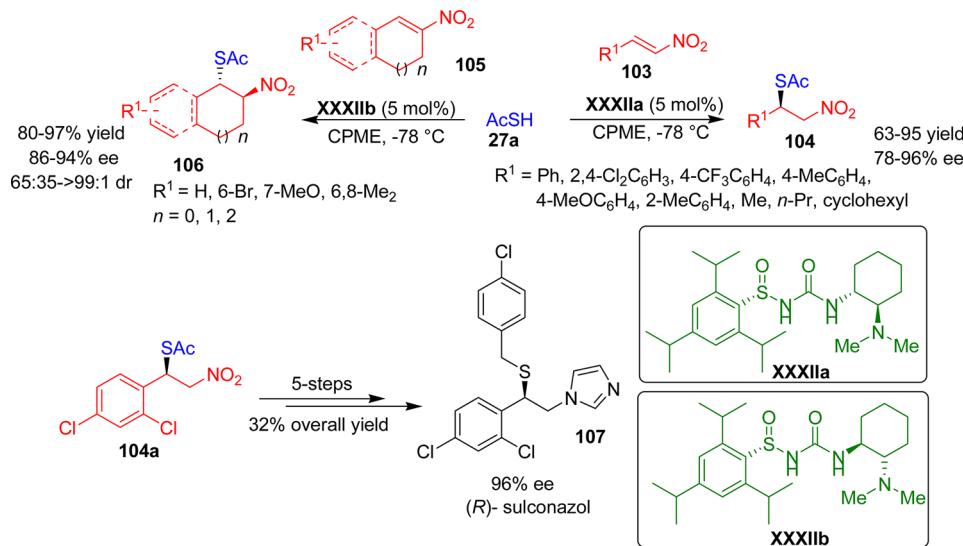
In 1977, Pracejus' group investigated the asymmetric addition of benzyl and *tert*-butylthiol to β -nitrostyrenes.⁴⁶ Among the various catalysts, brucine provided the best enantioselectivity of 27% ee. In 1981, Kobayashi's group studied the effect of catalyst loading on the enantioselectivity of the sulfa-Michael product in the quinine-catalyzed addition of thioglycolic acid to (*E*)- β -nitrostyrene.⁷² With 1 mol % of quinine, 88% of the (−)-sulfa-Michael adduct with 15% ee was obtained after 114 h, while 27 mol % quinine affords the adduct with only 1% ee. Further increasing the loading of quinine to a stoichiometric amount provided the (+)-sulfa-Michael adduct in 96% yield with 35% ee in 30 min. Furthermore, in a more diluted concentration of thioglycolic acid, a significant increase in the enantioselectivity (58% vs 35% ee with 1.09 equiv quinine) was observed. The authors reasoned that at a low catalyst loading of quinine, the ammonium salt (formed by reaction of quinine and thioglycolic acid) was the active catalyst, which gives a low ee. At intermediate levels of catalyst loading, the ammonium salt and quinine compete, and thus no observable asymmetric induction was observed. At high catalyst loading, quinine became an effective catalyst, yielding the opposite enantiomer of the product with higher enantioselectivity.

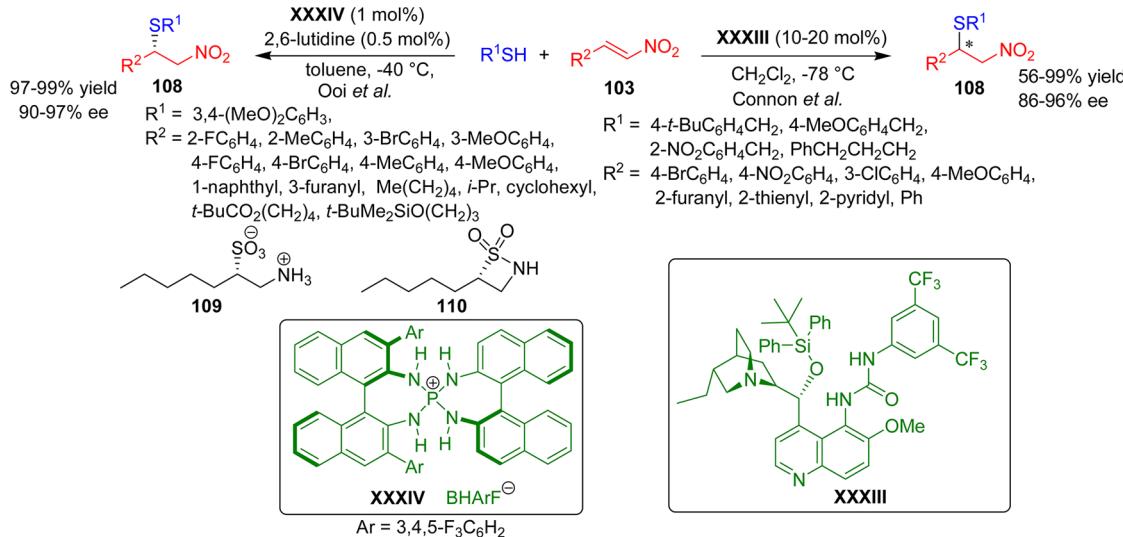
In 2006, W. Wang and co-workers reported a SMA of thioacetic acid with nitroolefins **103** catalyzed by the bifunctional tertiary amine-thiourea catalyst *ent*-VIII (Scheme 42).⁷³ Using 2 mol % of *ent*-VIII, the 1,2-nitrothiols **104** were

Scheme 42. SMA of Thioacetic Acid with Nitroolefins Employing Takemoto's Thiourea Catalyst

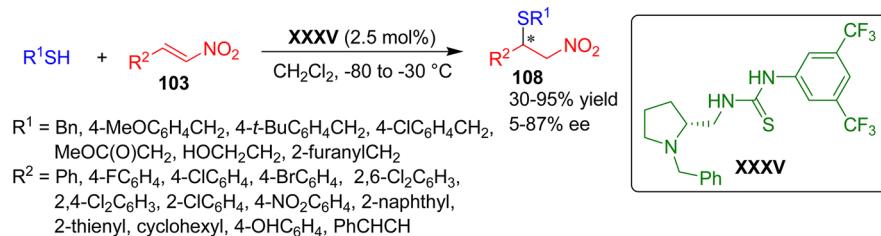
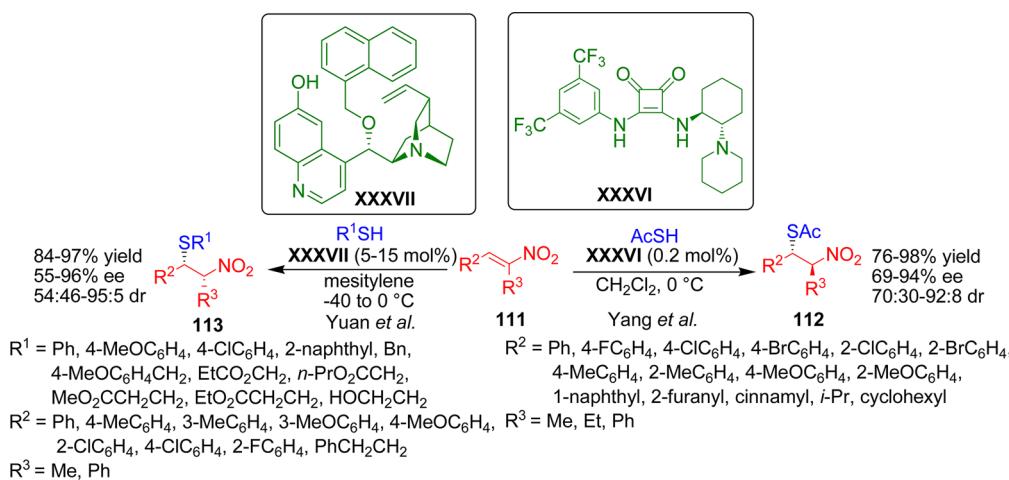


Scheme 43. Sulfinyl Urea-Catalyzed Enantioselective SMA of Thioacetic Acid to Nitroalkenes



Scheme 44. SMA of Thiols to β -Nitrostyrenes Catalyzed by XXXIII and XXXIV

Scheme 45. N-3,5-Bis(trifluoromethyl)phenyl Thiourea-Catalyzed SMA of Thiols to Nitroolefins

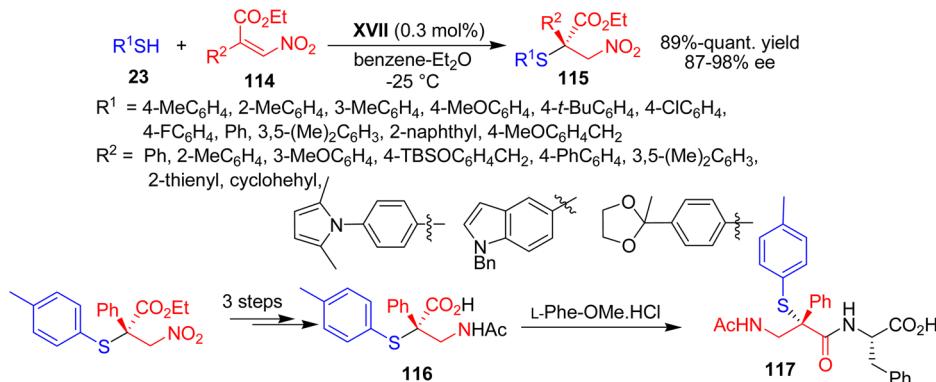
Scheme 46. Amino-squaramide- and Cupredine Derivative-Catalyzed SMA of Various Sulfur Nucleophiles to α,β -Disubstituted Nitroalkenes

to provide the corresponding β -nitro sulfides **108** in excellent yields (97–99%) and high enantioselectivities (90–97% ee). The potential synthetic utility of this method was demonstrated by the efficient synthesis of a chiral taurine derivative **109** and the 4-monosubstituted β -sultam **110**.

Recently, Kowalczyk's group developed a new *N*-3,5-bis(trifluoromethyl)phenyl thiourea **XXXV** as an effective organocatalyst for the asymmetric SMA of aliphatic thiols with nitroolefins **103**, thus providing the adducts **108** in 30–95% yields and 22–87% ee (Scheme 45).⁷⁸ The newly developed tertiary amine-thiourea also catalyzed the addition

of thiols to nitrodienes to give the corresponding products in good yields (64–93%) and poor to good enantioselectivities (5–82% ee).

In 2012, Yang and Du reported a highly stereoselective SMA of thioacetic acid to α,β -disubstituted nitroalkenes **111** (Scheme 46).⁷⁹ The chiral amino-squaramide **XXXVI** at very low catalyst loading (0.2 mol %) furnished the synthetically useful β -nitro sulfides **112** in good to excellent yields (76–98%) with moderate to good diastereoselectivities (70:30–92:8 dr) and moderate to high enantioselectivities (69–94% ee). The addition of thioacetic acid to (*E*)- β -nitrostyrene (R³ = H)

Scheme 47. SMA of Thiols with β,β -Disubstituted Nitroalkenes

afforded the corresponding Michael-adduct in 94% yield; however, the ee was only 52%.

Recently, Yuan's group published a similar asymmetric SMA of various sulfur nucleophiles to a wide range of α,β -disubstituted nitroalkenes **111** catalyzed by the bifunctional organocatalyst **XXXVII** derived from cupredine (Scheme 46).⁸⁰ The corresponding adducts **113** were obtained in good to high yields (84–97%) with low to very good diastereoselectivities (54:46–95:5 dr) and moderate to very good enantioselectivities (55–96% ee).

Xiao and co-workers reported an organocatalytic enantioselective SMA of β,β -disubstituted nitroalkenes **114** (Scheme 47).⁸¹ Various thiols were efficiently added to the electrophilic nitroacrylates using a low loading of the bifunctional tertiary amine-thiourea catalyst **XVII** derived from cinchona alkaloids to provide excellent yields (89%–quant.) and high enantioselectivities (87–98% ee) of the sulfa-Michael adducts **115** bearing a tetrasubstituted stereocenter. The addition product of this transformation was successfully transformed into the new $\beta^{2,2}$ -amino acid **116** and β -peptide **117**.

In 2008, W. Wang and co-workers reported a highly stereoselective domino sulfa-Michael/Michael reaction of the 3-(2-mercaptophenyl)-2-propenoic acid ethyl esters **118** with nitroalkene derivatives **103** catalyzed by a cinchona-derived thiourea **XVII** (Scheme 48).⁸² Using 2 mol % of **XVII**, a series of highly functionalized thiochromanes **119** bearing three adjacent stereogenic centers were obtained in low to high yields (32–99%) and excellent stereoselectivities (93–99% ee and

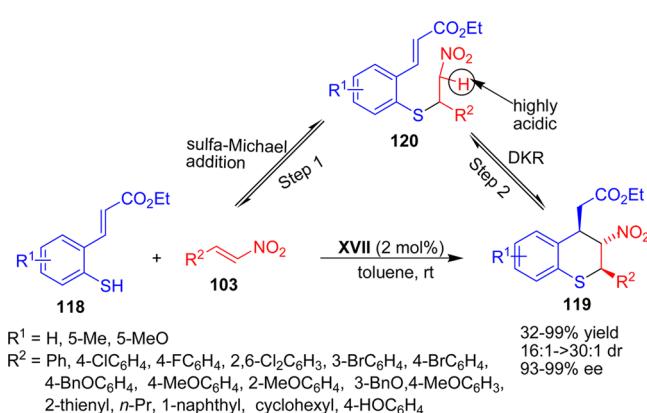
16:1–30:1 dr). Various nitrostyrene derivatives bearing electron-withdrawing and electron-releasing substituents were tolerated under the standard reaction condition; however, with aliphatic nitroalkenes, poor yields of the corresponding thiochromanes were observed with excellent stereoselectivities.

The thiourea **XVII**-catalyzed single conjugate addition reaction of thiols with nitroolefins resulted in low enantioselectivity. On the basis of this, a Michael/*retro*-Michael/Michael/Michael cascade pathway was proposed, which involves a DKR of the initially formed sulfa-Michael adduct **120** in the presence of the catalyst. Deprotonation of the highly acidic nitroalkane proton of **120** by the bifunctional amine-thiourea leads to a reversible and highly stereoselective *retro*-Michael/Michael/Michael process. This hypothesis was confirmed by treatment of the racemic Michael adduct with 10 mol % of thiourea **XVII** under the optimized reaction conditions, which provided the product in 94% yield, 95% ee, and >30:1 dr, with the same 2*R*,3*S*,4*S* configuration that was observed from the direct reaction.

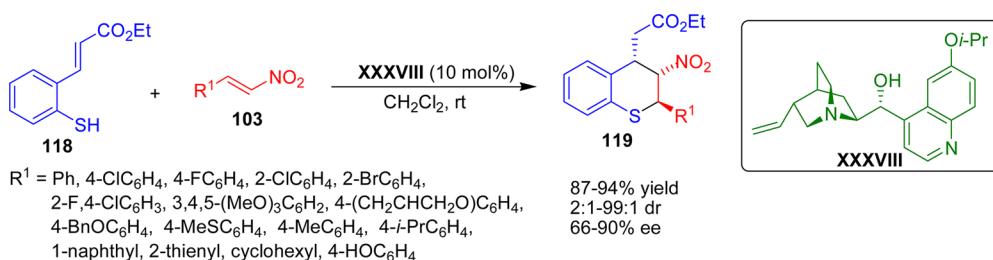
A newly synthesized quinine-derived catalyst was also found to promote the stereoselective synthesis of thiochromane derivatives **119** via a sulfa-Michael/Michael domino sequence (Scheme 49).⁸³ The quinine derivative **XXXVIII** turned out to be the best catalyst for the domino reaction of 3-(2-mercaptophenyl)-2-propenoic acid ethyl esters **118** with various nitroalkenes **103** to provide various densely functionalized thiochromanes **119** in high yields (87–94%), good to excellent diastereoselectivities (15:1–99:1 dr), and a good level of enantioselectivities (82–90% ee). The nitroalkene bearing a 4-hydroxy substituent gave the corresponding thiochromane in 89% yield, but with poor diastereoselectivity (2:1 dr) and low enantioselectivity (64% ee). It was observed that the catalyst in which the secondary OH was protected provided the Michael adduct with a sluggish reaction rate. Furthermore, cupreine bearing an additional OH group at the aromatic ring did not provide the desired thiochromane. On the basis of density functional theory (DFT) calculations under the generalized gradient approximation (GGA), it was also noticed that the positioning of the hydroxyl group was critical for the reaction success and the high asymmetric induction.

Xiao and co-workers explored the catalytic potential of the multifunctional tertiary amine-thiourea-sulfonamide catalysts **XIX** for a new domino sulfa-Michael/Michael reaction of thiols with nitroolefin enoates **121** (Scheme 50).⁸⁴ With 3 mol % of **XIX**, a series of highly functionalized chromanes **122** bearing a tetrasubstituted stereocenter was efficiently synthesized in good to high yields (73–92%), high diastereoselectivities (>95:5 dr),

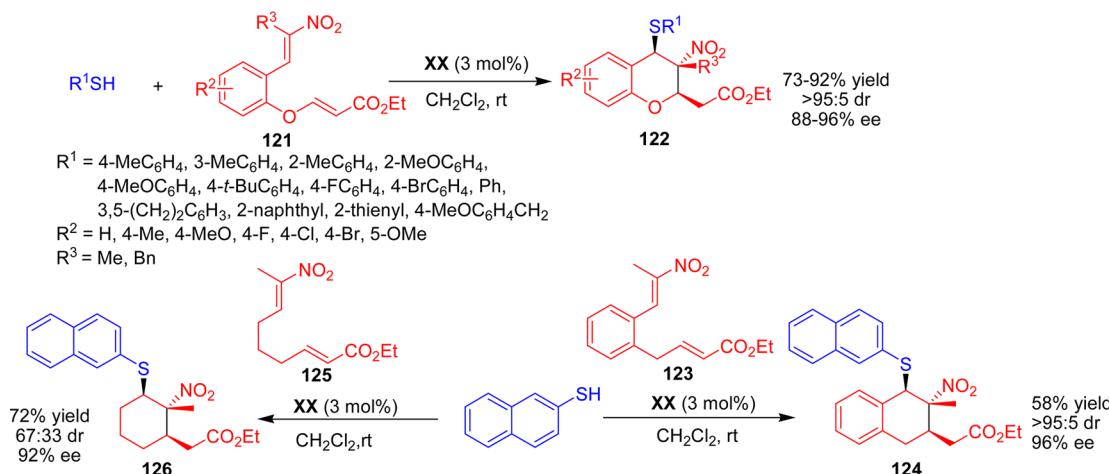
Scheme 48. Domino Sulfa-Michael/Michael Reaction of 3-(2-Mercaptophenyl)-2-propenoic Acid Ethyl Esters with Nitroalkenes



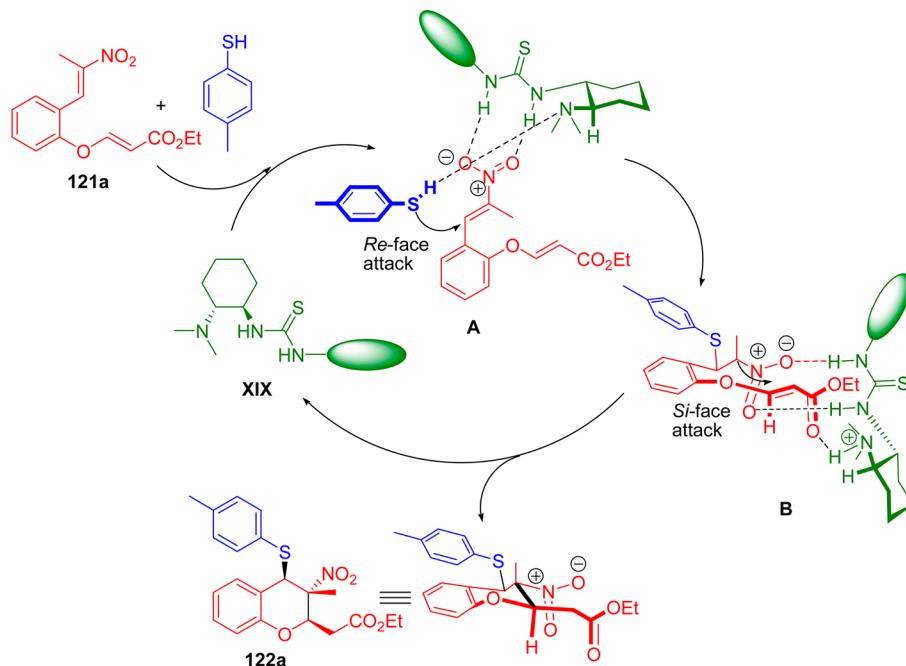
Scheme 49. Domino Reaction of 3-(2-Mercaptophenyl)-2-propenoic Acid Ethyl Esters with Various Nitroalkenes Catalyzed by a Quinine-Derived Catalyst



Scheme 50. Domino Sulfa-Michael/Michael Reaction of Thiols with Nitroolefin Enoates



Scheme 51. Plausible Catalytic Cycle for the Domino Sulfa-Michael/Michael Reaction of Thiols with Nitroolefin Enoates

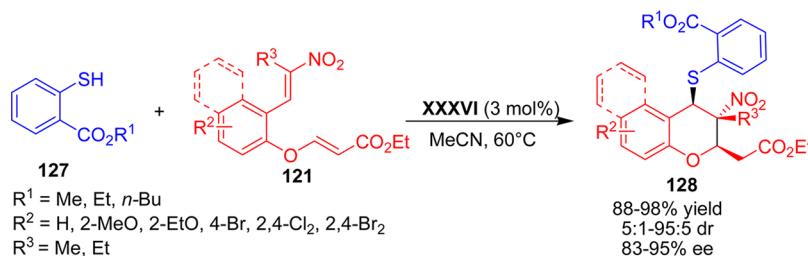


and very good enantioselectivities (88–96% ee). The asymmetric synthesis of the highly functionalized tetrahydronaphthalin **124** was also realized in 58% yield, >95:5 dr, and 96% ee, by reacting 2-mercaptoponaphthalin with **123**. The nitroalkene enoate **125** bearing an alkyl substituent instead of an ether provided the cyclohexane derivative **126** in moderate yield (72%) and high enantioselectivity (92% ee) with poor

diastereoselectivity (67:33 dr). A gram scale reaction was also carried out in the presence of only 0.5 mol % catalyst, giving rise to a slightly better yield (95%) of the product without any loss of stereoselectivity, thus highlighting the practical and preparative utility of the process.

A plausible catalytic cycle involves the activation of the nitroolefin enoate **121a** through a hydrogen-bonding inter-

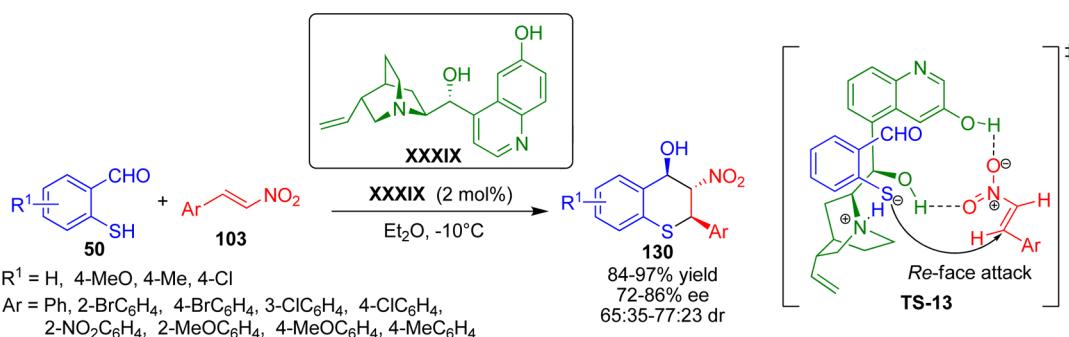
Scheme 52. Domino Sulfa-Michael/Michael Reaction of Thiols with Nitroolefin Enoates Promoted by a Tertiary Amine-squaramide Catalyst



Scheme 53. Domino Sulfa-Michael/ Michael Reaction of (*E*)-Ethyl-4-mercaptop-2-butenoate with Nitroalkenes



Scheme 54. Domino Sulfa-Michael/Henry Reaction between 2-Mercaptobenzaldehyde and Nitroolefins



Scheme 55. Domino Sulfa-Michael/Henry Reaction between 2-Mercaptoquinoline-3-carbaldehydes and Nitroolefins



action with the thiourea moiety of the catalyst and the tertiary amino group of the catalyst activates the nucleophile, thereby forming intermediate A, which undergoes the intermolecular sulfa-Michael addition to provide the intermediate B (Scheme 51). Another intramolecular Michael addition to this intermediate leads to the corresponding chromane 122a with release of the catalyst.

A similar asymmetric domino sulfa-Michael/Michael addition reaction between thiols 127 and nitroolefin enoates 121 via dynamic kinetic resolution has recently appeared in the literature (Scheme 52).⁸⁵ A low loading of the amino-squaramide XXXVI provided an easy access to highly functionalized chromanes 128 with three contiguous stereocenters in 88–98% yield, 5:1–95:5 dr, and 83–95% ee.

Ji, W. Wang, and co-workers described an asymmetric domino sulfa-Michael/Michael reaction between (*E*)-ethyl-4-mercaptop-2-butenoate (53b) and nitrostyrenes 103 (Scheme 53).⁸⁶ This stereoselective transformation mediated by a

tertiary amine-thiourea catalyst **VIII** yielded the trisubstituted tetrahydrothiophenes 129 bearing three stereogenic centers with moderate to good yields (51–93%), high enantioselectivities (92–97% ee), and high diastereoselectivities (6:1–30:1 dr). The aromatic nitroolefins bearing electron-neutral, electron-withdrawing, and electron-donating groups as well as aliphatic nitroalkenes were well tolerated under the optimized reaction conditions. The authors also demonstrated that a DKR occurred in this domino reaction in addition to the direct stereocontrol of the substrates by the bifunctional catalyst through hydrogen bonds.

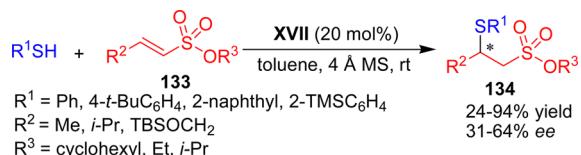
In 2008, Zhao and co-workers reported the enantioselective synthesis of 2,3,4-trisubstituted thiachromans 130 via a 6'-OH cinchona alkaloid-catalyzed asymmetric domino sulfa-Michael/Henry reaction (Scheme 54).⁸⁷ Cupreine XXXIX efficiently catalyzed the domino reactions of substituted 2-mercaptobenzaldehydes 50 with nitroalkenes 103 allowing a rapid access to 130 in high yields (84–97%), low to moderate diastereose-

lectivities (65:35–77:23 dr), and good enantioselectivities (72–86% ee). These thiochromane derivatives were obtained with high diastereoselectivities (87:13–9:1 dr) and enantioselectivities (85–99% ee) after a single crystallization. In the proposed transition state **TS-13, XXXIX** acts as a bifunctional catalyst by forming hydrogen bonds between the nitro-group of the nitroalkene with the 9-OH and the 6'-OH group, and the tertiary amine of the catalyst activating the sulfur nucleophile for the *Re*-face attack.

Very recently, a similar strategy for the domino sulfamichael/Henry reaction has been adopted by Zhou and co-workers for the synthesis of optically active $2H$ -thiopyrano[2,3-*b*]quinolines **132** with three contiguous stereocenters via the bifunctional amino-squaramide **XI**-catalyzed reaction between 2-mercaptoquinoline-3-carbaldehydes **131** and nitroolefins **103** (Scheme 55).⁸⁸ A series of $2H$ -thiopyrano[2,3-*b*]quinoline derivatives **132** were synthesized in very good yields (73–93%) and excellent enantioselectivities (95:5–99:1 dr and 86–99% ee).

2.1.1.3. Addition to α,β -Unsaturated Sulfonates and Sulphones. Organocatalytic asymmetric conjugate addition reactions of various nucleophiles to α,β -unsaturated sulfones and sulfonates provide a straightforward strategy to form optically active building blocks bearing a sulfur containing functionality.⁸⁹ Enders and Hoffman explored the reactivity of α,β -unsaturated sulfonates 133 for the enantioselective SMA (Scheme 56).⁹⁰ The cinchona alkaloid-derived thiourea XVII

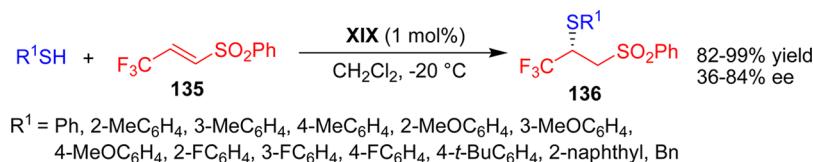
Scheme 56. SMA of Thiols with Alkyl-Substituted α,β -Unsaturated Sulfonates



efficiently catalyzed the SMA of aromatic thiols to various alkyl-substituted α,β -unsaturated sulfonates **133**, leading to β -sulfur-substituted sulfonic acid ester containing Michael adducts **134** in low to good yields (24–94%) and low to moderate enantioselectivities (31–64% ee). Phenyl-substituted α,β -unsaturated sulfonates turned out to be not suitable for SMAs in the presence of the thiourea catalyst.

Recently, C.-J. Wang and coauthors published a new asymmetric SMA of thiols to (*E*)-3,3,3-trifluoropropenyl phenyl sulfones **135** catalyzed by a bifunctional amine-thiourea-sulfonamide **XIX** (Scheme 57).⁹¹ At low catalyst loading of **XIX**, a variety of arylthiols as well as benzylthiols were added to the sulfones **135** to provide the desired sulfones **136** bearing a trifluoromethylated stereogenic center in high yields (82–99%) with low to good enantioselectivities (36–84% ee) in less than 2 h.

Scheme 57. SMA of Thiols to (*E*)-3,3,3-Trifluoropropenyl Phenylsulfones



2.1.2. Amino Catalysis via Iminium Activation

2.1.2.1. Secondary Amine Ca

2.1.2.1. Secondary Amine Catalysis. The secondary amine organocatalysts mainly derived from amino acids have emerged as powerful catalysts for the activation of α,β -unsaturated aldehydes via iminium ion formation for the Michael type addition of various carbon and heteroatom nucleophiles.^{92,93}

The first application of chiral secondary amine organocatalysts for asymmetric SMAs was explored by Jørgensen and co-workers in 2005.⁹⁴ They reported a multicomponent domino sulfa-Michael/amination reaction between alkyl thiols, enals 137, and azodicarboxylates 138 catalyzed by 2-[bis(3,5-bis(trifluoromethyl)phenyl)-trimethylsilyloxy]methyl]pyrrolidine XL (Scheme 58). A series of highly functionalized oxazolidinones 139 were synthesized in reasonable yields (38–72%), good to high diastereoselectivities (88:12–95:5 dr), and excellent enantioselectivities (97–99% ee) by the secondary amine XL-catalyzed domino reaction, followed by reduction of the corresponding aldehyde and subsequent base-catalyzed cyclization. A selective deprotection of the amine and the thio group in oxazolidinone 139a was successfully performed to provide 140 and 141 in good yields, respectively.

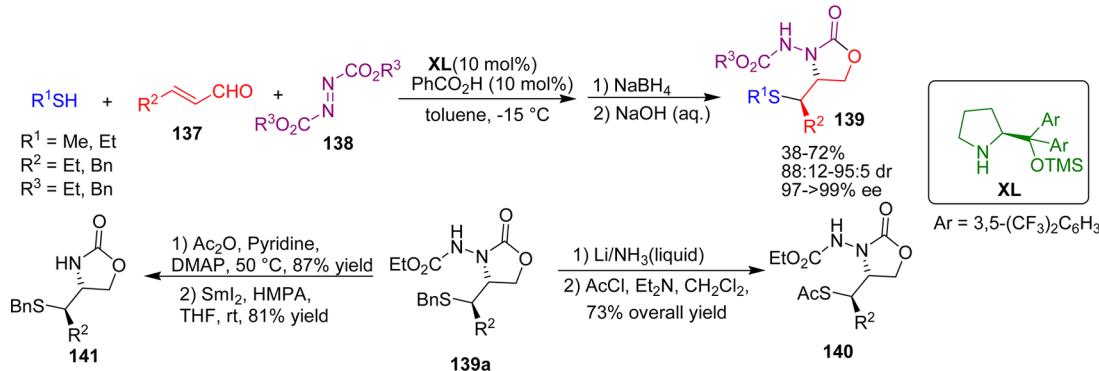
This domino sequence involves the initial formation of the iminium ion A derived from the enal and the secondary amine catalyst, which then stereoselectively reacts with the thiol to form the enamine B, which then undergoes a diastereoselective addition to the azo-dicarboxylate to form iminium ion C (Scheme 59). Hydrolysis of C returns the catalyst and forms the α,β -disubstituted aldehyde 142, the latter one being subjected to reduction and base-catalyzed cyclization to generate the desired product 139.

The application of chiral secondary amine organocatalysts for the asymmetric domino sulfa-Michael/aldol reaction was explored independently and simultaneously by the research groups of Wang and Córdova in 2006. W. Wang and co-workers developed a new organocatalytic domino sulfa-Michael/aldol reaction between the 2-mercaptopbenzaldehyde derivatives **50** and the α,β -unsaturated aldehydes **137** promoted by the secondary amine organocatalyst **XL** (Scheme 60).⁹³ Using 10 mol % of **XL**, synthetically useful chiral benzothiopyrans **143** were obtained in good to high yields (72–97%) and very good enantioselectivities (85–94% ee) from a broad range of α,β -unsaturated aldehydes and 2-mercaptopbenzaldehydes.

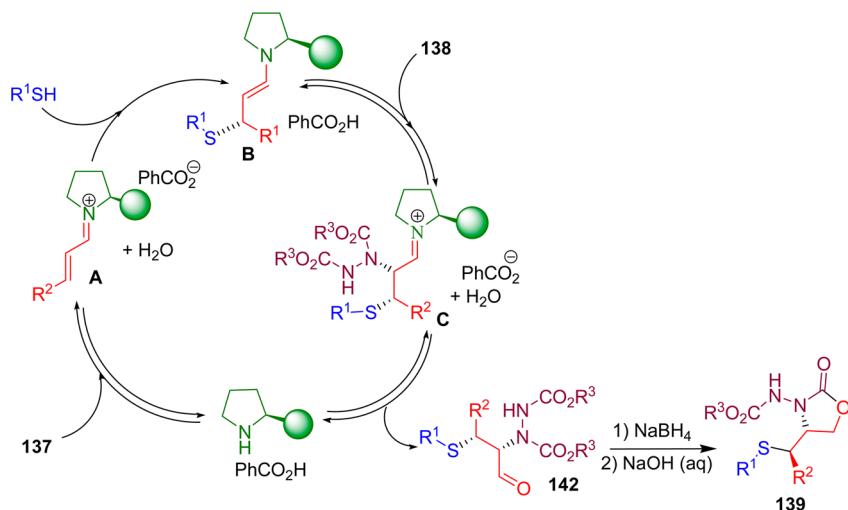
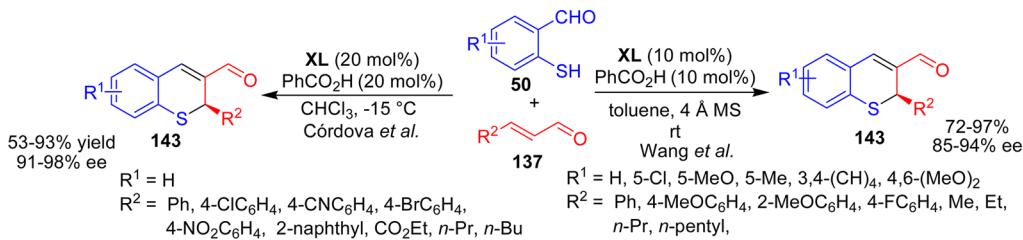
Simultaneously a similar domino reaction was reported by Córdova's group (Scheme 60).⁹⁶ With α,α -diarylprolinol trimethylsilylether XL as organocatalyst and benzoic acid as an additive, the reaction of 2-mercaptopbenzaldehydes 50 with various aryl and alkyl enals 137 proceeded smoothly to give the corresponding benzothiopyrans 143 in high yields and excellent enantioselectivities (91–98% ee).

These domino sulfa-Michael/aldol reactions proceed via the initial SMA of mercaptobenzaldehyde to the iminium ion A formed from 137 and catalyst the XL (Scheme 61). The resulting enamine intermediate B undergoes an intramolecular

Scheme 58. Domino Sulfa-Michael/Amination Reaction between Alkyl Thiols, Enals, and Azodicarboxylates



Scheme 59. Proposed Catalytic Cycle for the Domino Sulfa-Michael/Amination Reaction between Alkyl Thiols, Enals, and Azodicarboxylates

Scheme 60. Domino Sulfa-Michael/Aldol Reaction between 2-Mercaptobenzaldehydes and α,β -Unsaturated Aldehydes Promoted by a Secondary Amine Organocatalyst

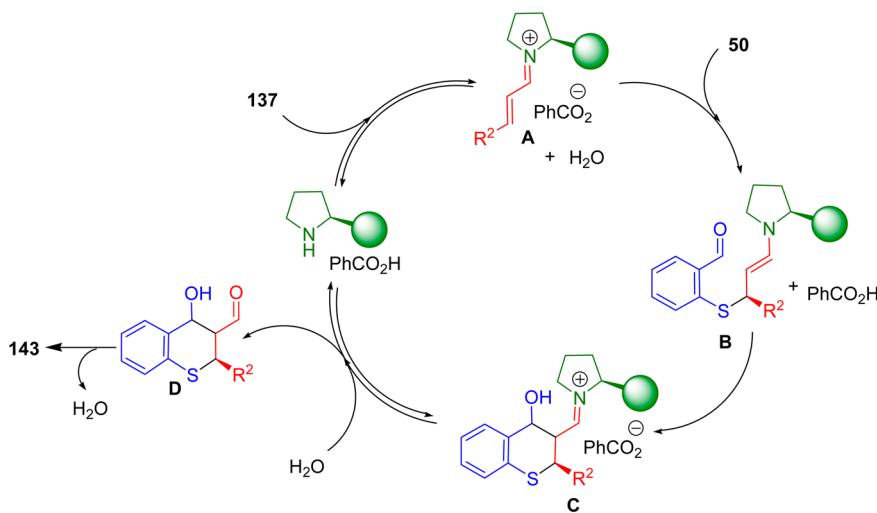
aldol reaction to generate iminium C, which is then hydrolyzed to generate the catalyst and the aldol product D. Subsequent dehydration of aldol product generates benzothiopyrans 143.

Córdova's group also reported the asymmetric synthesis of tetrahydrothioxanthenones via an organocatalytic enantioselective domino reaction between 2-mercaptobenzaldehyde (50) and α,β -unsaturated cyclic ketones (Scheme 62).⁹⁷ Prolinol XLI was found to be the best catalyst to catalyze the domino Michael/aldol reaction of six-membered cyclic enones 24a with 2-mercaptobenzaldehyde 50 to provide corresponding tetrahydrothioxanthenones 144a in 71–77% yields and 35–62% ee. Instead of prolinol, a secondary-tertiary amine catalyst XLII was found to be the best catalyst for the reactions of five- or seven-membered cyclic enones (24b and 24c), which afforded the desired adducts in 70–78% yield and 38–60% ee. Notably,

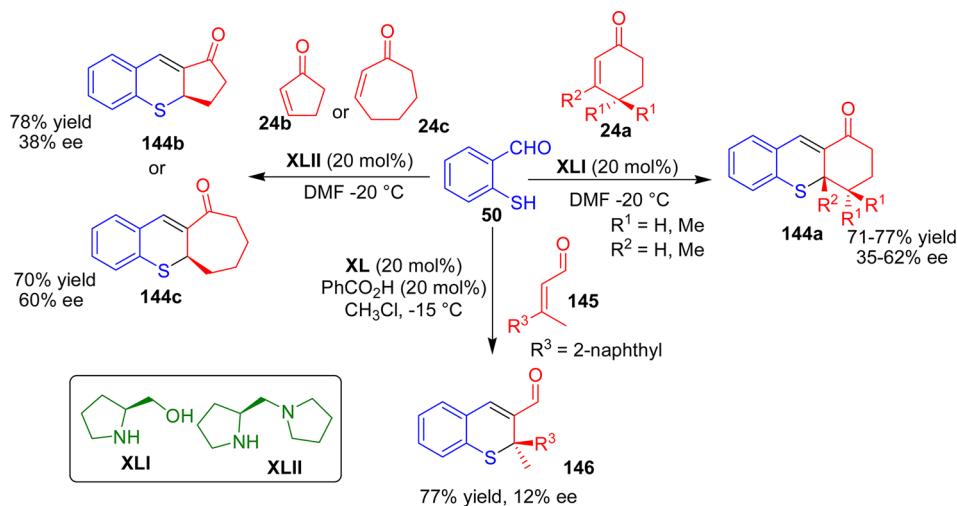
chiral alcohols were obtained in small amounts with high diastereoselectivity of >20:1 dr by rapid chromatography as the dehydrated products were formed by the dehydration upon silica gel column chromatography when a slow gradient system was used. The α,α -diarylprolinol trimethylsilylether XL-catalyzed domino reaction of β,β -disubstituted enal 145 with 2-mercaptobenzaldehyde 50 gave the thiachromene 146 bearing a tetrasubstituted stereocenter in 77% yield, but the enantioselectivity was rather poor (12% ee).

Recently, Y. Wang, Zhou, and co-workers published an efficient domino sulfa-Michael/aldol reaction of 2-mercaptopquinoline-3-carbaldehydes 131 with enals 137 catalyzed by the diphenylprolinol TMS ether XLIII (Scheme 63).⁹⁸ A series of pharmaceutically useful enantioenriched 2*H*-thiopyrano[2,3-

Scheme 61. Proposed Catalytic Cycle for the Domino Sulfa-Michael/Aldol Reaction between 2-Mercaptobenzaldehydes and α,β -Unsaturated Aldehydes



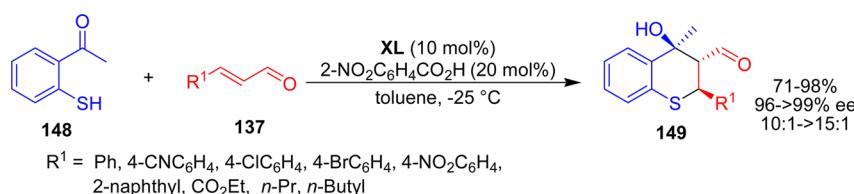
Scheme 62. Domino Sulfa-Michael/Aldol Reaction of 2-Mercaptobenzaldehyde with α,β -Unsaturated Cyclic Ketones



Scheme 63. Domino Sulfa-Michael/Aldol Reactions of 2-Mercaptoquinoline-3-carbaldehydes with Enals



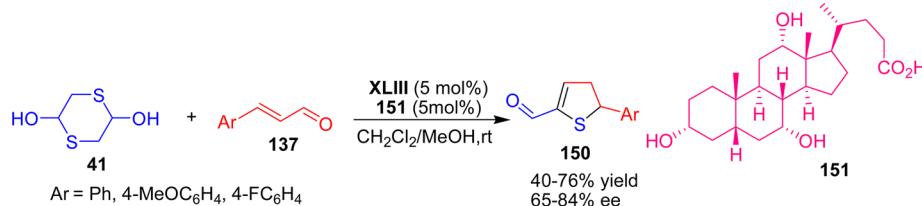
Scheme 64. Domino Sulfa-Michael/Aldol Reactions of 2-Mercaptoacetophenone with Enals



b]quinoline derivatives **147** were obtained in good to high yields (84–98%) and high enantioselectivities (90–99% ee).

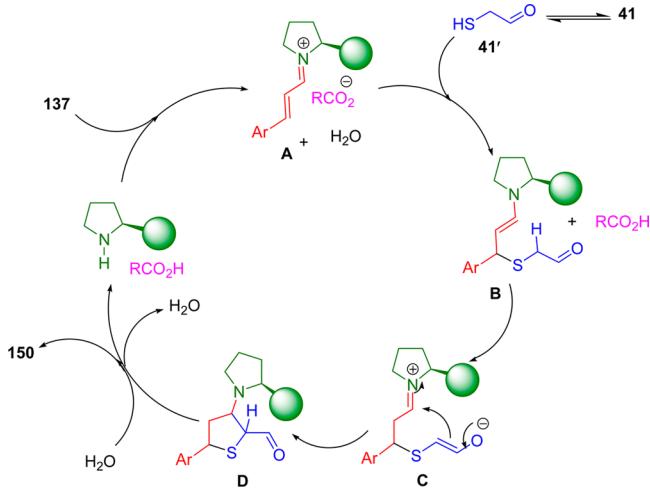
In 2008, Córdova et al. developed a domino sulfa-Michael/aldol reaction of 2-mercaptopacetophenone **148** and α,β -

unsaturated aldehydes **137** promoted by the TMS-protected prolinol **XL** as organocatalyst in the presence of 2-nitrobenzoic acid as an additive (Scheme 64).⁹⁹ A series of thiochromanes **149** bearing three concurrent stereogenic centers with one

Scheme 65. Domino Sulfa-Michael/Aldol Condensation Reactions of 1,4-Dithiane-2,5-diol with Cinnamaldehyde Derivatives

tetrasubstituted carbon were obtained by avoiding the dehydration step in the intramolecular aldol reaction. Good to high yields (71–98%), excellent enantioselectivities (96–99% ee), and good diastereoccontrol (10:1–15:1 dr) were generally observed for a wide range of enals.

In 2009, Risi et al. found that the (S)-diphenylprolinol trimethylsilyl ether catalyst **XLIII** in the presence of the bile acid **151** efficiently promotes the asymmetric domino sulfa-Michael/aldol condensation reactions between 1,4-dithiane-2,5-diol (**41**) and cinnamaldehyde derivatives **137** (Scheme 65).¹⁰⁰ The corresponding 4,5-dihydrothiophene-2-carbaldehydes **150** were isolated in up to 78% yield and 80% ee. The mechanism of this reaction involves the formation of the iminium ion intermediate **A** between the secondary amine and the enal. The sequential SMA of mercaptoacetaldehyde **41'** to the initially formed iminium intermediate gives rise to enamine **B**, which is protonated to form the enolate **C**. The latter one leads to the tetrahydrothiophenes **D** through the intramolecular Mannich-type addition. Finally, β -elimination returns the catalyst and leads to the final dihydrothiophenes (Scheme 66).

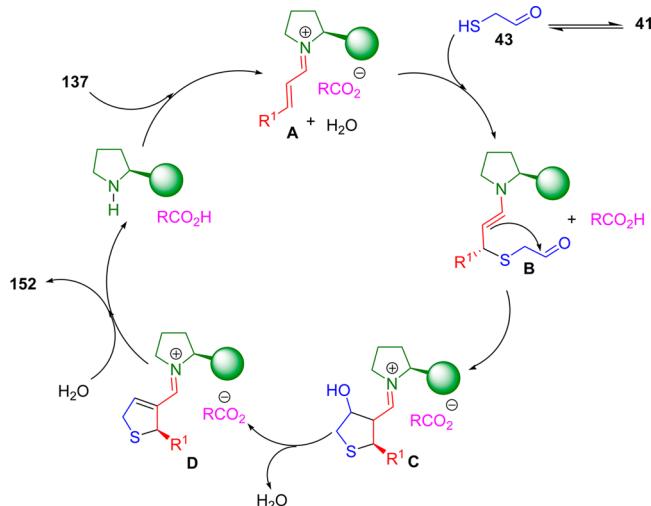
Scheme 66. Proposed Catalytic Cycle for the Domino Sulfa-Michael/Aldol Condensation Reactions of 1,4-Dithiane-2,5-diol with Cinnamaldehyde Derivatives

One year later, Xu and co-workers reported a closely related organocatalytic domino sulfa-Michael/aldol condensation reaction to produce a different type of tetrahydrothiophenes **152** (Scheme 67).¹⁰¹ The reaction of α,β -unsaturated aldehydes **137** with 1,4-dithiane-2,5-diol (**41**) catalyzed by the diphenylprolinol TMS ether **XLIII** provided a direct access to the chiral dihydrothiophenes **152** in good to high yields (70–90%) and good to excellent enantioselectivities (72–99% ee).

The catalytic mechanism of this domino reaction was confirmed by the APCI-MS detection of the proposed reaction

Scheme 67. Domino Sulfa-Michael/Aldol Condensation of α,β -Unsaturated Aldehydes with 1,4-Dithiane-2,5-diol

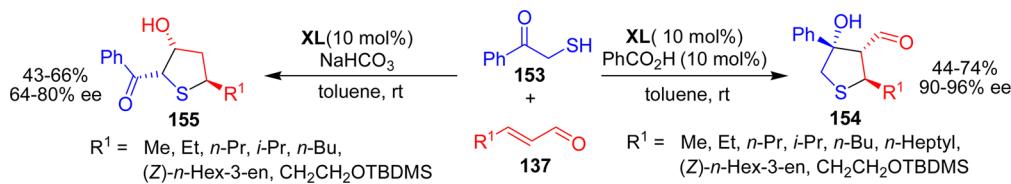
intermediates **A–D**. Thus, the catalytic cycle involves the activation of **137** by the catalyst **XLIII** through the formation of an iminium ion **A**, while the 2-mercaptopropanaldehyde **41'**, generated from **41** under equilibrium conditions, approaches from the *Re*-face to the β -position of the iminium ion (Scheme 68). The resulting enamine **B** then undergoes an intramolecular

Scheme 68. Proposed Catalytic Cycle for the Domino Sulfa-Michael/Aldol Condensation Reaction of α,β -Unsaturated Aldehydes with 1,4-Dithiane-2,5-diol

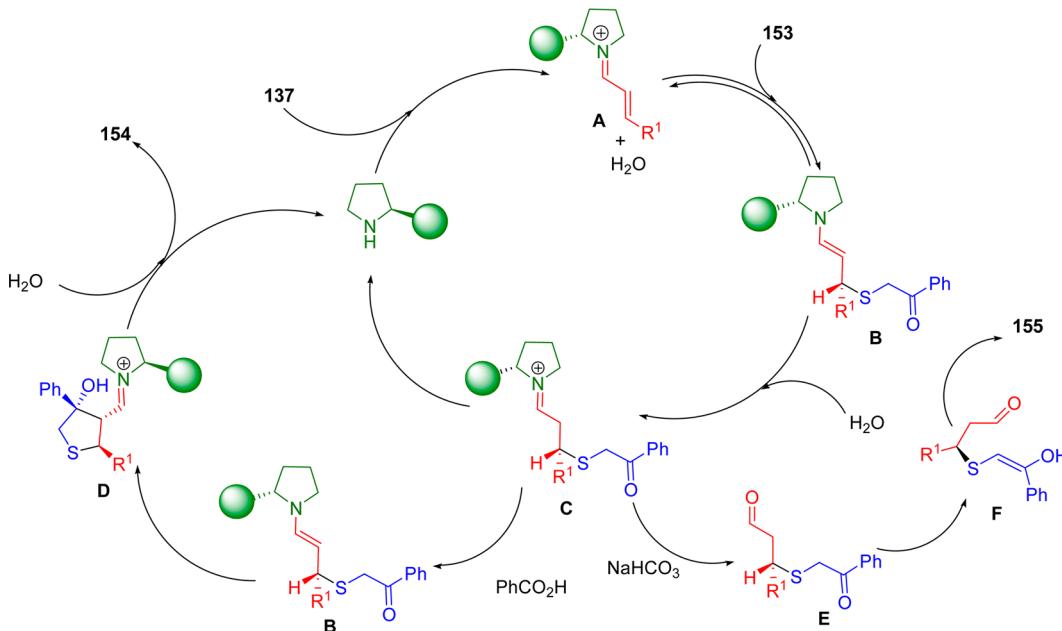
aldol reaction to form the intermediate **C**; subsequent dehydration results in the intermediate **D**, which upon hydrolysis affords the corresponding final product **152** and regenerates the catalyst. The authors assumed that the acid additive assists the formation of the iminium ion and successively activates the aldehyde and hydroxy moieties in the intramolecular aldol addition and dehydration steps through protonation, and also accelerates the imine hydrolysis.

Already in 2006 Jørgensen's group reported an asymmetric synthesis of highly enantioenriched functionalized tetrahydrothiophenes via an organocatalytic Michael/aldol domino sequence (Scheme 69).¹⁰² Diarylprolinol catalyst **XL** in the presence of benzoic acid as an additive catalyzed the domino reaction of thiol **153** with enals **137** to provide tetrahydrothiophene carbaldehydes **154** in moderate to good yields (44–

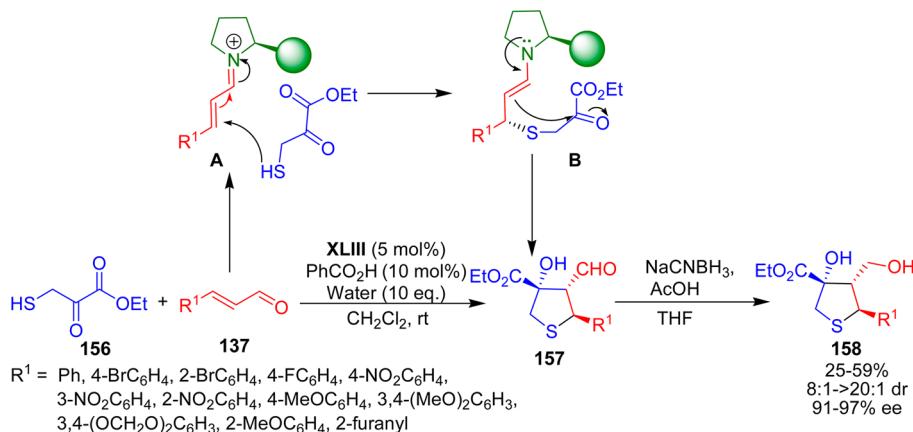
Scheme 69. Asymmetric Synthesis of Functionalized Tetrahydrothiophenes via an Organocatalytic Domino Michael/Aldol Reaction of Ketothiols with Enals



Scheme 70. Catalytic Cycle for the Domino the Michael/Aldol Reaction of Ketothiols with Enals



Scheme 71. Domino SMA/Aldol Reaction of Enals with Ethyl 3-Mercapto-2-oxopropanoate



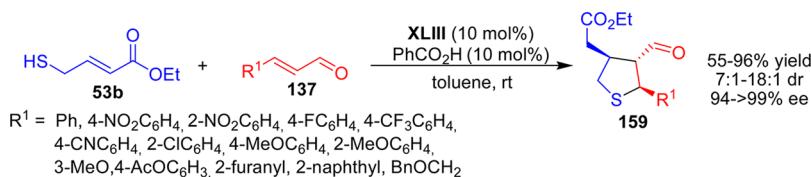
74%) and high enantioselectivities (90–96% ee). However, when a base was used as an additive instead of an acid, diastereomerically pure isomeric tetrahydrothiophenes **155** were obtained in moderate yields (43–66%) and moderate to good enantioselectivities (64–80% ee).

This domino reaction proceeds via the iminium ion formation between the catalyst and the enal followed by SMA of the thiol to the iminium ion **A** to generate intermediate **C** via enamine **B** (Scheme 70). This iminium **C** has a different fate under acidic and basic conditions. In the presence of the acid additive, **C** was converted to enamine **B**, which undergoes an aldol-type addition to generate the intermediate **D**.

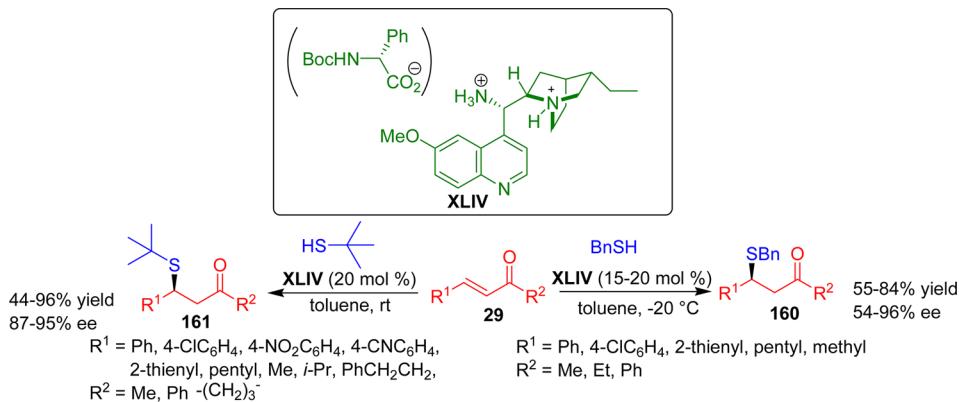
Hydrolysis of **D** provides the desired tetrahydrothiophene carbaldehyde **154**, and the catalyst is regenerated for next catalytic cycle. However, under basic conditions, hydrolysis of iminium **C** releases the catalyst and the thioether **E**. The latter one after enolization to **F** undergoes an intramolecular diastereoselective aldol reaction to form the tetrahydrothiophene **155**.

A catalytic asymmetric domino Michael/aldol reaction of enals **137** with ethyl 3-mercaptopropanoate **156** was reported by W. Wang's group (Scheme 71).¹⁰³ Using 5 mol % of **XLIII** and 10 mol % of benzoic acid as an additive in the presence of water, a series of trisubstituted tetrahydrothio-

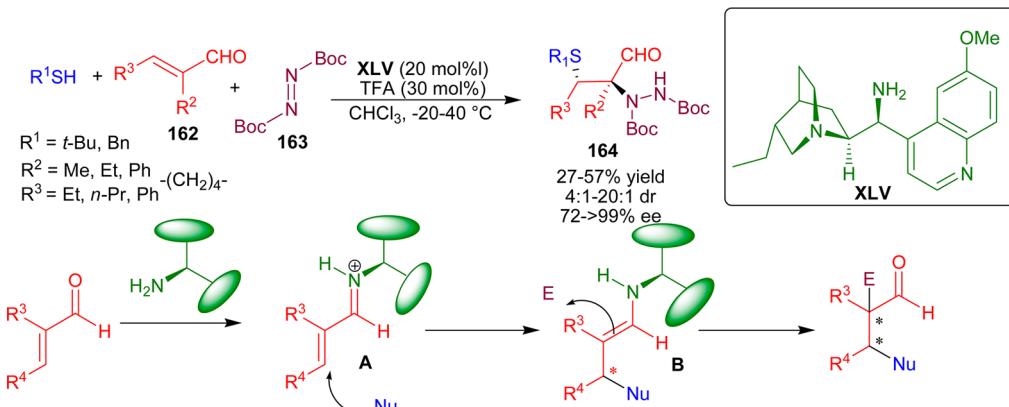
Scheme 72. Domino Sulfa-Michael/Michael Addition Reaction of α,β -Unsaturated Aldehydes with Ethyl 4-Mercapto-2-butenoate



Scheme 73. SMA of Benzyl and *tert*-Butyl Mercaptans to Enones



Scheme 74. Primary Amine-Catalyzed Domino Sulfa-Michael/Amination Reaction



phenes **158** was obtained after reduction of the aldehydes **157**. This one-pot procedure resulted in high enantio- and diastereoselectivities of the tetrahydrothiophenes bearing one tetrasubstituted stereocenter; however, only low to moderate yields were obtained. The reaction proceeds through iminium formation (**A**), followed by the SMA step to provide the enamines **B** and subsequent intramolecular aldol-type addition to the tetrahydrothiophenes **157**.

In 2007, W. Wang's group had already reported an organocatalytic enantioselective domino double Michael addition reaction of ethyl 4-mercaptop-2-butenoate **53b** with enals (Scheme 72).¹⁰⁴ Chiral diphenylprolinol TMS ether **XLIII** catalyzed the domino sulfa-Michael/Michael addition reactions of a diverse range of α,β -unsaturated aldehydes **137** with **53b** to provide chiral tetrahydrothiophenes **159** in moderate to high yields (55–96%), excellent enantioselectivities (94–99% ee), and good to high diastereoselectivities (7:1–18:1 dr).

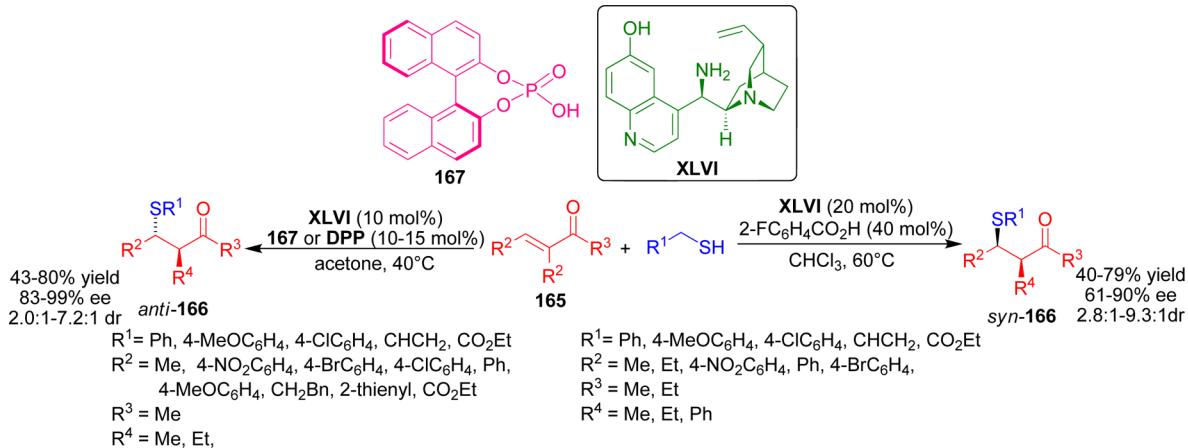
2.1.2.2. Primary Amine Catalysis. In 2007, the research groups of Chen¹⁰⁵ and Melchiorre¹⁰⁶ independently explored

the catalytic application of cinchona-derived primary amines for the 1,4-addition reaction of indoles to various enones for the first time. Since then, the primary amines derived from cinchona alkaloids and amino acids have left their imprint as powerful organocatalysts for the activation of enones as well as α -branched enals via iminium ion formations.¹⁰⁷

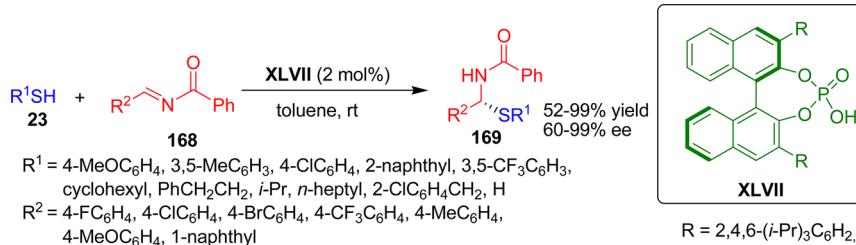
The first application of primary amine organocatalysts in asymmetric sulfa-Michael additions was published by Melchiorre and co-workers in 2008 (Scheme 73).¹⁰⁸ They reported a highly enantioselective organocatalytic SMA to α,β -unsaturated ketones **29** using the salt catalyst **XLIV** derived from amino-(9-deoxy)-*epi*-hydroquinine and D-N-Boc-phenylglycine. This salt efficiently catalyzed the SMA of benzyl and *tert*-butyl mercaptans to various enones to provide moderate to very good yields (44–96%) and moderate to high enantioselectivities (54–96% ee) of the corresponding 1,4-adducts **160** and **161**.

One year later, the same research group reported an asymmetric organocatalytic domino reaction of thiols, α -substituted α,β -unsaturated aldehydes **162**, and azo-dicarbox-

Scheme 75. Diastereodivergent Domino Sulfa-Michael/Protonation Reaction of α -Branched α,β -Unsaturated Ketones



Scheme 76. Asymmetric 1,2-Addition of Thiols to N-Acyl Imines



ylate **163** utilizing the cinchona derived primary amine catalyst **XLV** (Scheme 74).¹⁰⁹ A series of valuable sulfur-containing compounds **164** bearing vicinal tri- and tetrasubstituted stereocenters were obtained in low to moderate yields, high enantiomeric purities, and moderate to high diastereoselectivities. The reaction proceeds via activation of **162** by the TFA salt of **XLV**, which tunes into a well-established domino iminium/enamine sequence involving the Michael type addition of thiol to iminium ion **A**, followed by nucleophilic reaction of the resulting enamine **B** to the azo-compounds. This protocol was also successfully applied for domino Friedel-Crafts/amination reactions involving indole derivatives as nucleophiles instead of thiols.

Melchiorre's group also reported an elegant organocatalytic diastereodivergent sulfa-Michael/protonation reaction of α -branched α,β -unsaturated ketones (Scheme 75).¹¹⁰ The quinidine derived organocatalyst **XLVI** in the presence of 2-fluorobenzoic acid as an additive catalyzed the Michael addition of aliphatic sulfur nucleophiles to the α -branched enones **165** to give the major *syn*-diastereomer of the Michael adducts **166** in moderate to good yields (40–79%), good to high enantioselectivities (61–90% ee), and moderate to good diastereoselectivities (*syn:anti* 2.8:1–9.3:1dr). A complete switch in the diastereoselectivity was observed when phosphoric acid **167** or diphenyl phosphoric acid (DPP) were used as additive instead of 2-fluorobenzoic acid. With these additives, several *anti*-configured Michael adducts *anti*-**166** were obtained in moderate to good yields (43–80%), high enantioselectivities (83–99% ee), and moderate to good diastereoselectivities.

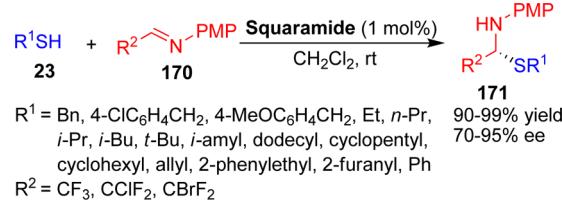
2.2. Reactions of Sulfur Nucleophiles with Other Acceptors

2.2.1. 1,2-Addition Reactions. The asymmetric 1,2-addition of various nucleophiles to imines represents a very important class of reactions for providing chiral amine

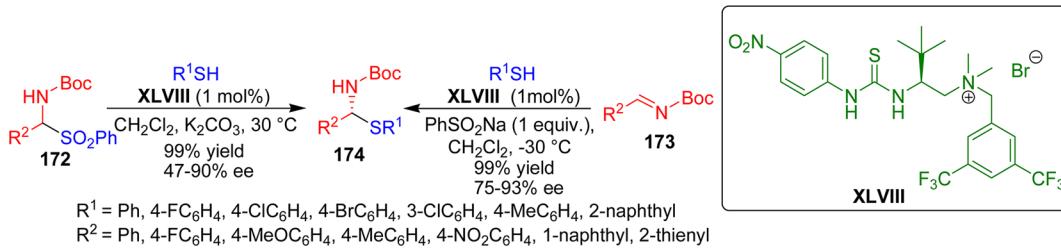
derivatives.¹¹¹ However, enantioselective organocatalytic 1,2-additions of sulfur nucleophiles to imines were not reported until 2011, when Antilla's group published a catalytic asymmetric 1,2-addition of thiols to imines (Scheme 76).¹¹² The authors found that a low loading of the chiral phosphoric acid **XLVII** (TRIP) catalyzes a rapid addition of thiols **23** to *N*-acyl imines **168**, thus generating enantioenriched *N,S*-acetalts **169** in moderate to excellent yields (52–99%) and enantioselectivities (60–99% ee). A variety of electron-rich and electron-deficient aromatic *N*-acyl imines as well as a broad range of aliphatic and aromatic thiols were tolerated under the optimized reaction conditions.

C.-J. Wang and co-workers reported an efficient organocatalytic addition of thiols **23** to trifluoromethylaldimine **170** for the asymmetric synthesis of trifluoromethylated *N,S*-acetals **171** (Scheme 77).¹¹³ Using a low loading (1 mol %) of the

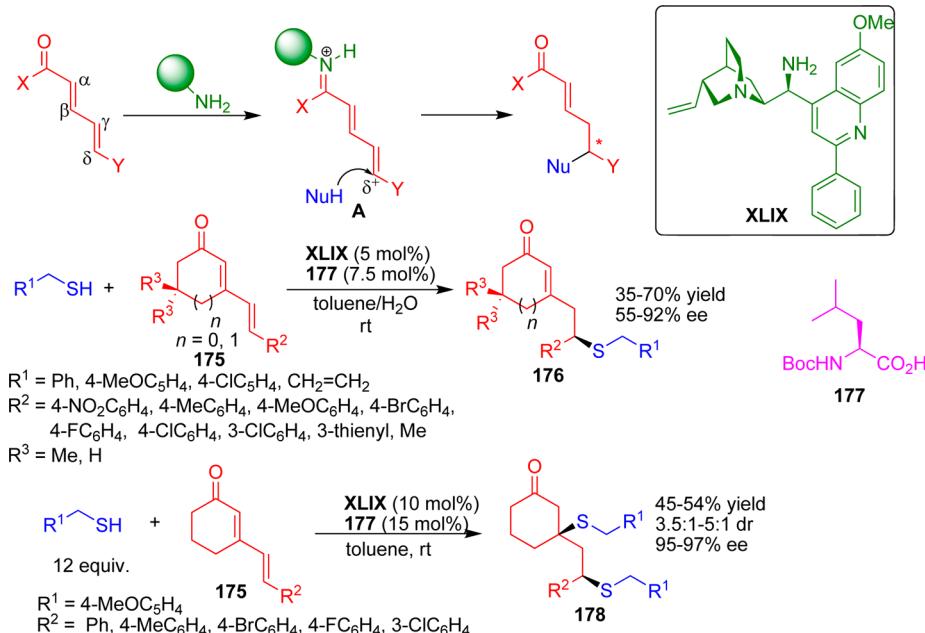
Scheme 77. 1,2-Addition of Thiols to Trihalogenomethylaldimines



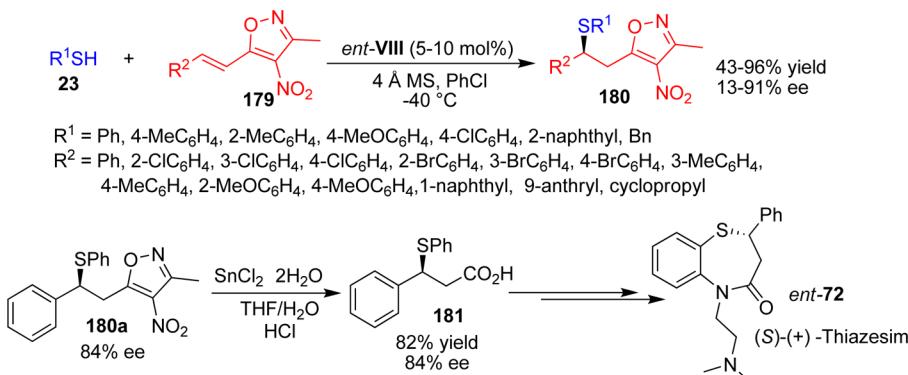
squaramide derived from cinchonidine, the addition of various benzyl- and alkyl-thiols to **170** provided a new family of important trifluoromethylated *N,S*-acetals **171** in high yields (90–99%) and excellent enantioselectivities (90–95% ee). Thiophenol exhibited high reactivity in this transformation, affording the corresponding adduct in good yield (96%) albeit

Scheme 78. 1,2-Addition of Thiols to the α -Amidosulfones and Imines

Scheme 79. 1,6-Addition of Thiols to 2,4-Dienones



Scheme 80. 1,6-Addition of Thiols to 3-Methyl-4-nitro-5-alkenyl-isoxazoles

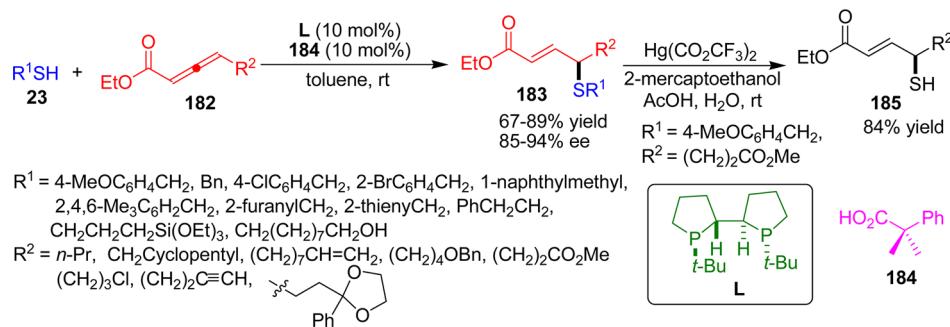
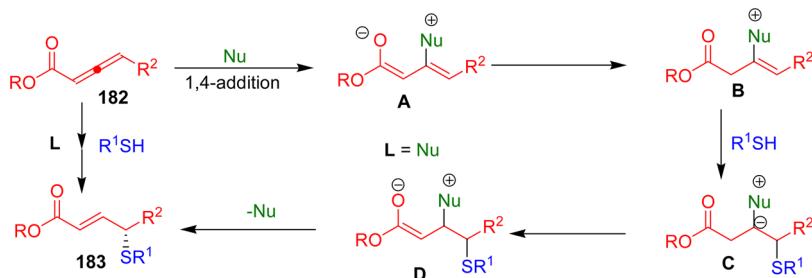
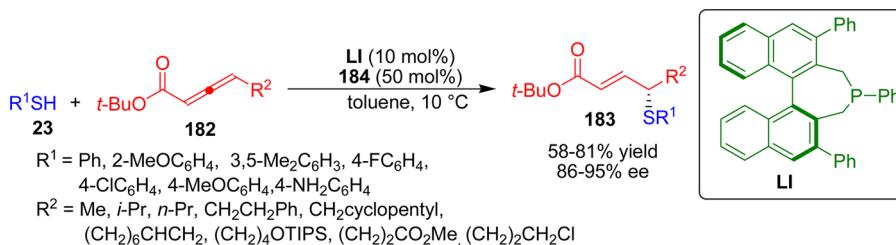


with a moderate enantioselectivity (70% ee). Not only trifluoromethylated, but also difluorochloro/bromo-*N,S*-acetals were obtained in this manner in high yields and very good enantioselectivities.

Very recently, Zhao and co-workers applied the asymmetric phase-transfer catalysis for the first time to synthesize chiral *N,S*-acetals (Scheme 78).¹¹⁴ At low loading of the amino acid-based bifunctional thiourea-ammonium salt catalyst XLVIII, the reaction of thiols with the α -amidosulfones 172 took place rapidly to provide the corresponding *N,S*-acetals 174 in excellent yields (up to 99%) and moderate to good enantioselectivities (47–90% ee). Furthermore, *N*-Boc imines

173 also reacted with thiols under the catalytic influence of XLVIII to give *N,S*-acetals 174 in almost quantitative yield and good enantioselectivities (75–93% ee). The reaction of thiols with 173 could be performed successfully on a gram scale to give up to 93% ee and 99% yield within 5 min using only 0.1 mol% of XLVIII.

2.2.2. 1,6-Addition Reactions. Melchiorre and co-workers discovered the LUMO-lowering activating effect transmitted through the conjugated π -system of 2,4-dienones 175 upon selective condensation with a chiral primary amine catalyst XLIX in the presence of a chiral acid 177 (Scheme 79).¹¹⁵ The resulting vinyllogous iminium ion activation was used to

Scheme 81. Bisphosphine TangPhos-Catalyzed γ -Addition of Thiols to AllenoatesScheme 82. Mechanism of the Bisphosphine TangPhos-Catalyzed γ -Addition of Thiols to AllenoatesScheme 83. γ -Addition of Aryl Thiols to Allenoates Catalyzed by a Chiral Phosphepine

develop an asymmetric organocatalytic 1,6-addition of thiols to provide the adducts **176** in 35–70% yields, moderate to good enantioselectivities (55–92% ee), and good 1,6-addition selectivity. Furthermore, **XLIX** also catalyzed the cascade reaction involving both 1,6- and 1,4-additions of thiols to 2,4-dienones. This cascade reaction proceeded successfully by using a large excess of thiol and a relatively long reaction time, thus providing double addition adducts **178** with moderate diastereoselectivities (3.5:1–5:1 dr) and excellent enantioselectivities (95–97% ee).

Yuan and co-workers reported an enantioselective organocatalytic 1,6-addition of thiols to various 3-methyl-4-nitro-5-alkenyl-isoxazoles **179** catalyzed by the bifunctional thiourea-tertiary amine *ent*-**VIII** (Scheme 80).¹¹⁶ A wide range of 1,6-adducts **180** were synthesized in good to high yields (71–97%) and good enantioselectivities (71–91% ee) from various isoxazoles **179** and aryl thiols. However, benzyl thiol gave only low yields and poor enantioselectivities of the desired products. The 1,6-adduct **180a** was successfully transformed into the β -thio-acetic acid **181**, which served as a precursor for the asymmetric synthesis of *S*-(+)-thiazesim (*ent*-**72**), a simple member of the benzothiazepin family.

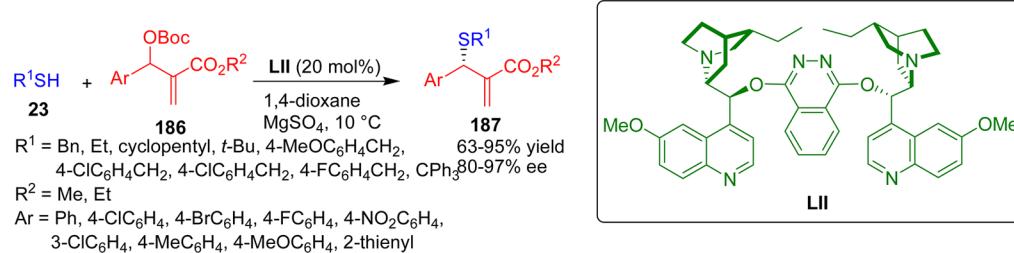
2.2.3. γ -Addition Reactions. The first catalytic asymmetric γ -sulfonylation of carbonyl compounds has been developed by Fu's group in 2010. In the presence of a nucleophilic bisphosphine TangPhos **L** and 2-Methyl-2-phenylpropanoic

acid (**184**), various alkyl thiols added to the γ -position of allenotes **182** to give good yields (67–89%) and high enantioselectivities (85–94% ee) of the corresponding γ -addition adducts **183** (Scheme 81).¹¹⁷ The enantioenriched thioether was successfully converted into a corresponding thiol **185** in good yield.

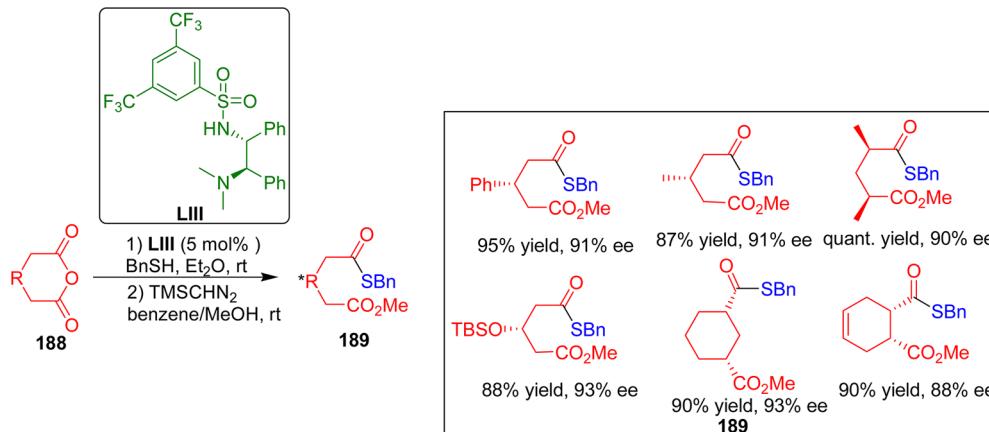
Chen and co-workers investigated the mechanism of the TangPhos-catalyzed asymmetric γ -addition of thiols to the allenotes with the density functional theory (Scheme 82).¹¹⁸ The uncatalyzed addition of thiols occurs at the β -carbon to form a β -sulfenylated ester with the transfer of a proton to the γ -carbon. In the TangPhos-catalyzed case, the nucleophilic thiol attacks the γ -carbon after the addition of TangPhos to the β -carbon (intermediates **A–D**). The proton is transferred first from the phosphorus of TangPhos to the carbonyl oxygen and then to the β -carbon to generate the γ -thioester.

Fu and co-workers further reported an effective method for the catalytic enantioselective γ -addition of aryl thiols to allenotes **182** catalyzed by the phosphepine **LI** (Scheme 83).¹¹⁹ This process provided an easy access to the γ -thioether-substituted enoates **183** in moderate to good yields (58–81%) and very good enantioselectivities (86–95% ee). In this phosphepine-catalyzed enantioselective γ -addition of an aryl thiol to an allenote, the resting state of the catalyst was found to be the phosphepine, not the protonated catalyst or a phosphepine-allenoate adduct, as indicated by ^{31}P NMR. The

Scheme 84. Addition of Thiols to Morita–Baylis–Hillman (MBH) Carbonates



Scheme 85. Sulfonamide-Catalyzed Thiolysis of Cyclic Anhydrides with Benzyl Mercaptan



rate law for the process was first order in the catalyst and allenolate, and zero order in the thiol and pivalic acid. During the reaction, the enantioselectivity of the product remained constant, but a modest kinetic resolution of the unreacted allene was also observed. These data were found to be consistent with a rate-determining irreversible 1,4-addition of the phosphepine catalyst to the allenotes.

2.2.4. Reactions with Morita–Baylis–Hillman Carbonates. Recently, the metal-free organic Lewis base-catalyzed substitution reaction of Morita–Baylis–Hillman (MBH) adducts has emerged as a powerful tool for the construction of multifunctional products.¹²⁰ Cheng and co-workers reported a highly efficient and practical organocatalytic enantioselective carbon–sulfur bond formation reaction between simple thiols and MBH carbonates **186** (Scheme 84).¹²¹ A wide range of alkyl thiols and MBH carbonates were tolerated under the catalytic influence of dimeric cinchona alkaloid **LII** [(DHQD)₂PHAL]. The S_N2'-S_N2'-reaction provides a number of optically active α -methylene β -mercapto esters **187** in good yields with moderate to high enantioselectivities.

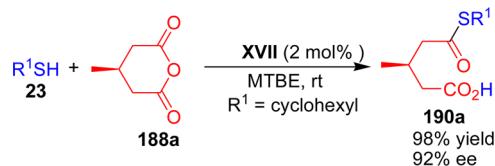
2.3. Desymmetrization Reactions

The catalytic asymmetric desymmetrization of anhydrides, azlactones, epoxides, aziridines, etc., with sulfur nucleophiles leads to synthetically valuable enantiomerically enriched compounds.

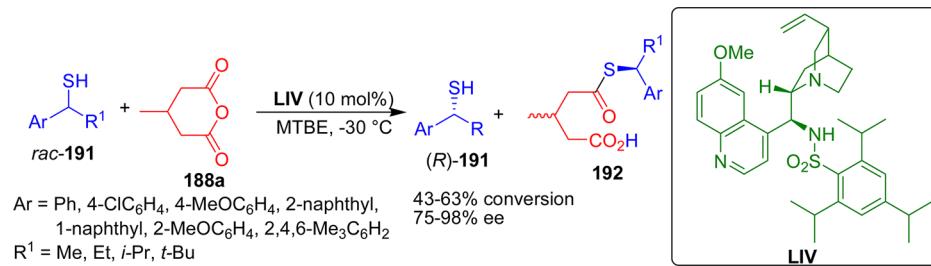
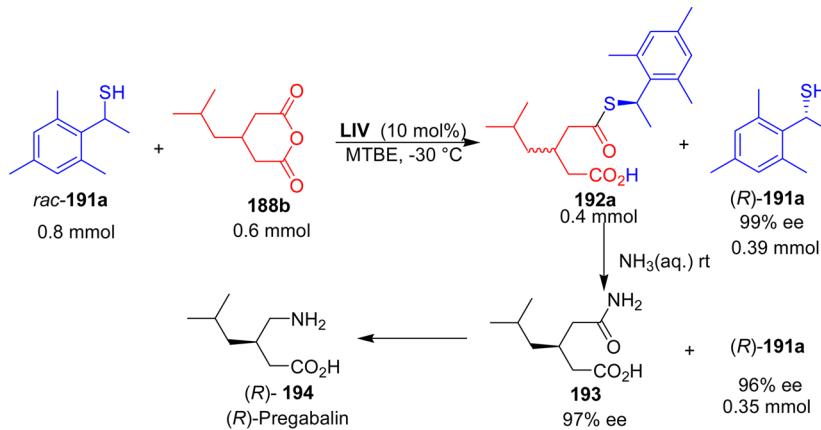
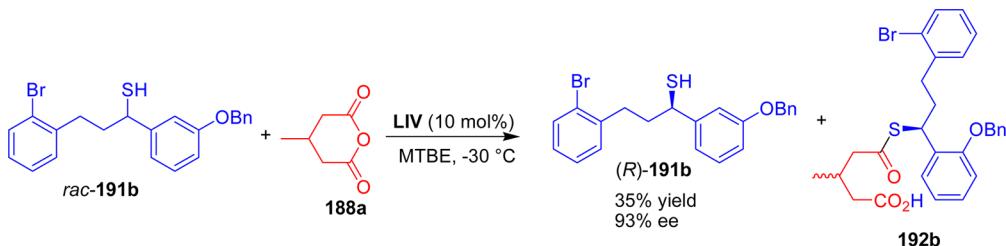
2.3.1. Desymmetrization of Anhydrides. Enantioselective desymmetrization of prochiral cyclic anhydrides generates enantiomerically enriched hemiesters/thioesters bearing one or two stereogenic centers and two chemically differentiated carbonyl functionalities, which are versatile chiral building blocks for asymmetric synthesis.¹²² In 2005, Nagao and co-workers reported an efficient enantioselective organocatalytic thiolysis of cyclic anhydrides **188** with benzyl mercaptan

(Scheme 85). The sulfonamide **LIII** was found to be the best catalyst for providing chiral thioesters **189**, after in situ esterification of acids in very good to excellent yields and good enantioselectivities.¹²³

In 2008, Connon's group demonstrated that the cinchona-derived urea/thiourea efficiently catalyzes the desymmetrization of azlactone and *meso*-anhydrides by alcoholysis and thiolysis.¹²⁴ Treatment of *meso*-glutaric anhydride **188a** with cyclohexyl thiol in the presence of tertiary amine-thiourea **XVII** afforded **190a** in 98% yield and 92% ee (Scheme 86).

Scheme 86. Cinchona-Derived Thiourea-Catalyzed Desymmetrization of *meso*-Anhydrides by Thiolysis

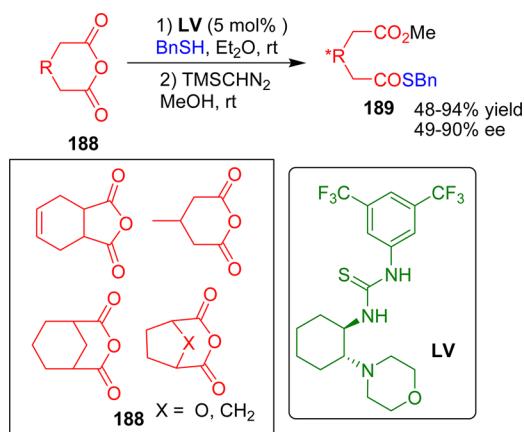
Later in 2010, Connon and co-workers also developed a new sulfonamide catalyst **LIV** for the highly enantioselective desymmetrization of the *meso*-anhydride **188a** with the simultaneous kinetic resolution of racemic secondary thiols **191** in good to excellent enantioselectivity (Scheme 87).¹²⁵ The synthetic potential of this methodology was extended for the large-scale synthesis of the precursor **193** of (R)-pregabalin **194** from the anhydride **188b** (Scheme 88). In a second example, the core **192b** of the antiasthmatic drug (R)-montelukast **13** was synthesized in 93% ee by desymmetrization of the corresponding anhydride with the secondary thiol **191b** (Scheme 89).

Scheme 87. Desymmetrization of a *meso*-Anhydride with a Simultaneous Kinetic Resolution of Racemic Secondary Thiols**Scheme 88. Large-Scale Synthesis of the Precursor of (R)-Pregabalin from the Desymmetrized Anhydride****Scheme 89. Asymmetric Synthesis of the (R)-Montelukast Core**

In 2010, Bolm and co-workers showed that the cyclohexane-based tertiary amine-thiourea LV efficiently catalyzed an enantioselective desymmetrization of cyclic *meso*-anhydrides using alcohols and benzyl mercaptan as nucleophiles (Scheme 90). Thiolysis of both succinic and glutaric anhydrides **188** furnished the corresponding products **189** in moderate to high yields and enantioselectivities.¹²⁶ The authors have also revealed that by using quinine in catalytic or stoichiometric amount, the thiolysis of the anhydride afforded the corresponding thioesters in 83–90% yield and 58–77% ee.

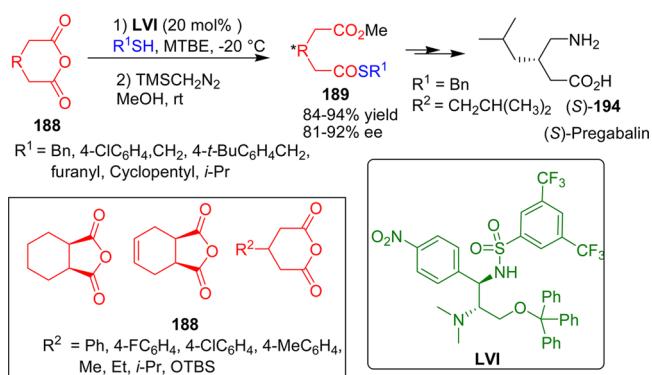
Recently, a highly enantioselective thiolysis of cyclic anhydrides **188** catalyzed by an amino alcohol derived sulfonamide LVI was reported by Chen and co-workers (Scheme 91).¹²⁷ Different thiols were used as nucleophiles to provide the corresponding thioesters **189** in good yields and enantioselectivities. In addition, the synthesis of the γ -amino acid (*S*)-pregabalin **194** has also been demonstrated by subsequent transformations of the corresponding thioester.

2.3.2. Desymmetrization of Azlactones. Racemic 4-substituted oxazol-5-(4*H*)-ones (azlactones) are recognized as valuable precursors of highly enantioenriched α,α -disubstituted α -amino acids.¹²⁸ The main contribution to the organocatalytic asymmetric thiolysis of azlactones comes from the research

Scheme 90. Tertiary Amine-thiourea LV-Catalyzed Enantioselective Desymmetrization of Cyclic *meso*-Anhydrides

group of S. J. Connon. They have screened various tertiary amine-urea/thiourea catalysts **IX**, **XVII**, and **LVII** derived from cinchona alkaloids for the thiolysis of azlactones **195** with

Scheme 91. Thiolysis of Cyclic Anhydrides Catalyzed by an Amino Alcohol-Derived Sulfonamide



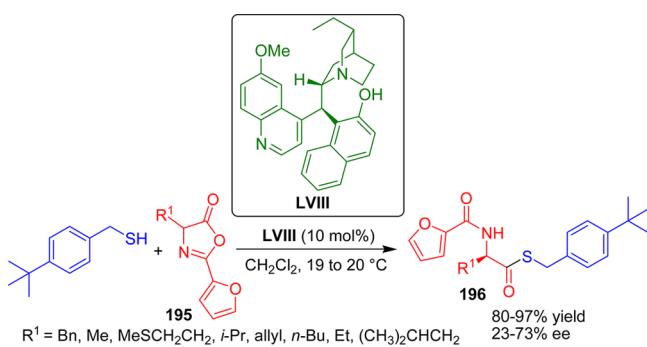
benzyl/cyclohexyl thiols leading to the corresponding thioesters **196** in excellent yields with only up to 64% ee (Scheme 92).

The desymmetrization of azlactones **195** by thiolysis with unhindered thiols catalyzed by cinchona derived urea- and squaramides failed to provide the desired α -amino acid thioesters in good enough enantioselectivity.¹²⁹ However, a significant improvement in the enantioselectivity of α -amino acid thioesters **196** as well as an extension in the substrate scope for the DKR of azlactones **195** was achieved, when the C-9 arylated cinchona alkaloid **LVIII** was used as catalyst in the thiolysis of azlactones (Scheme 93).

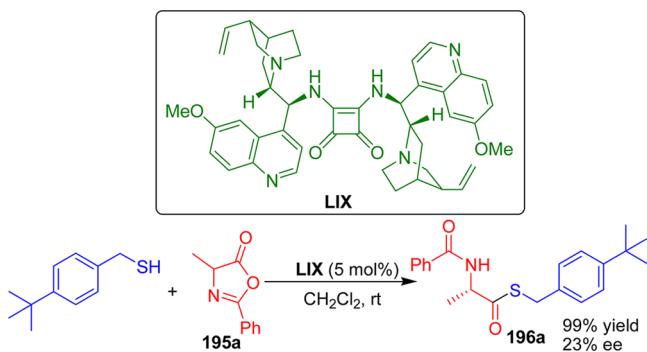
A C-2 symmetric squaramide **LIX** developed by Song and co-workers catalyzes the thiolysis of azlactone **195a** to provide the α -amino thioester **196a** in excellent yield, but with only 23% ee (Scheme 94).¹³⁰ Recently, Connon and Palacio developed a new class of C-5'-hydroxylated cinchona-derived catalysts for catalyzing the DKR of a wide range of azlactones **195** derived from both unbranched- and branched-chain amino acids (Scheme 95).¹³¹ With the new catalyst **LX**, good enantioselectivities ranging from 84% to 90% ee were obtained; however, the product yields turned out to be low to moderate (26–60%).

X.-W. Wang and co-workers reported an elegant organocatalytic domino sulfa-Michael/ring-opening reaction of (*Z*)-olefinic azlactones **197** with aromatic thiols (Scheme 96).¹³² With 10 mol % of Takemoto's catalyst *ent*-**VIII**, the enantioenriched *syn*- β -thio- α -amino acid derivatives **198** were synthesized in one pot with excellent yields (90–98%), high levels of diastereoselectivities (92:8–98:2 dr), and good to very good enantioselectivities (75–88% ee). A simple filtration of the reaction mixture gave **198** in slightly lower yields (71–82%) with a significant improvement in the stereoselectivities (98:2–99:1 dr and 90–96% ee). A gram-scale reaction was also

Scheme 93. C-9 Arylated Cinchona Alkaloid-Catalyzed Thiolysis of Azlactones



Scheme 94. C-2 Symmetric Squaramide-Catalyzed Thiolysis of an Azlactone

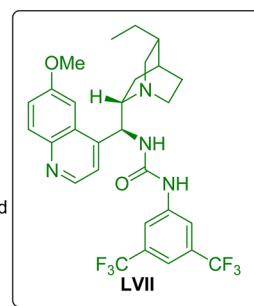
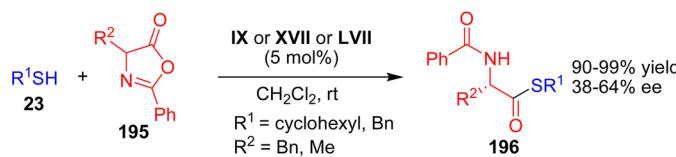


performed successfully, which provided the desired product in 74% yield, >99:1 dr, and 93% ee by a simple filtration and washing procedure without any purification by column chromatography.

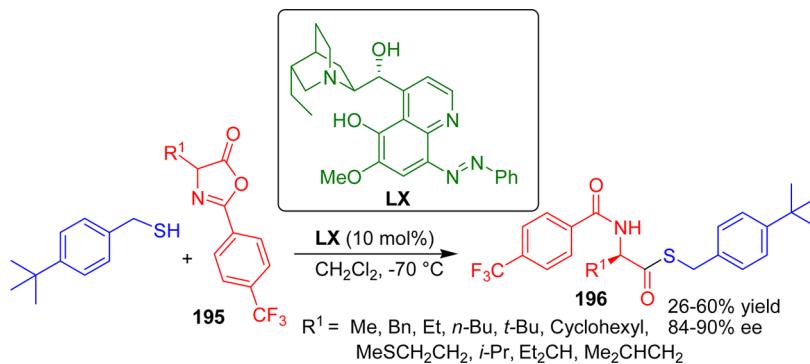
2.3.3. Desymmetrization of *meso*-Aziridines. Aziridines are valuable as building blocks for chemical bond elaborations as well as functional group transformations, and the asymmetric desymmetrization of aziridines with various nucleophiles provides an easy access to valuable chiral amines.¹³³ In 2007, Hou's group developed an asymmetric desymmetrization of *meso*-N-sulfonylaziridines **199** with thiols catalyzed by cinchonine-derived chiral quaternary ammonium salts **LXIa** and **LXIb** (Scheme 97).¹³⁴ The corresponding vicinal amino-thiols **200** were synthesized in high yields (80–99%) and in poor to moderate enantioselectivities (3–73% ee).

One year later, B. Wang, Wu, and co-workers published an asymmetric desymmetrization of *N*-protected *meso*-aziridines **199** with aryl thiols catalyzed by quinine IV to afford β -amino

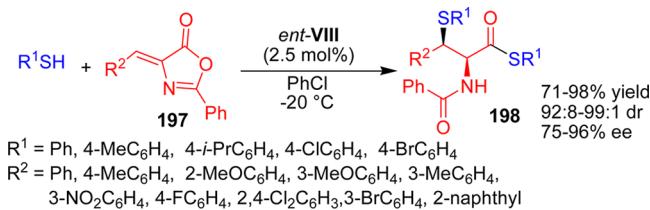
Scheme 92. Cinchona-Derived Urea/Thiourea Promoted Thiolysis of Azlactones with Benzyl/Cyclohexyl Thiols



Scheme 95. C-5'-OH Cinchona Alkaloid Promoted Thiolysis of Azlactones



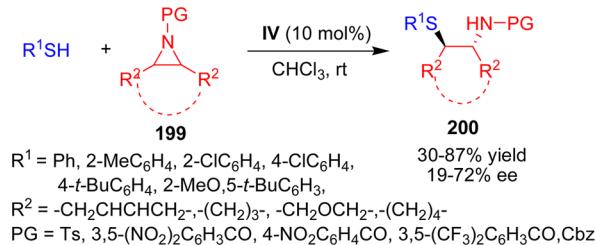
Scheme 96. Domino Sulfa-Michael/Desymmetrization of (Z)-Olefinic Azlactones



sulfides **200** in low to good yields (30–87%) and low to moderate enantioselectivities (19–72% ee) (Scheme 98).¹³⁵

In 2009, Lattanzi and Sala identified α,α -diphenyl-L-prolinol **LXII** as an efficient catalyst for the desymmetrization of *meso*-N-acylaziridines **201** with aryl thiols to afford the aminothiols **202** in low to good yields and poor to moderate enantioselectivities (Scheme 99).¹³⁶ In the proposed transition state **TS-14**, the catalyst **LXII** provides synergistic activation to both substrates by activating the aziridines through hydrogen bonding to the acyl carbonyl oxygen via the secondary alcohol and by deprotonation of the thiols through the secondary amine of the catalyst.

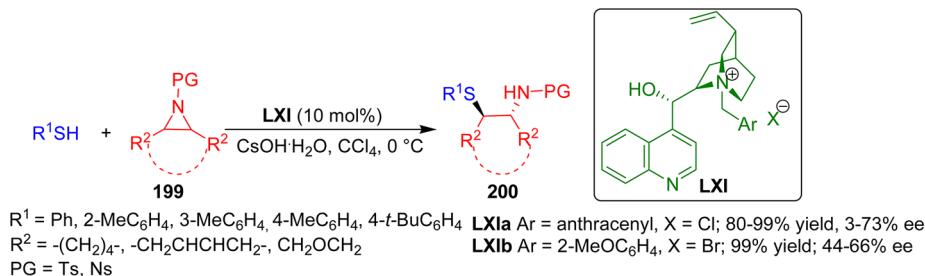
Lattanzi and Sala have further reported on an improved approach for the synthesis of enantioenriched β -aminothioethers via VAPOL phosphoric acid (*R*)-**LXIII**-catalyzed desymmetrization of *meso*-N-acylaziridines **203** with Me_3SiSPh (Scheme 100).¹³⁷ A series of β -(*N*-acylamino)phenylthioethers **204** were synthesized in good to excellent yields and enantioselectivities (78–99% ee). The selection of the suitable aziridine/nucleophile/catalyst molar ratio was found to be crucial for high enantioselectivity. Later on, Sala re-examined the VAPOL hydrogen phosphate-catalyzed desymmetrization of *meso*-aziridines with different silylated compounds.¹³⁸ He

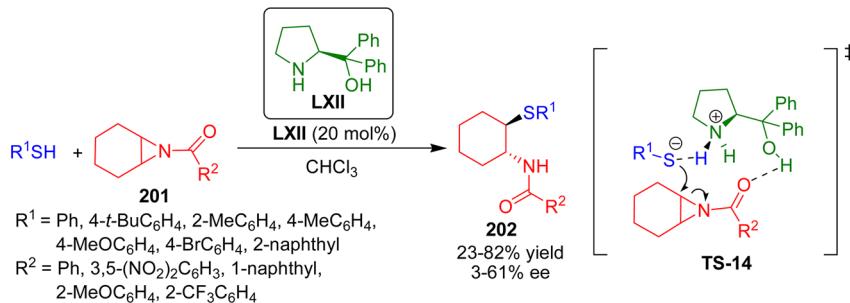
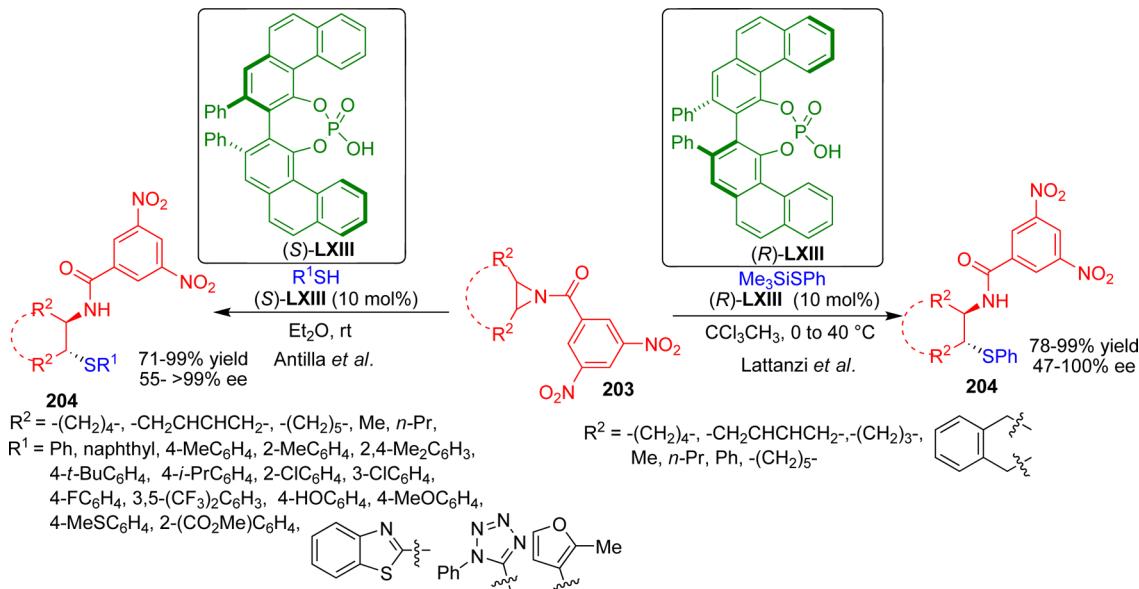
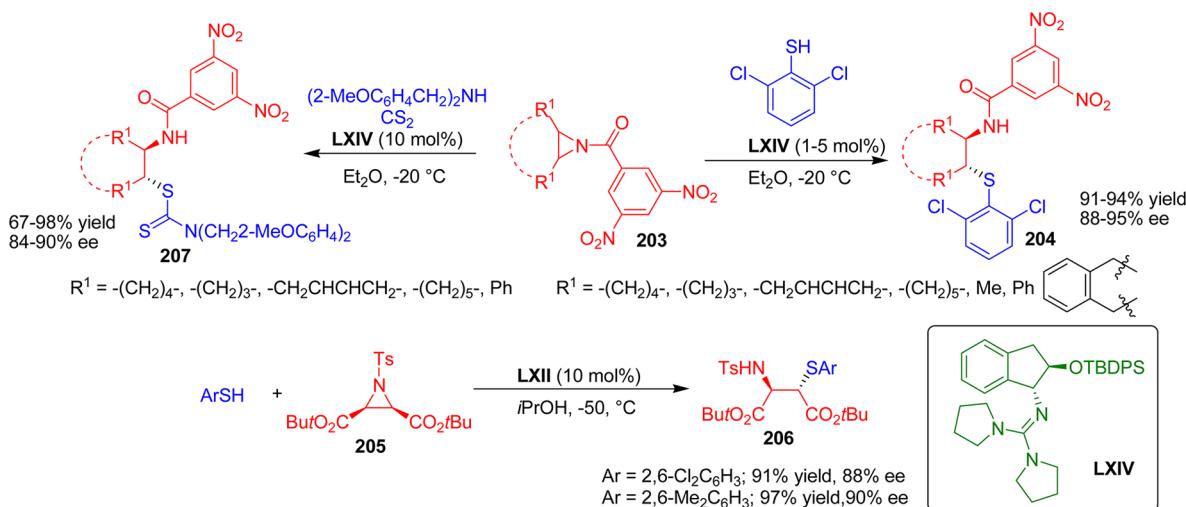
Scheme 98. Quinine-Catalyzed Desymmetrization of *N*-Protected *meso*-Aziridines with Aryl Thiols

found a significant amount of metal phosphate impurities by NMR spectroscopy and ICPOES analysis of synthetic as well as purchased samples of the VAPOL hydrogen phosphate purified on silica gel. While metal-free phosphoric acid exhibited low activity and enantioselectivity, calcium and magnesium phosphate salts proved to be the true catalysts in these reactions. Reproducible high enantioselectivities were obtained in the ring-opening of cyclic *meso*-aziridines with Me_3SiX (SPh, SePh, N3) employing a 1:1 mixture of calcium and magnesium VAPOL phosphates.

Antilla's group disclosed the enantioselective ring-opening of *meso*-N-acyl aziridines **203** with aromatic thiols catalyzed by VAPOL phosphoric acid (*S*)-**LXIII** (Scheme 100).¹³⁹ This protocol tolerated a wide range of aromatic and heteroaromatic thiols and provided the corresponding β -aminothioethers **204** in good to excellent yields (71–99%) and moderate to virtually complete enantioselectivities (55–99% ee); however, benzyl or alkyl thiols only resulted in low yields (15–42%) and poor enantioselectivities (18–62% ee).

Huang, Tan, and co-workers have developed an aminoindanol derived chiral guanidine as an efficient Brønsted base catalyst for the desymmetrization of *meso*-aziridines **203** with

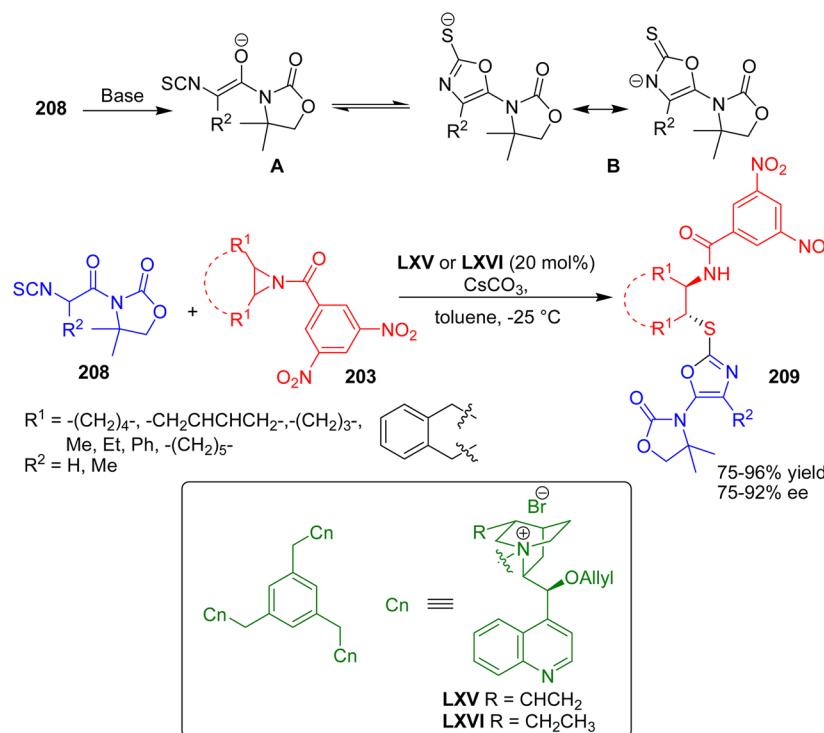
Scheme 97. Desymmetrization of *meso*-N-Sulfonylaziridines with Thiols Catalyzed by Cinchonine-Derived Chiral Quaternary Ammonium Salts

Scheme 99. α,α -Diphenyl-L-prolinol-Catalyzed Desymmetrization of *meso*-N-Acylaziridines with Aryl ThiolsScheme 100. VAPOL Phosphoric Acid-Catalyzed Desymmetrization of *meso*-N-Acylaziridines with Me_3SiSPh and ThiolsScheme 101. Guanidine-Catalyzed Desymmetrization of *meso*-Aziridines with Thiols and Carbamodithioic Acids

thiols and carbamodithioic acids as nucleophiles (Scheme 101).¹⁴⁰ The newly synthesized chiral guanidine LXIV provided the corresponding 1,2 ring-opened products **204** by thiolytic of **203** with aryl thiols in high yields (91–94%) and enantioselectivities (88–95% ee). Guanidine LXIV also proved to be an efficient catalyst for the desymmetrization of the *N*-tosyl *meso*-aziridines **205** with thiols to give **206** in good yields

and enantioselectivities. Additionally, the authors have used *in situ* generated carbamodithioic acid as a nucleophile for the asymmetric ring-opening of aziridines for the first time. The guanidine-catalyzed three-component reaction of bis(2-methoxybenzyl)-amine, carbon disulfide, and *N*-3,5-dinitrobenzoyl *meso*-aziridines **203** afforded the β -amino sulfides **207** in

Scheme 102. Cinchona-Derived Quaternary Ammonium Salt-Catalyzed Asymmetric Ring-Opening of *meso*-Aziridines with α -Isothiocyanato Imides



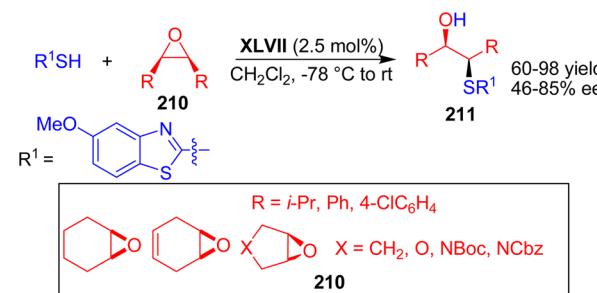
moderate to high yields (67–98%) and good enantioselectivities (84–90% ee).

Recently, R. Wang and co-workers used aziridines **203** as suitable electrophiles to trap the 2-thioxazole intermediate **B** generated from α -isothiocyanato imide **208** under basic conditions (Scheme 102).¹⁴¹ Under phase-transfer conditions, the trinuclear cinchona-derived quaternary ammonium salts **LXV** and **LXVI** efficiently catalyzed the asymmetric ring-opening reactions between *meso*-aziridines **203** and α -isothiocyanato imides **208** to provide the β -aminothioxazoles **209** in good to high yields (75–96%) and good enantioselectivities (75–92% ee).

2.3.4. Desymmetrization of *meso*-Epoxides. The catalytic enantioselective desymmetrization of *meso*-epoxides via ring-opening with various nucleophiles represents a straightforward strategy for the synthesis of 1,2-difunctionalized chiral molecules with two vicinal stereocenters.¹⁴² Lewis acids such as transition-metal complexes and enzymes are widely explored for these transformations. Only recently, the catalytic potential of chiral Brønsted acid organocatalysts for the asymmetric nucleophilic ring-opening of *meso*-epoxides with thiols has been realized by Sun's group (Scheme 103).¹⁴³ In the presence of the phosphoric acid catalyst **XLVII**, the desymmetrization by thiolytic of bicyclic and monocyclic *meso*-epoxides **210** occurs smoothly to afford the corresponding β -hydroxy sulfides **211** in moderate to high yields and moderate to good enantioselectivities.

2.3.5. Desymmetrization of Oxetanes. Oxetanes are emerging as a versatile four-membered heterocyclic scaffold in organic synthesis and medicinal chemistry.¹⁴⁴ Oxetanes substituted at the 3-position are prochiral and lead to the formation of various useful chiral building blocks by enantioselective ring-opening with various nucleophiles.¹⁴⁵ Recently, Sun and coauthors reported an elegant organo-

Scheme 103. Desymmetrization of *meso*-Epoxide by Thiolytic



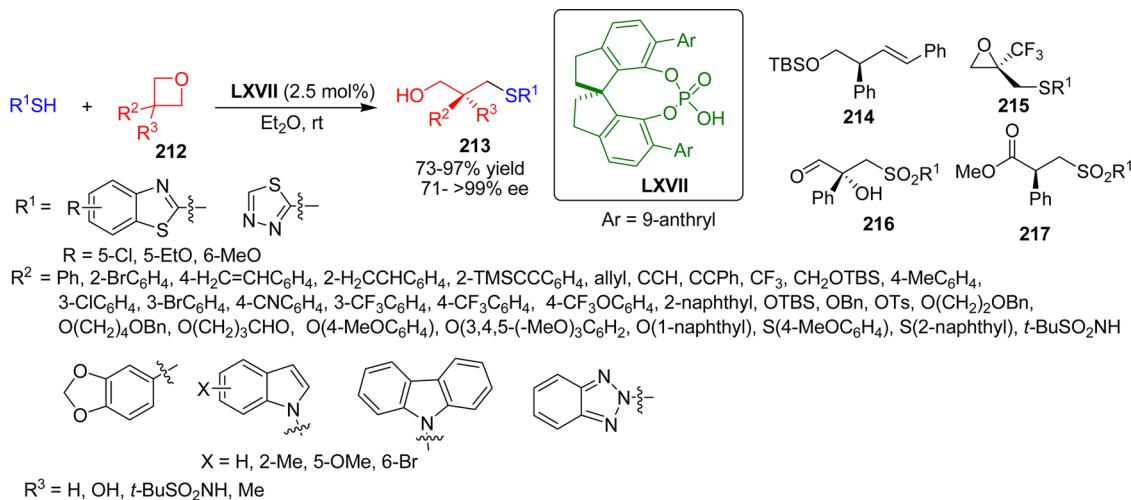
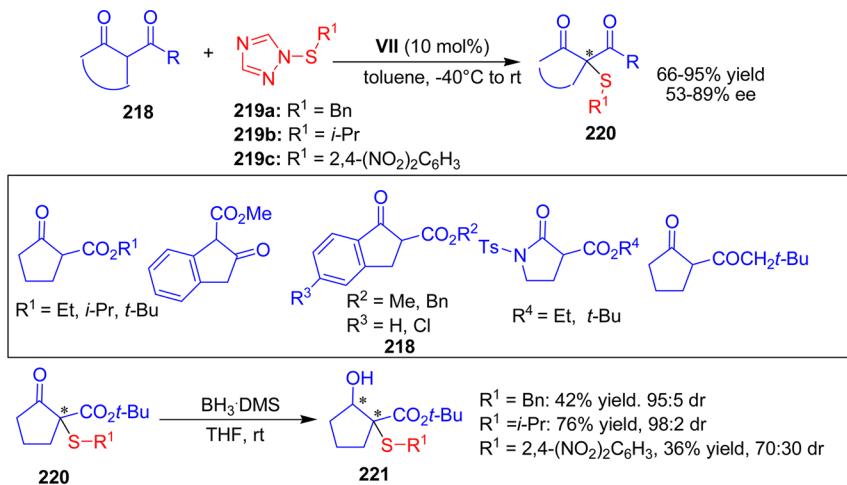
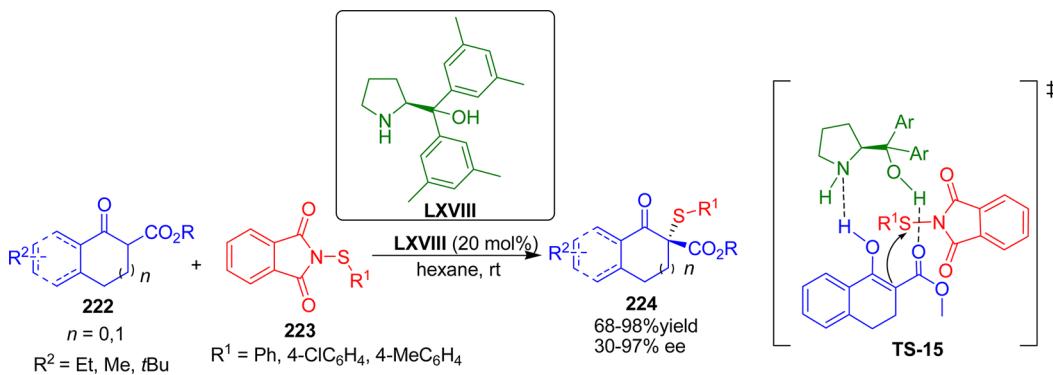
catalytic asymmetric desymmetrization of 3-substituted oxetanes with various sulfur nucleophiles (Scheme 104).¹⁴⁶ The spinol-derived phosphoric acid **LXVII** was found to be an efficient catalyst for the ring-opening of various 3-substituted oxetanes **212** with 2-mercaptopbenzothiazoles and 1,3,4-thiadiazole-2-thiol to provide enantioenriched products **213** in 73–97% yields and good to excellent enantioselectivities of 71–99% ee. The key feature of this transformation includes mild reaction conditions, low catalyst loading, broad substrate scope, and the formation of tetrasubstituted stereocenters, including all-carbon quaternary stereocenters. Moreover, the enantioenriched products **213** also served as versatile precursors for other useful chiral building blocks, such as **214–217**.

2.4. Sulfenylation Reactions

The organocatalytic enantioselective α -sulfenylation of carbonyl compounds is an important alternative for the construction of new carbon–sulfur bonds with a high level of stereoselectivity.

2.4.1. Lewis Base–Brønsted Acid or Lewis Base Catalysis. In 2005, Jørgensen's group reported an organo-

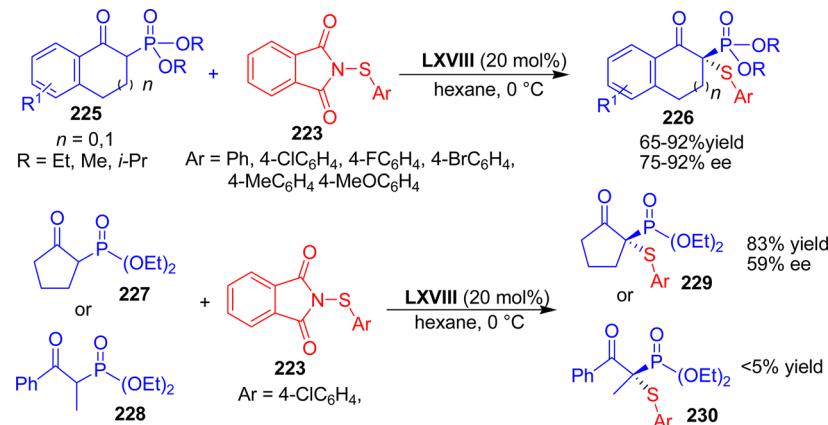
Scheme 104. Desymmetrization of 3-Substituted Oxetanes with Various Sulfur Nucleophiles

Scheme 105. α -Sulfonylation of β -Dicarbonyl Compounds with 1-Sulfanyl-1,2,4-triazole Catalyzed by a Dimeric Cinchona AlkaloidScheme 106. α -Sulfonylation of β -Ketoesters with a Diaryl Prolinol Secondary Amine Catalyst

catalytic enantioselective α -sulfonylation of β -dicarbonyl compounds **218** with 1-benzylsulfanyl-sulfanyl-1,2,4-triazole **219a** catalyzed by a dimeric cinchona alkaloid **VII** (Scheme 105).¹⁴⁷ The other electrophilic sulfur reagents such as isopropylsulfanyl-[1,2,4]triazole **219b** and 1-(2,4-dinitrophenylsulfanyl)-[1,2,4]triazole **219c** were also employed with comparable efficiency. The dimeric cinchona alkaloid affords a series of tetrasubstituted α -sulfonylated β -dicarbonyl com-

pounds **220** in 66–95% yields and 53–89% ee. A diastereoselective reduction of the α -sulfonylated β -keto esters **220** using BH₃/DMS gave optically active α -sulfonylated β -hydroxy esters **221** in moderate to good diastereoselectivities (70:30–98:2 dr).

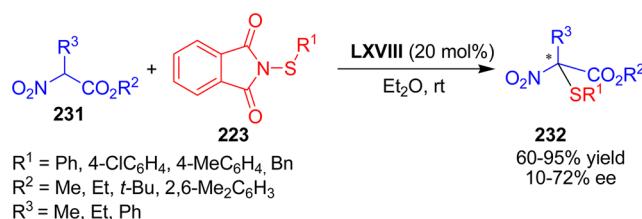
In 2009, Zhu and co-workers reported the α -sulfonylation of β -ketoesters **222** mediated by a diaryl prolinol secondary amine catalyst **LXVIII** (Scheme 106).¹⁴⁸ The corresponding adducts

Scheme 107. α,α -Diaryl Prolinol-Catalyzed α -Sulfonylation of β -Keto Phosphonates

224 bearing a tetrasubstituted carbon center were synthesized in good yields (68–98%) and low to excellent enantioselectivities (30–97%) by the reaction of various six-/five-membered β -ketoesters **222** with *N*-(arylthio)-phthalimides **223** using the commercially available catalyst **LXVIII**. However, the methyl ester derived from 1-indanone failed to give a high asymmetric induction, albeit its reactivity was higher and no acceptable improvement was achieved by cooling the reaction mixture at -25°C . The NMR analysis of a mixture of the catalyst and the model β -ketoester showed a weak intermolecular NOE between the methyl group of the substrate and the aromatic methyl group. This observation associated with the absence of signals corresponding to the enamine formation led authors to suggest a plausible noncovalent activation of the β -ketoester by the organocatalyst **LXVIII** toward the electrophilic attack by the sulfur reagent as shown in TS-15.

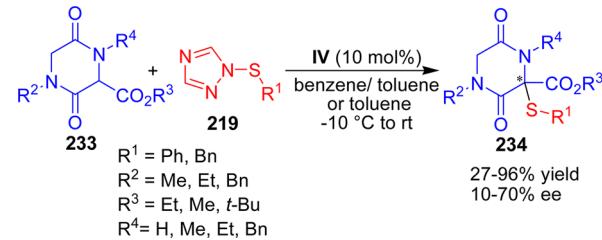
Zhu and co-workers further extended the applicability of the α,α -diaryl prolinol organocatalyst **LXVIII** for the α -sulfonylation of β -keto phosphonates **225** (Scheme 107).¹⁴⁹ A series of chiral sulfenylated β -keto phosphonates **226** was obtained in good yields (65–92%) and moderate to high enantioselectivities (75–92% ee) by reacting a variety of cyclic β -keto phosphonates **225** with different *N*-(arylthio)phthalimides **223**. The enantiomeric excess of the product depends on the nature of the ester group and also on the ring size of the β -keto phosphonates. The five-membered cyclic ester derivative **227** led to the formation of **229** with only modest enantiomeric excess. However, the sulfenylation of the acyclic β -keto phosphonate **228** under the optimized reaction condition gave only a poor yield of the desired product **230**.

Very recently, an organocatalytic enantioselective sulfenylation of α -nitroesters **231** with *N*-(arylthio)phthalimides **223** catalyzed by the α,α -diaryl prolinol **LXVIII** was published (Scheme 108).¹⁵⁰ A variety of α -sulfenylated α -nitroesters **232**

Scheme 108. α,α -Diaryl Prolinol-Catalyzed α -Sulfonylation of α -Nitroesters

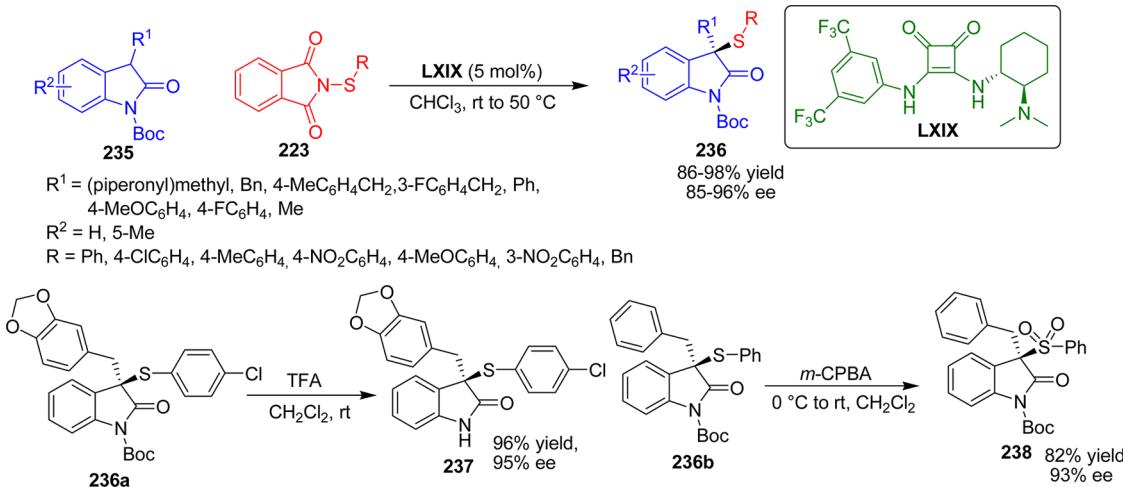
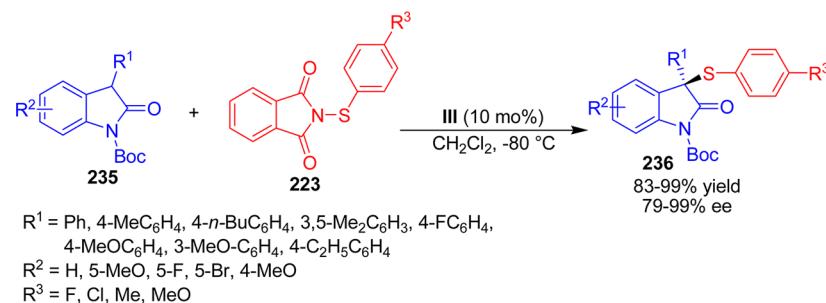
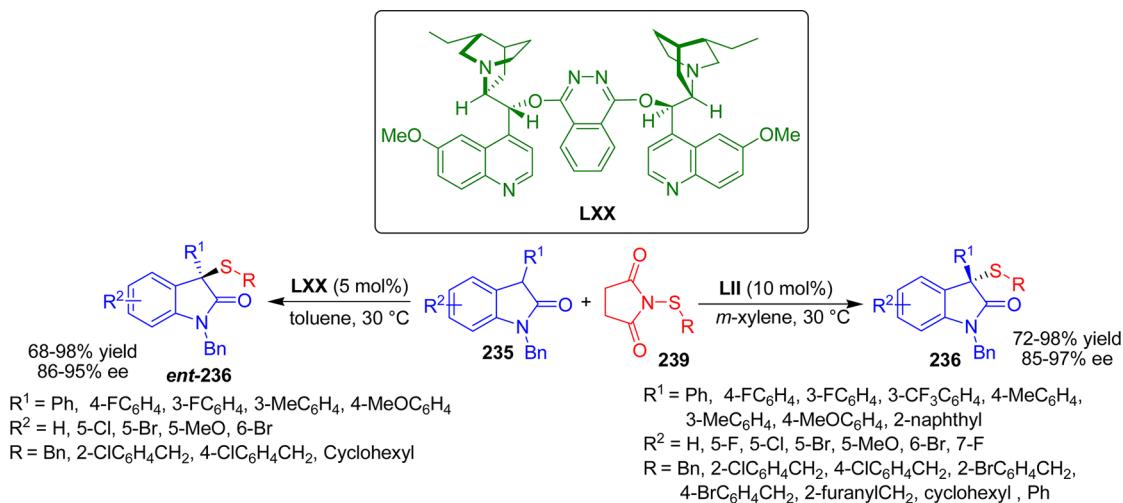
bearing a tetrasubstituted stereocenter were obtained in moderate to good yields and low to moderate enantioselectivities. Following the same protocol, the enantioselective sulfenylation of ethyl 2-cyanopropanoate afforded the desired product in 81% yield, but only with 30% ee.

Olenyuk and co-workers described an asymmetric organocatalytic α -sulfonylation of substituted piperazine-2,5-diones **233** with the electrophilic sulfur transfer reagents **219** (Scheme 109).¹⁵¹ Using 10 mol % of quinine as catalyst, poor to moderate enantiomeric excesses of the sulfenylated adducts **234** have been observed.

Scheme 109. α -Sulfonylation of Substituted Piperazine-2,5-diones Catalyzed by Quinidine

In 2012, three independent reports were published on the enantioselective sulfenylation of oxindoles. Enders and co-workers reported an amino-squaramide **LXIX**-catalyzed asymmetric sulfenylation of *N*-Boc oxindoles **235** by using *N*-(sulfanyl)phthalimides **223** as the sulfenylating agents (Scheme 110).¹⁵² A series of oxindoles **236** bearing a tetrasubstituted stereocenter were synthesized in excellent yields (86–98%) and good to excellent enantioselectivities (85–96% ee). Aliphatic, aromatic, as well as benzylic groups at the C-3 position of the oxindoles were tolerated under the optimized reaction conditions. The synthetic utility of the products was demonstrated by deprotection of the Boc group to provide **237** and the transformation of the thioether moiety into the corresponding sulfone **238**, as expected without any loss in enantiomeric excess.

Li, Cheng, and co-workers independently published the same organocatalytic enantioselective sulfenylation reaction of 3-substituted *N*-Boc oxindoles **235** with the electrophilic sulfur reagents **223**, however, catalyzed by quinidine at very low temperature (Scheme 111).¹⁵³ Whereas the sulfenylated oxindoles **236** were obtained in good to excellent yields (83–99%) and enantioselectivities (79–99% ee), the oxindoles

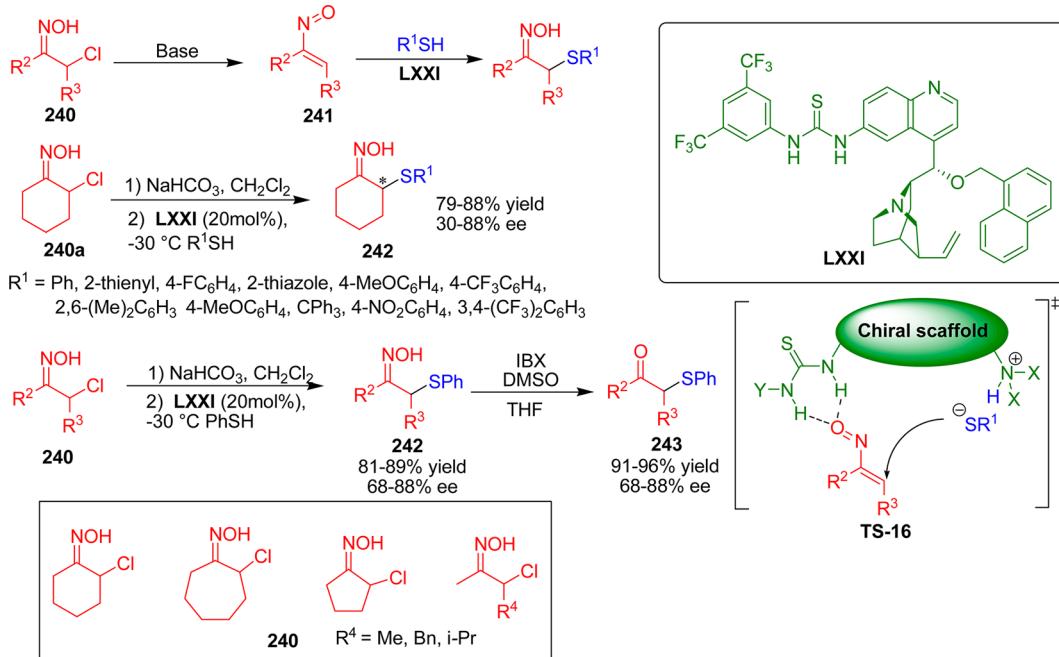
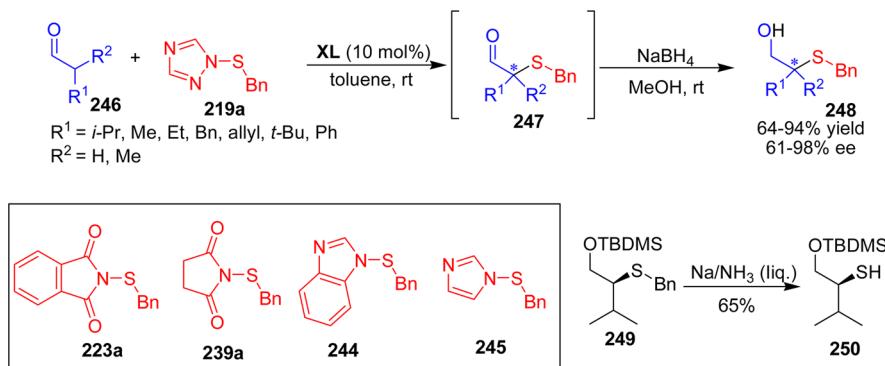
Scheme 110. Amino-quaramide-Catalyzed Asymmetric Sulfenylation of *N*-Boc Oxindoles with *N*-(Sulfanyl)phthalimides**Scheme 111.** Quinidine-Catalyzed Asymmetric Sulfenylation of *N*-Boc Oxindoles**Scheme 112.** Dimeric Cinchona Alkaloid Promoted Asymmetric Sulfenylation of *N*-Benzyl Oxindoles

bearing substituents other than Boc as well as the corresponding NH oxindole did not provide good results in terms of enantioselectivity.

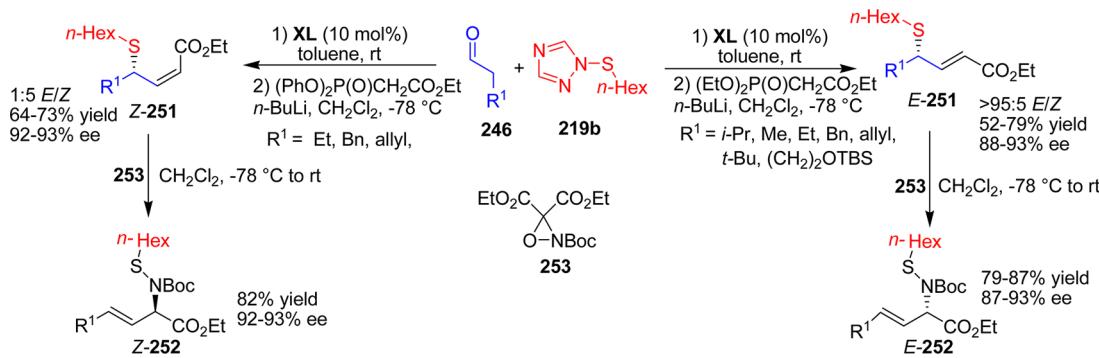
Simultaneously, Jiang's group reported an efficient organocatalytic enantioselective sulfenylation of *N*-benzyl-3-aryloxindoles **235** with *N*-(sulfanyl)succinimides **239** (Scheme 112).¹⁵⁴ Using the pseudoenantiomeric catalysts **LII** and **LXX**, both enantiomers of the 3-benzylthio-, alkylthio-, and arylthio-substituted oxindoles **236** bearing a 3,3-disubstituted stereocenter were obtained in good to excellent yields (68–98%) and enantioselectivities (85–97% ee).

Very recently, Jiang and co-workers reported a highly enantioselective α -sulfonylation of 4-alkyl and benzyl-substituted azlactones **195** with *N*-(sulfanyl)succinimides **239** catalyzed by a cinchona-derived amino-squaramide **XI** in the presence of 4 Å molecular sieves.¹⁵⁵ Various sulfenylated azlactones were synthesized in 34–96% yields and 81–94% ee.

Coltart and co-workers have developed an efficient asymmetric organocatalytic formal α -sulfonylation of ketones via *in situ* formed nitrosoalkenes **241** from α -chlorooximes **240** (Scheme 113).¹⁵⁶ This transformation proceeding in an umpolung fashion uses simple thiols instead of an electrophilic

Scheme 113. Asymmetric Organocatalytic Formal α -Sulfonylation of Ketones via SMA to in Situ Formed NitrosoalkenesScheme 114. Organocatalytic Enantioselective α -Sulfonylation of Aliphatic Aldehydes

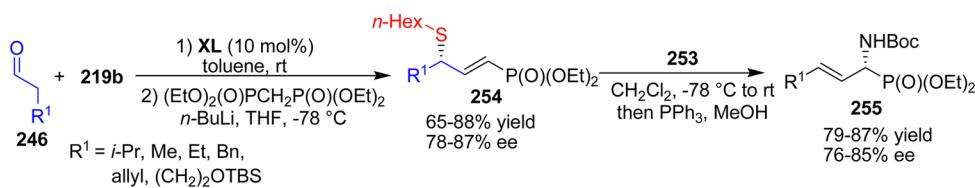
Scheme 115. Asymmetric Synthesis of Vinyl Glycines by a One-Pot Sulfonylation/Olefination and Allylic Sulfimide [2,3]-Sigma tropic Rearrangement



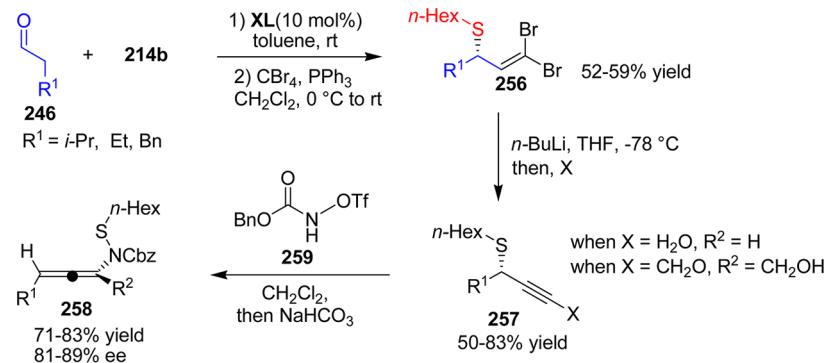
sulfur reagents. The screening of various thiols with α -chloro oxime 240a derived from cyclohexanone under the catalytic influence of the tertiary amine-thiourea **LXXI** shows that thiophenol provides the highest enantioselectivity of 88% ee. A series of chiral α -sulfonylated oximes 242 were synthesized in 81–89% yield with 68–88% ee. The reaction proceeds through in situ generation of the corresponding nitrosoalkene 241 ,

which gets activated by the thiourea moiety of the catalyst while simultaneously the nucleophilic thiol gets activated by the tertiary amine of the catalyst as shown in **TS-16**. The SMA leads to the α -sulfonylated oximes 242 , which were successfully converted to the corresponding α -sulfonyl ketones 243 without racemization via IBX-mediated oxidative oxime cleavage.

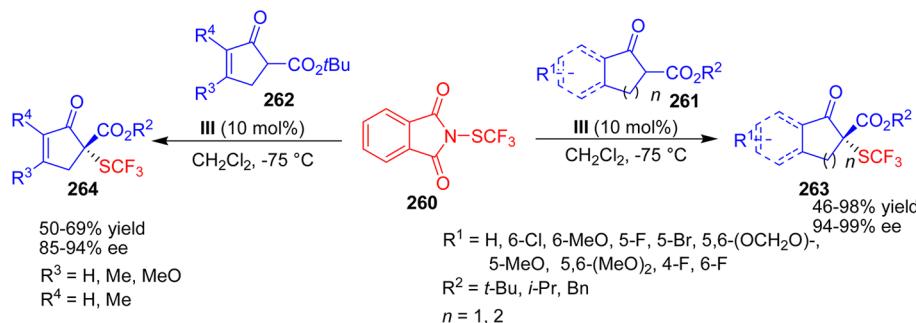
Scheme 116. Organocatalytic Sulfenylation and [2,3]-Sigmatropic Rearrangement for the Synthesis of Enantiomerically Enriched β,γ -Unsaturated- α -aminophosphonates



Scheme 117. Asymmetric Synthesis of Allenamides via α -Sulfonylation of Aldehydes Followed by Corey–Fuchs Alkylation and Sulfinimide [2,3]-Sigmatropic Rearrangement



Scheme 118. Enantioselective Trifluoromethylsulfonylation of β -Ketoesters Catalyzed by Quinidine

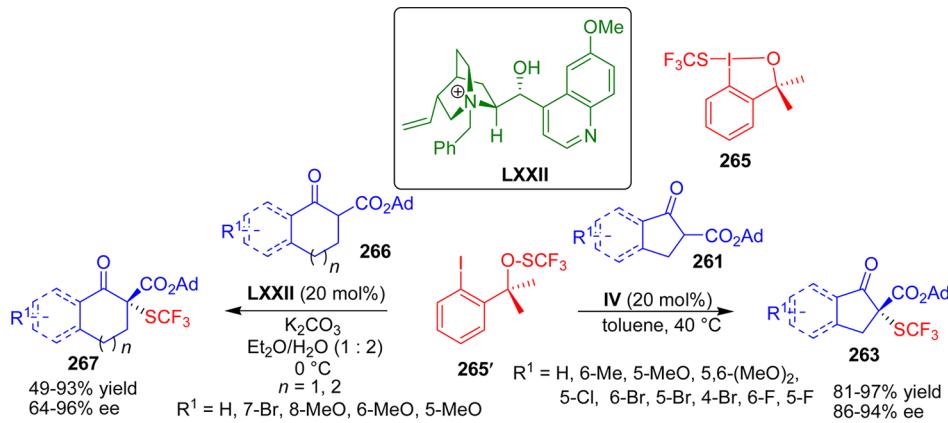
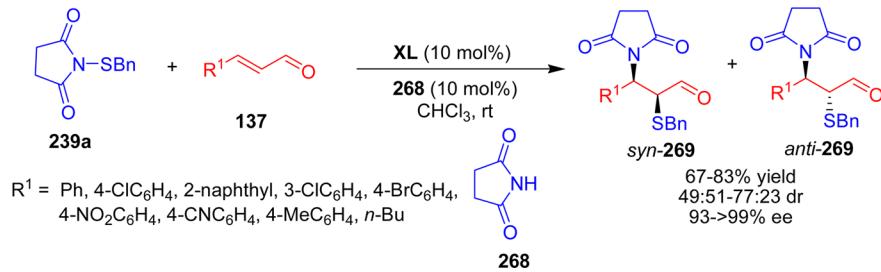


2.4.2. Amino Catalysis via Enamine Activation. The enamine formation between chiral secondary amines and carbonyl compounds is a well established and widely explored mode of activation in covalent organocatalysis.¹⁵⁷ The first organocatalytic enantioselective sulfenylation of aliphatic aldehydes catalyzed by a secondary amine was reported by Jørgensen and co-workers in 2005.^{158,159} After screening different electrophilic sulfur reagents (219a, 223a, 239a, 244, and 245), N-benzylsulfanyl-1,2,4-triazole (219a) turned out to be the best sulfenylating agent for the TMS-prolinol XL-catalyzed α -functionalization of various aliphatic aldehydes 246 (Scheme 114). To facilitate the workup procedure, the α -sulfenylated aldehydes 247 were directly reduced *in situ* without racemization to the corresponding sulfenylated alcohols 248 in moderate to good yields (64–94%) and excellent enantioselectivities (95–98%). Only a moderate level of enantioselectivity (61% ee) was observed in case of an α,α -disubstituted aldehyde (R² = Me). The synthetic utility of the sulfenylated alcohols has been demonstrated by selective benzyl group deprotection of the hydroxy silyl-protected product 249 with Na/NH₃ (liq) to afford the free thiol 250 in good yield. It should also be mentioned that the α -sulfenylated aldehydes 247 can undergo a reductive amination with dibenzylamine and

triacetoxyborohydride to form vicinal amino thioethers with only a slight recemicization.

In 2007, Armstrong and co-workers utilized the Jørgensen strategy of the enantioselective organocatalytic α -sulfonylation of aldehydes for the efficient asymmetric synthesis of vinyl glycines 252 by allylic sulfinimide [2,3]-sigmatropic rearrangement (Scheme 115).¹⁶⁰ A one-pot asymmetric α -sulfonylation/olefination of aldehydes 246 provided the allylic sulfides 251 in 52–79% yield and 88–93% ee. Further reaction of 251 with the oxaziridine 253 led to a stereospecific [2,3]-sigmatropic rearrangement to afford the allylic sulfides 252 without any change of enantiomeric excess. Both enantiomeric products could be obtained using the same catalyst XL through the choice of *E*- or *Z*-selective olefination, respectively.

The organocatalytic sulfenylation and [2,3]-sigmatropic rearrangement strategy was further extended for the synthesis of enantiomerically enriched β,γ -unsaturated- α -aminophosphonates 255 (Scheme 116).¹⁶¹ The total reaction sequence involves a one-pot organocatalytic α -sulfonylation/olefination of aldehydes to form 254, followed by oxaziridine 253-mediated sulfimidation and sulfinimide [2,3]-sigmatropic rearrangement of 254 to afford the α -aminophosphonates 255 in good yields and enantioselectivities.

Scheme 119. Enantioselective Trifluoromethylsulfenylation of β -Ketoesters Catalyzed by Quinine or a Phase-Transfer CatalystScheme 120. Domino Aminosulfonylation Reaction of α,β -Unsaturated Aldehydes with 1-(Benzylthio)pyrrolidine-2,5-dione

Armstrong and his co-worker also developed a procedure for the synthesis of allenamides **258** by [2,3]-sigmatropic rearrangement of propargylic sulfinimides mediated by a new sulfimidation reagent **259** (Scheme 117).¹⁶² The branched propargylic sulfides **257** were prepared by an enantioselective organocatalytic aldehyde α -sulfonylation followed by Corey–Fuchs alkynylation via **256**. The enantioselectivity (81–89% ee) of the allenamides **258** was good, although slightly lower than usually observed in organocatalytic α -sulfonylations of aldehydes.

2.5. Trifluoromethylsulfenylation Reactions

Recently, the research groups of Rueping and Shen published two independent reports on the organocatalytic enantioselective trifluoromethylsulfenylation of β -ketoesters.^{163,164} Rueping and co-workers developed a highly enantioselective trifluoromethylsulfenylation of β -ketoesters **261** and **262** by employing *N*-trifluoromethylthiophthalimide **260** as electrophilic SCF_3 source and quinidine as the catalyst (Scheme 118).¹⁶³ The corresponding β -ketoesters **263** and **264** bearing a trifluoromethanesulfenyl group were obtained in good yields and excellent enantioselectivities. Employing quinine as catalyst, the opposite enantiomer of the product was synthesized with a similar level of enantioselectivity.

Simultaneously, Shen and co-workers devised a similar strategy for the enantioselective trifluoromethylsulfenylation of β -ketoesters catalyzed by a chiral Lewis base or a phase-transfer catalyst (Scheme 119).¹⁶⁴ In the presence of quinine, the various five-membered cyclic β -ketoesters **261** underwent trifluoromethylsulfenylation with an electrophilic trifluoromethylthiolated hypervalent iodine reagent **265** (the relevant structure **265'** by Buchwald et al.¹⁶⁵) to generate a trifluoromethylsulfur bearing quaternary stereogenic centers on **263** in very good yields and enantioselectivities. When six- or seven-membered cyclic β -keto esters **266** were subjected to

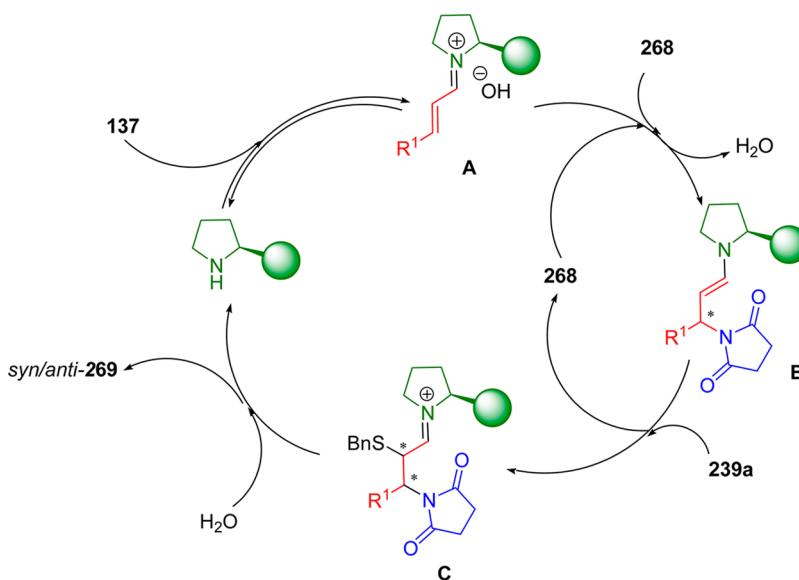
the optimized reaction conditions, only poor conversion was observed. However, these β -keto esters under the phase-transfer conditions using catalyst **LXXII** gave moderate to very good yields and enantioselectivities of **267**.

Rueping's group successfully extended the strategy of enantioselective trifluoromethylthiolation with *N*-(trifluoromethylthio)phthalimide for oxindole derivatives.¹⁶⁶ The dimeric cinchona-alkaloid catalyst **VII** provided a direct entry to the optically active oxindoles with a tetrasubstituted stereogenic center bearing a CF_3S^- group in 75–90% yield and 85–94% ee. Very recently, Tan and co-workers reported a highly enantioselective organocatalytic trifluoromethylsulfenylation of oxindoles with trichloroisocyanuric acid (TCCA) and $AgSCF_3$ instead of *N*-(trifluoromethylthio)phthalimide using dimeric cinchona-alkaloid catalyst **VII**.¹⁶⁷

2.6. Aminosulfonylation Reactions

In 2008, Córdova's group used both the electrophilic sulfur and the nucleophilic nitrogen of 1-(benzylthio)pyrrolidine-2,5-dione (**239a**) in the organocatalytic domino aminosulfonylation reaction of α,β -unsaturated aldehydes **137** (Scheme 120).¹⁶⁸ In the α,α -diphenyl prolinol TMS ether **XL**-catalyzed aminosulfonylation reaction, only a catalytic amount of succinimide (**268**) was required to initiate the domino process, and the reaction was accomplished with the masked *N*-nucleophile, released as nucleofuge after electrophilic sulfenylation. The reaction of the enals **137** with *N*-(benzylsulfonyl)succinimide (**239a**) provided the corresponding β -amino- α -mercaptoaldehyde derivatives **269** in good yields (67–83%) as a *syn/anti*-mixture and excellent enantioselectivities of 93–99% ee; however, the diastereomeric ratio was poor (49:51–77:23 dr). The aminosulfonylation reaction is initiated by the addition of **268** to the iminium ion **A** to give the enamine **B**, which then reacts with the sulfur electrophile **239a** resulting in the iminium cation **C** and **268** as a nucleophile. The catalyst is returned and

Scheme 121. Catalytic Cycle for the Domino Aminosulfonylation Reaction of α,β -Unsaturated Aldehydes with 1-(Benzylthio)pyrrolidine-2,5-dione



Scheme 122. TRIP-Catalyzed Sulfamination of Amino-alkenes

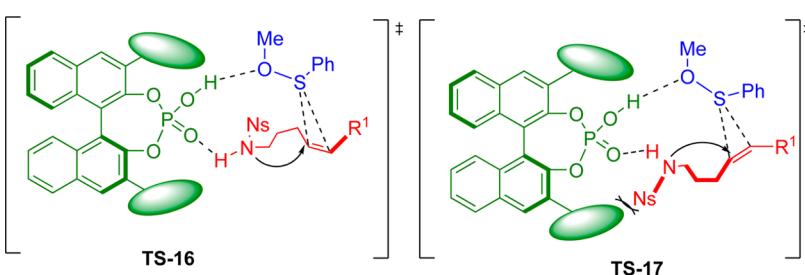
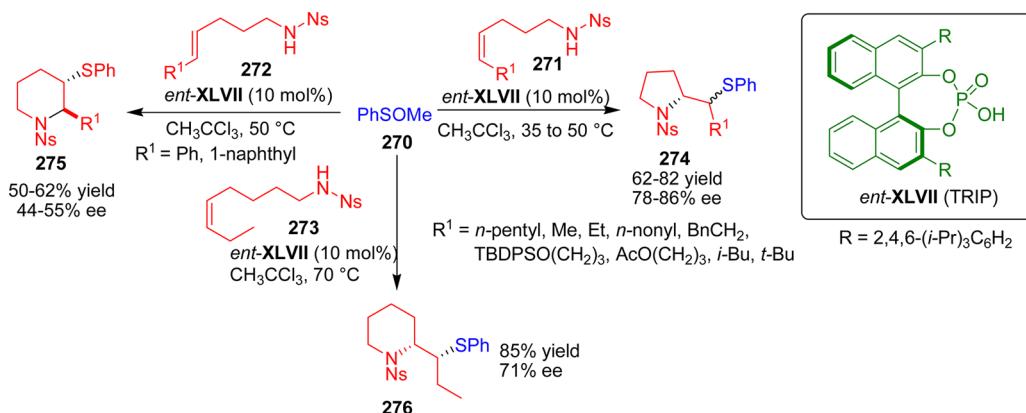


Figure 5. Proposed transition state for the TRIP-catalyzed sulfamination of amino-alkenes.

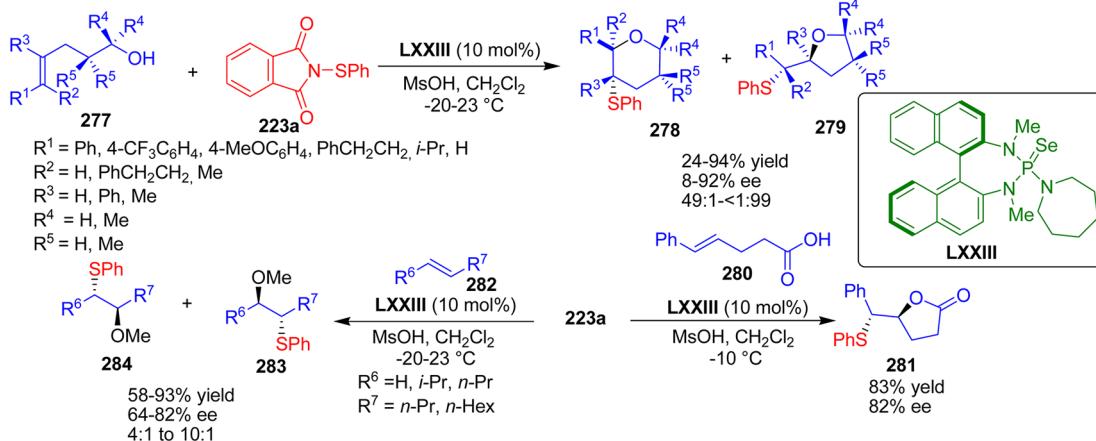
the product formed upon hydrolysis of C to complete the catalytic cycle (Scheme 121).

Recently, Shi and co-workers described a Brønsted acid-catalyzed asymmetric sulfamination of amino-alkenes 271–273 with methyl phenyl sulfoxide (270) to provide enantiomerically enriched 2-substituted pyrrolidines 274 and piperidines 275,276 (Scheme 122).¹⁶⁹ Using *ent*-XLVII as catalyst, a variety of (Z)- γ -amino-alkenes 271 regioselectively cyclized to form the corresponding pyrrolidines 274 in 62–82% yield and 78–86% ee. When (Z)- δ -amino-alkene 273 was subjected to the *ent*-XLVI-catalyzed sulfamination conditions, piperidine 276 was obtained regioselectively in 85% yield and 71% ee.

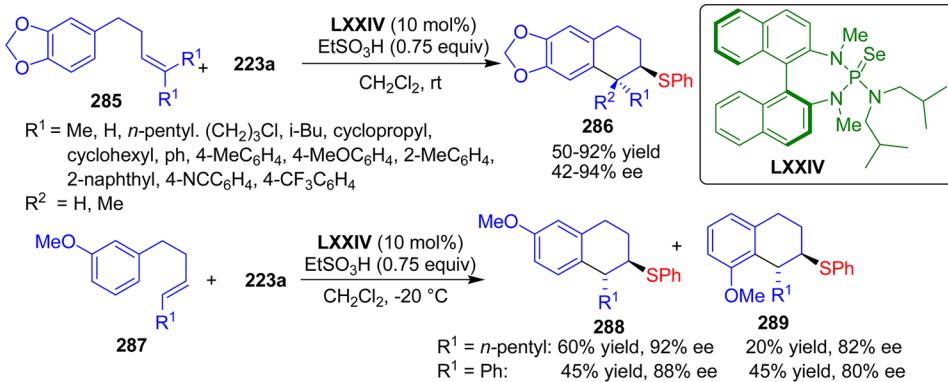
However, when the (E)- γ -aminoalkene (E)-N-(dec-4-en-1-yl)-4-nitrobenzene-sulfonamide bearing an alkyl substituent was used as substrate, a mixture of 5-*exo* and 6-*endo* products was obtained. With the aryl-substituted (E)- γ -aminoalkene 272, the cyclization occurred regioselectively to form the 6-*endo* 2,3-*trans*-disubstituted piperidines 275 in 50–62% yield and 44–55% ee.

On the basis of the absolute configuration of the pyrrolidines, the authors proposed a transition state for the cyclization of the (Z)- δ -aminoalkenes. In the transition state, the phosphoric acid forms a hydrogen-bonded ternary complex with PhSOMe and the sulfonamide NH-function of the aminoalkenes (Figure 5).

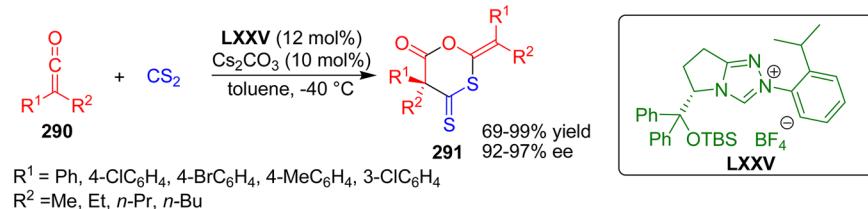
Scheme 123. Oxsulfenylation of Double Bonds Using a BINAM-Based Phosphoramido Catalyst



Scheme 124. Asymmetric Carbosulfonylation of Olefins



Scheme 125. N-Heterocyclic Carbene-Catalyzed [2+2+2] Cycloaddition Reaction of Ketenes with Carbon Disulfide



The reaction proceeded mainly via **TS-16**, which is free of steric hindrance, while **TS-17** is disfavored due to the steric interaction between the triisopropylphenyl group of the catalyst and the sulfonamide group of the alkene.

2.7. Oxsulfenylation Reactions

Denmark and co-workers reported an elegant asymmetric oxsulfenylation of alkenes using a BINAM-based phosphoramido catalyst **LXXIII** and a Brønsted acid (methanesulfonic acid, **MsOH**) as an additive (Scheme 123).¹⁷⁰ Various alkene alcohols **277** as well as an acid **280** reacted efficiently with an electrophilic *N,S*-sulfur reagent **223a** in the presence of **LXXIII** to afford sulfenylated tetrahydropyrans **278**, tetrahydrofurans **279**, and tetrahydrofuranone **281** in low to high yields and enantioselectivities by ring closure with pendant hydroxyl as in **277** or carboxyl groups as in **280**. Intermolecular thiofunctionalizations of alkenes **282** with simple alcohols or carboxylic acids as the nucleophiles also occurred with good regioselectivity to provide the desired products **283** and **284** in moderate to good yields and enantioselectivities.

2.8. Carbosulfonylation Reactions

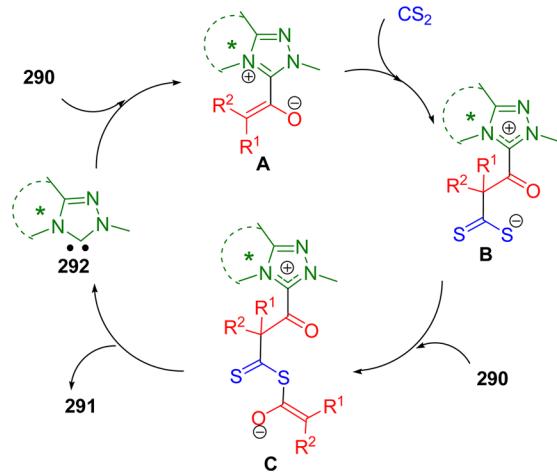
Recently, Denmark and Jaunet developed a catalytic asymmetric carbosulfonylation of olefins **285** by using a cocatalytic system of a Brønsted acid (**EtSO₃H**) and a chiral Lewis base **LXXIV** (Scheme 124).¹⁷¹ With this catalytic system, a broad range of *E*-olefins **285** underwent asymmetric carbosulfonylation to give access to enantioenriched *trans*-tetrahydronaphthalenes **286** in moderate to high yields (50–92%) with complete diastereoselectivity and moderate to high enantioselectivities (62–94% ee). In some cases, tetrahydronaphthalenes with a quaternary carbon were obtained in good yields (82–90%) and moderate enantioselectivities (42–60% ee). Under the optimized reaction conditions, the substrates **287** bearing a methoxy group at the 3-position with respect to the tethered alkene afforded a mixture of cyclized products **288** and **289**.

2.9. Cycloaddition Reactions

In 2011, Ye and co-workers reported an *N*-heterocyclic carbene-catalyzed [2+2+2] cycloaddition reaction of ketenes with carbon disulfide (Scheme 125).¹⁷² This cycloaddition

strategy uses LXXV as NHC precatalyst and cesium carbonate as base and requires 1 equiv of carbon disulfide and 2 equiv of ketenes 290 to give 1,3-oxathian-6-ones 291 in good to excellent yields and excellent enantioselectivities. These reactions are initiated by addition of the NHC 292 (generated from LXXV and base) to ketenes rather than CS_2 , giving rise to the enolate intermediate A, which then adds to CS_2 to afford thioenolate B (Scheme 126). The latter one reacts with another

Scheme 126. Proposed Catalytic Cycle for the *N*-Heterocyclic Carbene-Catalyzed [2+2+2] Cycloaddition Reaction of Ketenes with Carbon Disulfide



molecule of ketene to provide intermediate C, which after ring-closing leads to the final [2+2+2] cycloadduct 291 and regenerates the NHC catalyst. Very recently, Wei and co-workers reported a theoretical investigation based on the density functional theory (DFT) to elucidate the mechanisms of the NHC-mediated stereoselective [2+2+2] cycloaddition of ketene and carbon disulfide.¹⁷³ The DFT calculations revealed that this reaction occurs through four steps involving the complexation of the NHC with ketene rather than with CS_2 , addition of ketenes to CS_2 without dimerization of ketene, formal [4+2] cycloaddition with the second molecule of ketene rather than intramolecular [2+2] cycloaddition, and finally

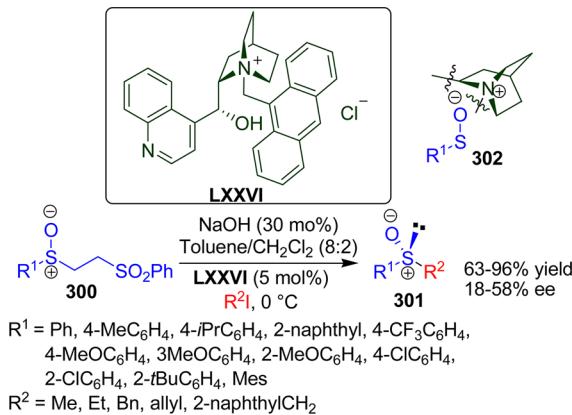
regeneration of NHC-catalyst. The second step is revealed to be the rate-determining step.

Recently, Jørgensen's group reported a new asymmetric organocatalytic thio-Diels–Alder reaction of thiocarbonyl heterodienophiles 293 with dienals 294 and 295 to provide the enantioenriched sulfur-based heterocycles 296 and 297 (Scheme 127).¹⁷⁴ Using diphenyl prolinol TMS ether *ent*-XLIII as catalyst and benzoic acid as an additive, a series of synthetically useful dihydrothiopyrans 296 and 297 were synthesized in high yields and excellent enantioselectivities. On the basis of DFT calculations, the authors assumed that the process may proceed via a stepwise mechanism involving zwitterionic intermediates. The amino-catalyzed cross-triennamine¹⁷⁵ pathway was also successfully employed for thio-Diels–Alder cycloaddition of 293a with 298 to form the bicyclic compound 299 in 72% yield, 72:28 dr, and >96% ee.

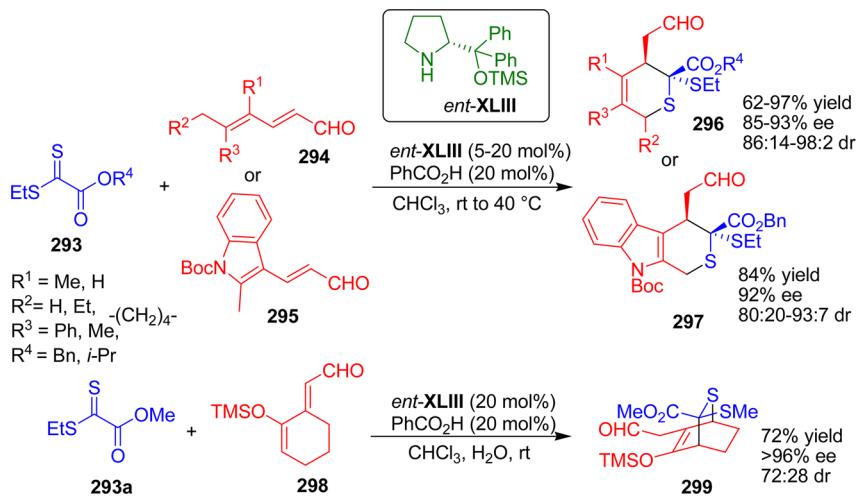
2.10. Asymmetric Alkylation of Sulfenate Salts

Perrio and co-workers reported a new strategy for the synthesis of chiral sulfoxides 301 via a phase-transfer catalyst promoted asymmetric alkylation of *in situ* generated sulfenate salts from corresponding sulfoxides 300, with alkyl iodides (Scheme 128).¹⁷⁶ A series of sulfoxides 301 were obtained in moderate

Scheme 128. Asymmetric Alkylation of *In Situ* Generated Sulfenate Salts with Alkyl Halides Promoted by a Phase-Transfer Catalyst



Scheme 127. Asymmetric Thio-Diels–Alder Reaction of Thiocarbonyl Heterodienophiles with Dienals



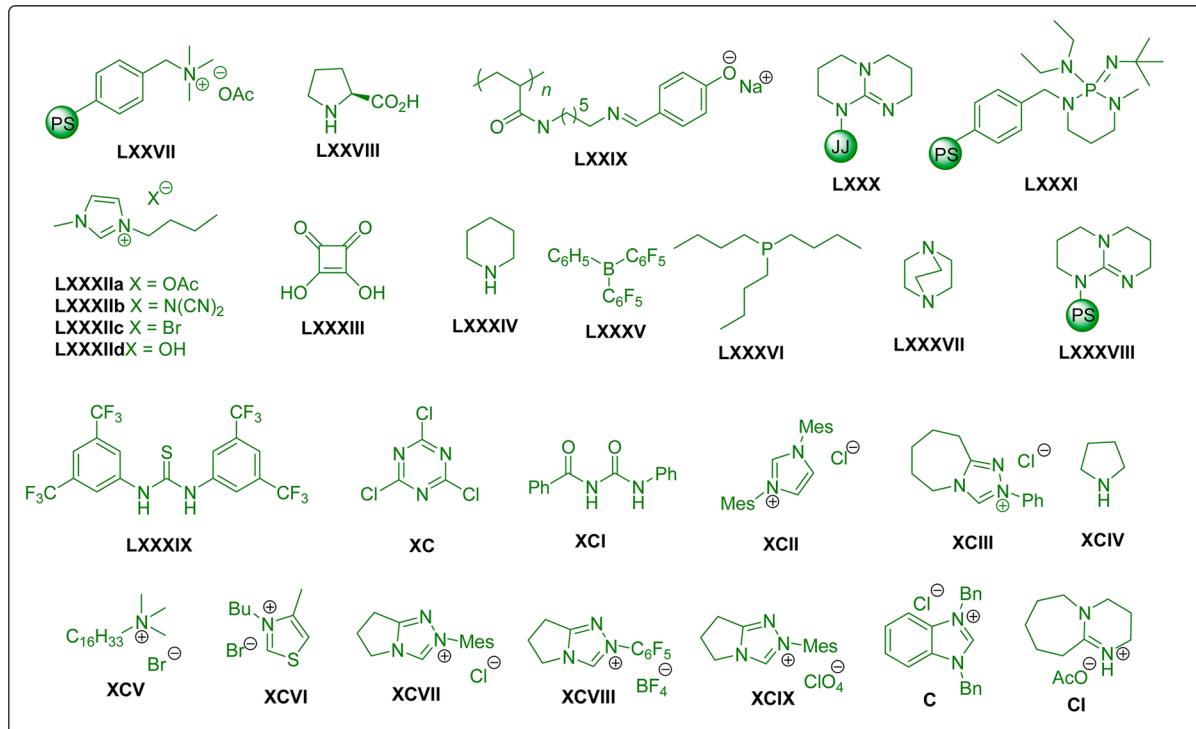


Figure 6. Structures of organocatalysts used in nonenantioselective C–S bond formations.

to excellent yields and low to moderate enantioselectivities using cinchonidine derived phase-transfer catalyst **LXXVI**. This transformation may proceed via an ion pair intermediate **302** to which electrophilic attack took place to generate the new C–S bond.

3. NONENANTIOSELECTIVE ORGANOCATALYTIC C–S BOND FORMATIONS

Small organic molecules not only catalyze asymmetric C–S bond formations, but also facilitate some important nonenantioselective C–S bond formations with high efficiency. In this section, we discuss the organocatalytic C–S bond formation reactions leading to racemates or achiral compounds (Figure 6).

3.1. Sulfa-Michael Additions

In 1951, Caston and Wanzer showed that a few drops of piperidine were sufficient to promote the SMA of aryl and benzyl thiols with nitroalkenes, giving rise to the corresponding Michael adducts in 51%-quantitative yield.¹⁷⁷ Huang and co-workers examined the catalytic potential of a series of polymer supported basic anion-exchange resins for the SMA of thiophenol to α,β -unsaturated carbonyl compounds.¹⁷⁸ The resin **LXXVII** bearing acetate as anion provided good to high yields (70–98%) of the SMA products (Table 1, entry 1).

In 2005, Ménand and Dalla identified tetrabutyl ammonium fluoride (TBAF) as a useful organocatalyst for the conjugate addition of oxazolidinone and thiols to a range of Michael acceptors (Table 1, entry 2).¹⁷⁹ With 2–4 mol % of catalyst, the addition of sulfur nucleophiles to unsaturated acceptors including esters, ketones, nitroolefins, and cinnamaldehyde provided the desired sulfa-Michael adducts in 60%-quantitative yield.

One year later, Kotrusz and Toma found that (S)-proline **LXXVIII** efficiently catalyzed the SMA of various thiols to

different enones in an ionic liquid, that is, [bmim]PF₆ (Table 1, entry 3).¹⁸⁰ With 5 mol % of (S)-proline, the desired products were obtained in low to excellent yields (18–99%) by simple extraction of the reaction mixture with an organic solvent.

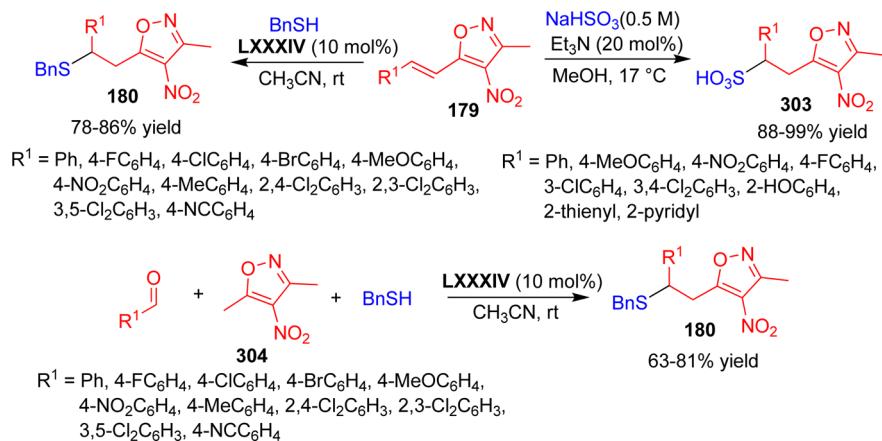
Tamami et al. utilized polyacrylamide supported phenolate **LXXIX** as a heterogeneous recyclable catalyst for aza- and sulfa-Michael additions in aqueous media (Table 1, entry 4).¹⁸¹ The SMA of various thiols and dithiol to methyl vinyl ketone and cyclic enones proceeded smoothly with 10 mol % of catalyst to provide the corresponding sulfa-Michael adducts in very good yields (80–96%).

In 2011, Vaccaro and co-workers found JandaJel (JJ) to be an efficient support for improving the catalytic efficiency of TBD for carbon–sulfur bond formations under solvent-free conditions (Table 1, entry 5).¹⁸² It was assumed that the greater spacing between the linear polymeric chains in JandaJel as compared to that of polystyrene matrixes facilitates the entry of reactants in the active sites of TBD, without the help of a swelling medium. The SMA of thiols with enones catalyzed by a low loading of JandaJel supported TBD **LXXX** provided the corresponding β -ketosulfides in 88–99% yield. The same research group also reported an efficient Michael addition of carbon-, sulfur-, and nitrogen-nucleophiles to α,β -unsaturated carbonyl compounds catalyzed by 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) supported on polystyrene PS-BEMP **LXXXI**.¹⁸³ The solvent-free condition was found to be crucial for the improved efficiency of all Michael additions, while using an organic reaction medium gave inferior results in terms of product yield. The SMA of thiols with enones and other unsaturated acceptors using equimolar amounts of substrate and 0.5 mol % of **LXXXI** yielded the addition products in high yields (93–97%) after simple filtration with the minimal amount of organic solvent (Table 1, entry 6).

Table 1. Organocatalytic Nonenantioselective SMAs

Entry	Catalyst (x mol%)	Reaction condition	Thiol (R^1)	Michael Acceptors (R^2 , R^3 , EWG, R^4 , R^5 and n)	Yield (%)	Ref.
1.	LXXVII (20 mol%)	MeOH, rt	$R^1 = \text{Ph}$	$R^2 = \text{Me, Ph,}$ $(\text{Me})_2\text{CCHCH}_2\text{CH}_2$, $R^3 = \text{Me, H}$ EWG = COMe, CHO	70-98	178
2.	TBAF (2-4 mol%)	MeCN, rt	$R^1 = \text{Ph, PhCH}_2\text{CH}_2, \text{MeCO}_2\text{CH}_2$	$R^2 = \text{Me, }i\text{-Pr, Ph}$ EWG = $\text{CO}_2\text{Et, CO}_2\text{Me,}$ COPh, CHO, NO_2 $R^3 = \text{H}$ $R^4 = \text{H}$ $R^5 = \text{H}$ $n = 1$	60-100	179
3.	LXXVIII (5 mol%)	[bmim]PF ₆ , rt	$R^1 = \text{Ph, 4-MeOC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4,$ $4\text{-MeC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4\text{CH}_2,$ $2\text{-furanylCH}_2, 3\text{-MeOC}_6\text{H}_4, 2\text{-pyridyl,}$ $\text{HOCH}_2\text{CH}_2,$ 	$R^2 = \text{Ph, }i\text{-Pr, H, Me}$ $R^3 = \text{H, Me}$ EWG = COPh, COCH ₃ , NO ₂ , CN, CHO, CO ₂ Et $R^4 = \text{H, Me}$ $R^5 = \text{H, CH}_2\text{OH}$ $n = 1$	18-99	180
4.	LXXIX (10 mol%)	Water, rt	$R^1 = \text{Ph, 4-MeC}_6\text{H}_4, \text{Bn, cyclohexyl,}$	$R^2 = \text{H, Ph}$ $R^3 = \text{H}$ EWG = COMe $n = 0, 1$ $R^4 = \text{H}$ $R^5 = \text{H}$	80-96	181
5.	LXXX (0.5 mol%)	Neat, 30 °C	$R^1 = \text{Ph, }n\text{-Bu, 4-MeC}_6\text{H}_4, \text{Bn}$	$R^2 = \text{Ph, 4-ClC}_6\text{H}_4, n\text{-Pr}$ $R^3 = \text{H}$ EWG = COMe $R^4 = \text{H}$ $R^5 = \text{H}$ $n = 1$	88-99	182
6.	LXXXI (0.5 mol%)	Neat, 30 °C	$R^1 = \text{Ph, }n\text{-Bu, 4-MeC}_6\text{H}_4, \text{Bn}$	$R^2 = \text{Ph, H}$ $R^3 = \text{H}$ EWG = COMe, CO ₂ Me $R^4 = \text{H}$ $R^5 = \text{H}$ $n = 1$	93-97	183
7.	LXXXIIa or LXXXIIb (0.1 mol%)	Neat, rt	$R^1 = \text{Ph, 4-NO}_2\text{C}_6\text{H}_4,$	$R^2 = \text{Ph}$ $R^3 = \text{H}$ EWG = COMe	89-93	184

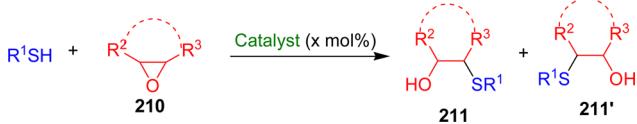
Scheme 129. 1,6-Additions of Sulfur Nucleophiles to 3-Methyl-4-nitro-5-styrylisoxazoles

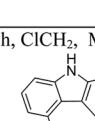


Chakraborti's group demonstrated the catalytic potential of 1-butyl-3-methylimidazolium-based ionic liquids for the

addition of thiols to α,β -unsaturated carbonyl compounds (Table 1, entry 7).¹⁸⁴ The ionic liquids **LXXXIIa** and **LXXXIIb**

Table 2. Organocatalytic Nonenantioselective Thiolysis of Epoxides



Entry	Catalyst (x mol%)	Reaction condition	Thiol (R ¹)	Epoxide (R ² , R ³)	Yield (%)	Ref.
1	TBAF (5 mol%)	Neat, 25-100 °C	R ¹ = Ph, Bn, cyclohexyl, HOCH ₂ CH(OH)CH ₂	R ² = PhOCH ₂ , MeOCH ₂ , CH ₂ CH ₂ OCH ₂ , PhCO ₂ CH ₂ , n-hexyl, Ph R ³ = H, Ph  210a	88-100	188
2	LXXXV (5 mol%)	CH ₂ Cl ₂ , Rt	R ¹ = Ph	R ² = Ph, BnOCH ₂ , BnOCH ₂ CH ₂ , 2-naphthylOCH ₂ , Ph(CH ₂) ₂ CH(OTBS)CH ₂ , PhCH(OTHP) R ³ = H R ² and R ³ = -(CH ₂) ₃ -	78-93	189
3	LXXXVI (10 mol%)	water, 25-40 °C	R ¹ = Ph, 4-MeOC ₆ H ₄ CH ₂	R ² = Ph, Me, n-Bu R ³ = Me, H R ² and R ³ = -(CH ₂) ₄ -,-(CH ₂) ₃ -	85-88	190
4.	LXXXVII or Et ₃ N (10 mol%)	water, rt, air	R ¹ = Ph, 4-MeOC ₆ H ₄ , 4-ClC ₆ H ₄ , Bn, n-Bu,	R ² = Me ₂ , CH ₂ CHCH ₂ CH ₂ Ph, R ³ = Me, H, R ² and R ³ = -(CH ₂) ₄ -,-(CH ₂) ₃ -	with LXXXVII 53-98; with Et ₃ N 61-99	193
5.	LXXXVIII (5 mol%)	Neat, Rt	R ¹ = Ph, n-Bu, 2-NH ₂ C ₆ H ₄ , 2-HOC ₆ H ₄ , allyl	R ² = Ph, Bn, HOCH ₂ CH ₂ CHCH ₂ OCH ₂ R ³ = H, R ² and R ³ = -(CH ₂) ₄ -	77->99	195
6.	LXXXIX (10 mol%)	water, rt	R ¹ = Ph	R ² = Ph R ³ = H	76	196
7.	LXXXIIC (23 mol%)	Neat, rt	R ¹ = Ph, 4-ClC ₆ H ₄ , Bn	R ² = n-hexyl, ClCH ₂ , PhOCH ₂ , Ph, Bn, HOCH ₂ CH ₂ CHCH ₂ OCH ₂ R ³ = H, COMe R ² and R ³ = -(CH ₂) ₄ -,-(CH ₂) ₅ -,-(CH ₂) ₆ -	80-95	197
8.	XC (2 mol%)	Neat, rt	R ¹ = Ph, 4-MeC ₆ H ₄ , 4-ClC ₆ H ₄ , Bn	R ² = Ph, Me, ClCH ₂ , PhOCH ₂ R ³ = H R ² and R ³ = -(CH ₂) ₄ -	95-100	198
9	Me ₂ SBr ₂ (10 mol%)	Neat, rt	R ¹ = Ph, Et, Bu, pentyl, decyl, HSCH ₂ CHCH ₂ , 4-NH ₂ C ₆ H ₄ , 4-BrC ₆ H ₄ , SPh	R ² = Ph, ClCH ₂ , Me,  PhOCH ₂ R ³ = H R ² and R ³ = -CH ₂ NBoc CH ₂ -	78-95	199
10	XCI	Neat or water, rt	R ¹ = Ph	R ² = Ph, 4-ClC ₆ H ₄ , 4-MeC ₆ H ₄ R ³ = H	73-80	200

were found to efficiently promote the SMAs of thiophenols to enones, even at low catalyst loading of 0.1 mol %. The sulfa-Michael adducts were synthesized in very good yields (89–93%) in a very short reaction time.

Azizi and co-workers reported a simple and environmentally benign protocol for the conjugate addition of aromatic amines and thiols to α,β -unsaturated carbonyl compounds in water promoted by the squaric acid **LXXXIII** as catalyst.¹⁸⁵ The corresponding products were obtained in good to excellent yields.

Adamo and co-workers devised a mild procedure for the sulfonylation of activated alkenes with an equimolar amount sodium bisulfite.¹⁸⁶ Using triethylamine as catalyst, the sulfamichael-type addition of sodium bisulfite to various unsaturated

acceptors such as chalcones and (*E*)- β -nitrostyrene provided the desired sulfonic acid derivatives in good yields.

3.2. 1,6-Addition Reactions

In 2010, Adamo and co-workers identified triethylamine as an effective catalyst to promote 1,6-addition reactions of sodium bisulfite with 3-methyl-4-nitro-5-styrylisoxazoles **179** to give the 1,6-addition adducts **303** in good to excellent yields (Scheme 129).¹⁷⁹ Later in 2011, the same research group published an efficient procedure for 1,6-addition reactions of benzyl thiol to styrylisoxazoles **179** catalyzed by piperidine **LXXXIV**.¹⁸⁷ Under mild reaction conditions, good yields of the corresponding 1,6-adducts **180** were obtained. The three-component reactions between various aldehydes, 3,5-dimethyl-4-nitroisoxazole **304**, and benzyl thiol catalyzed by piperidine were also successfully

performed, which involved the *in situ* generation of the styrylisoxazoles 179.

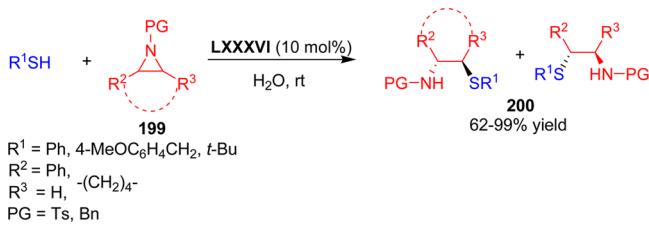
3.3. Ring-Opening of Epoxides, Aziridines, and Cyclopropanes

In 1994, Penso and co-workers used tetrabutylammonium fluoride (TBAF) as a powerful catalyst for the thiolysis of epoxides.¹⁸⁸ With 5 mol % of TBAF, good to excellent yields (88–100%) of β -hydroxysulfides 211 were obtained in a short reaction time (Table 2, entry 1). In the case of styrene oxide and epoxide 210a, both regioisomers 211 and 211' were obtained in 64% and 34% yield, and 64% and 23% yield, respectively.

Chandrasekhar's group has developed an effective protocol for the ring-opening of epoxides with allyl and propargyl alcohols, aniline, and thiophenol in the presence of catalytic amounts of tris(pentafluorophenyl)boron LXXXV (Table 2, entry 2).¹⁸⁹ Various epoxides underwent the desymmetrization with thiophenols to afford the corresponding vicinal thioether alcohols 211' in the case of styrene oxide in 84% yield and 211 in case of other epoxides in 78–90% yield.

Hou and his co-workers used tributylphosphine LXXXVI as an effective catalyst for the ring-opening reaction of various epoxides and aziridines with several heteroatom nucleophiles such as phenol, amines, and thiols in water under an inert atmosphere.¹⁹⁰ The tributylphosphine-catalyzed thiolysis of epoxides provided the corresponding adducts in 85–88% yields with 67:33–95:5 (211:211') regioselectivity (Table 2, entry 3), while the ring-opening of aziridines 199 afforded the corresponding β -amino sulfides 200 in 62–99% yield (Scheme 130). Aziridines different from *meso*-aziridines yielded both

Scheme 130. Tributylphosphine-Catalyzed Thiolysis of Aziridines



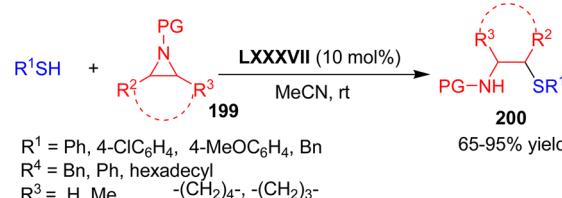
regioisomers in a 1:1 ratio with 98% yield. Tributylphosphine was also found to be an effective catalyst for the thiolysis of aziridines in acetonitrile as solvent to produce β -amino sulfides in 72–98% yield.¹⁹¹

Pizzo and co-workers investigated the thiolysis of alkyl- and aryl-epoxides under solvent-free conditions in the presence of the Lewis acid InCl₃, the Brønsted acid (*p*-TsOH), and base catalysts (*n*-Bu₃P and K₂CO₃).¹⁹² However, the catalytic activity of the organocatalysts, that is, *p*-TsOH and *n*-Bu₃P, turned out to be lower than that of InCl₃.

Wu and Xia demonstrated the catalytic potential of tertiary amines for the ring-opening of epoxides with various amines or thiols in water (Table 2, entry 4).¹⁹³ With 1 mol % of DABCO (1,4-diazabicyclic[2.2.2]octane, LXXXVII) or triethylamine, the thiolysis of epoxides afforded the corresponding β -hydroxy sulfides in good to excellent yields (53–98% with DABCO and 61–99% with Et₃N) under aerobic conditions. However, styrene oxide gave the desired 1,2-hydroxy sulfide adducts in 98% yield with 85:15 and 75:25 ratio of 211: 211' with DABCO and Et₃N, respectively.

Simultaneously with this, the same research group described an efficient ring-opening of aziridines with various thiols catalyzed by 5 mol % LXXXVII to afford the corresponding 1,2-aminothioethers 200 in good to excellent yields (65–95%) under mild reaction conditions (Scheme 131).¹⁹⁴

Scheme 131. DABCO-Catalyzed Thiolysis of Aziridines



A low loading of JandaJel supported TBD LXXX was found to catalyze the thiolysis of various epoxides under solvent-free conditions to give the corresponding ring-opened products in 85–99% yield with 66:34–99:1 ratio of 211:211'.¹⁸² The efficiency of the catalyst LXXX and the solvent-free conditions was demonstrated by the development of a continuous-flow reactor, which demonstrated that the catalyst could be recycled many times without losing its efficiency.

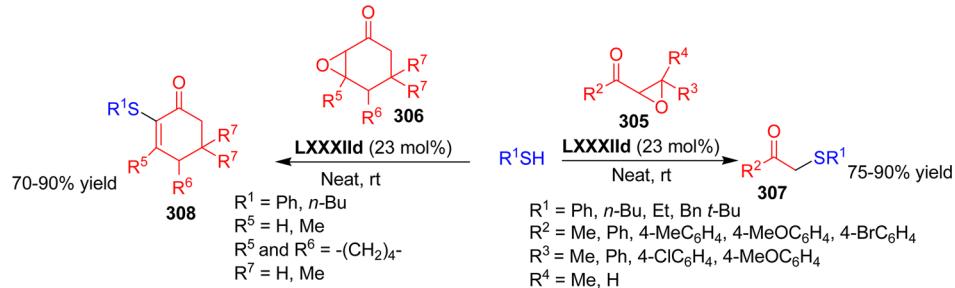
Fringuelli, Vaccaro, and co-workers developed a polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD) LXXXVIII as a recyclable catalyst for the thiolysis of epoxides with aryl and alkyl thiols (Table 2, entry 5).¹⁹⁵ The corresponding β -hydroxy sulfides have been isolated in good to excellent yields (77–99%) under neat conditions with the regiosomeric ratio of >99:1–25:75 for 211:211'. The catalyst could be recovered and reused several times without any loss of efficiency and selectivity of the process.

In 2006, Schreiner and Kleiner studied the effects of hydrogen-bonding organocatalysts and water for the rate acceleration of epoxide ring-openings with a variety of nucleophiles (Table 2, entry 6).¹⁹⁶ A significant improvement in the reaction rate and yield has been observed in the thiourea LXXXIX-catalyzed ring-opening of epoxides with amines, alcohols, and thiophenol in water. The thiourea-catalyzed reaction of thiophenol with styrene oxide gave the desired product in 76% yield with a 4:1 ratio of the regioisomers in favor of the α -addition product 211'.

Ranu's group have found the ionic liquid 1-methyl-3-butylimidazolium bromide [bmim]Br LXXXIIC to be an efficient catalyst for the thiolysis of epoxides (Table 2, entry 7).¹⁹⁷ Under the catalytic influence of LXXXIIC, a variety of epoxides underwent a facile cleavage by thiols to produce the corresponding β -hydroxy sulfides with high regioselectivity. A basic ionic liquid LXXXIID catalyzed the thiolysis of α,β -epoxy ketones 305 and 306, thus providing β -keto sulfides 307 and 308 through a simultaneous *retro*-aldol cleavage (Scheme 132). These ionic liquids could be recycled without losing their catalytic efficiency.

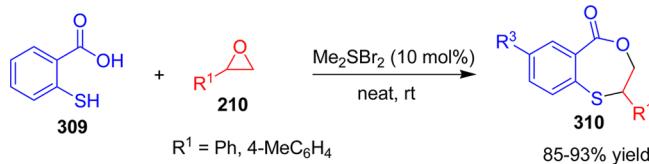
Bandgar and co-workers developed 2,4,6-trichloro-1,3,5-triazine XC as an efficient catalyst for the ring-opening of epoxides with thiols under solvent-free conditions (Table 2, entry 8).¹⁹⁸ Using 2 mol % of catalyst, the corresponding β -hydroxy sulfides were synthesized in excellent yields (95%) in a very short reaction time.

Rao and co-workers reported a highly regioselective ring-opening of epoxides with thiols promoted by (bromodimethyl)sulfonium bromide (Table 2, entry 9).¹⁹⁹

Scheme 132. Synthesis of β -Keto Sulfides via [bmim]OH-Catalyzed Thiolysis of α,β -Epoxy Ketones

With 10 mol % of catalyst, the β -hydroxy sulfides were obtained in good to high yields (78–95%) under solvent-free reaction conditions. The ring-opening of epoxides with disulfides took place in ethanol as solvent to afford the desired products in 85–92% yield. Furthermore, (bromodimethyl)sulfonium bromide efficiently catalyzed the thiolysis of epoxides with thiosalicylic acid 309 to provide benzoxathiepinones 310 in 85–93% yields (Scheme 133).

Scheme 133. (Bromodimethyl)sulfonium Bromide-Catalyzed Thiolysis of Epoxides with Thiosalicylic Acid



Very recently, Yadav and co-workers developed a one-pot procedure for the synthesis of symmetrical and unsymmetrical N-acylureas from carboxamides and in situ generated isocyanates from *N,N*-dibromo-*p*-toluenesulfonamide in the presence of the mild base K₂CO₃.²⁰⁰ The application of these acylureas as hydrogen-bonding organocatalysts was also explored for the ring-opening of epoxides with aniline, phenol, and thiophenol in water as well as under neat conditions. The N-acylurea XCI efficiently promoted the thiolysis of styrene oxide in good yields and regioselectivities of 78:22–84:16 in favor of α -addition product 211' (Table 2, entry 10).

Peng and co-workers described pyridine-N-oxide as an efficient catalyst for the ring-opening reactions of *N*-tosylaziridines with various aryl thiols to provide the corresponding β -amino sulfides in good to excellent yields.²⁰¹

Hou and co-workers reported a NHC-catalyzed tosyl group transfer reaction of *N*-tosylimines 56 with aziridines and

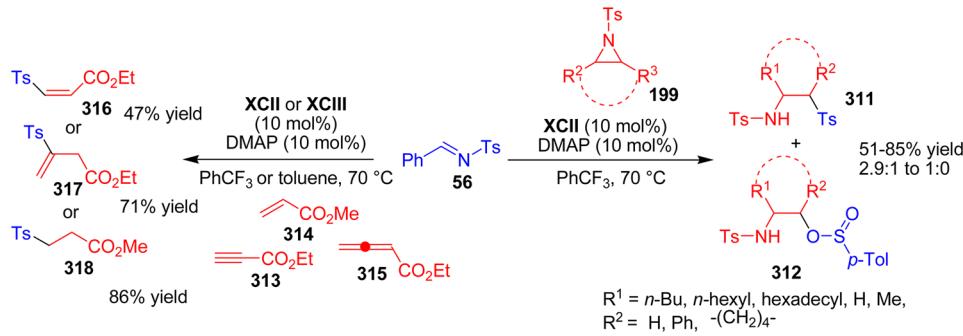
electron-deficient unsaturated compounds (Scheme 134).²⁰² In the presence of a catalytic amount of NHC precatalyst XCII and DMAP as base, the ring-opening of aziridines 199 via tosyl transfer provided a mixture of the corresponding S- or O-attacked products 311 and 312 in good to high yields. The NHC precatalysts XCII and XCIII also catalyzed the tosyl group transfer reaction of electron-deficient unsaturated compounds such as the propargyl ester 313, the unsaturated ester 314, and the allenyl ester 315 with *N*-tosylimines 56 to afford the corresponding adducts 316–318 in moderate to good yields. It was noteworthy that in these cases only S-attacked products were detected.

Q. Wang and co-workers developed an unprecedented nucleophilic ring-opening of cyclopropane carbaldehydes 319 with benzenethiols catalyzed by proline (Scheme 135).²⁰³ The reaction proceeds with high regioselectivity to provide moderate yields of 4-phenylthio-substituted butyraldehydes 320. When *o*-thiosalicylaldehydes 50 were used as nucleophiles, a domino homoconjugate addition/aldol reaction occurred, which provided pharmaceutically valuable 2,3-dihydrobenzo[b]thiepine-4-carbaldehydes 321 in low to moderate yields. The enantiomerically enriched cyclopropanealdehyde 319a reacted with *o*-thiosalicylaldehydes 50 under the optimized reaction conditions, giving rise to optically active benzo[b]-thiepines 322 in reasonable yields without much loss in enantioselectivity.

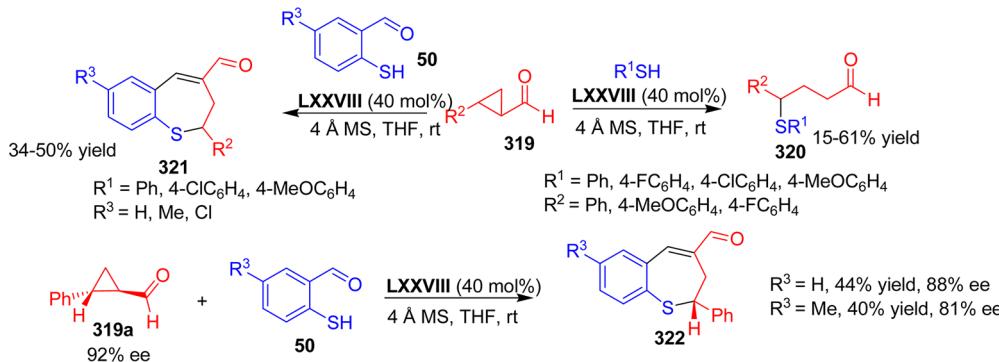
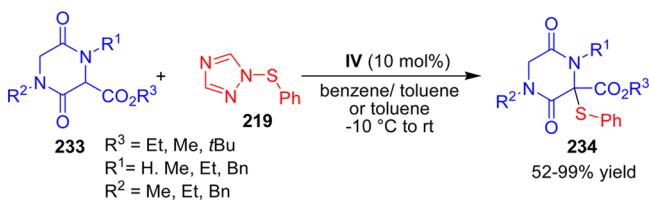
3.4. Sulfenylation Reactions

Olenyuk and co-workers reported a procedure for the α -sulfonylation of substituted piperazine-2,5-diones using cinchona alkaloids as organocatalysts (Scheme 136).²⁰⁴ In the presence of quinine IV as catalyst, 1-phenylsulfanyl[1,2,4]-triazole 219 reacted with a number of substituted piperazine-2,5-diones 233 to provide the respective sulfonylated thioethers 234 in moderate to excellent yields.

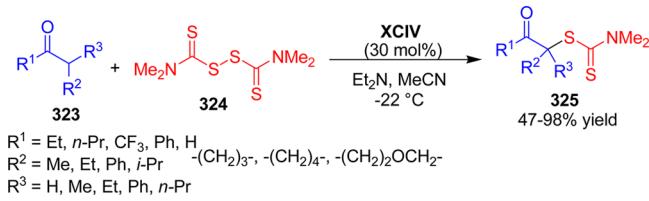
Scheme 134. NHC-Catalyzed Tosyl Transfer Reaction



Scheme 135. Ring-Opening of Cyclopropane Carbaldehydes

Scheme 136. α -Sulenylation of Substituted Piperazine-2,5-diones

Enders and co-workers reported a pyrrolidine XCIV-catalyzed α -sulenylation of aldehydes and ketones 323 using commercially available tetramethylthiuram disulfide (thiram) 324 (Scheme 137).²⁰⁵ The dithiocarbamoyl derivatives 325 were synthesized in good to excellent yields (47–98%). The construction of quaternary stereocenters was also realized when α -substituted aldehydes were used as substrates.

Scheme 137. α -Sulenylation of Aldehydes and Ketones with the Tetramethylthiuram Disulfide

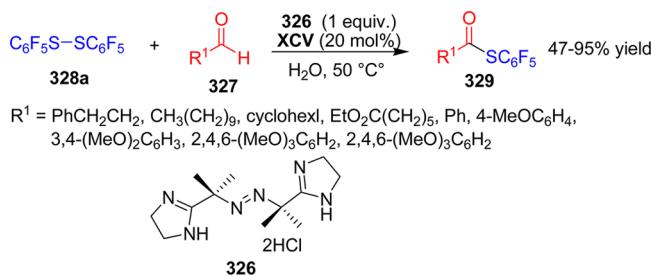
were synthesized in good to excellent yields (47–98%). The construction of quaternary stereocenters was also realized when α -substituted aldehydes were used as substrates.

3.5. Thioesterification Reactions

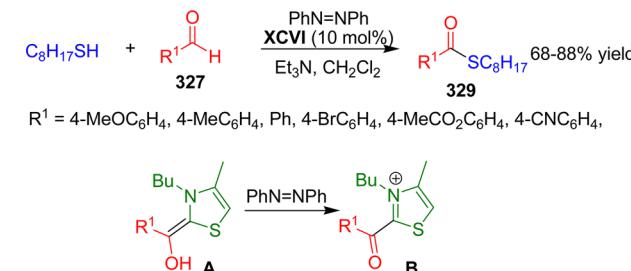
Kita and co-workers found that a combination of a water-soluble radical initiator 2,2-azobis[2-(2-imidazolin-2-yl)-propane] dihydrochloride 326 and a catalytic amount of the surfactant cetyltrimethylammonium bromide XCIV is suitable for thioesterifications of aldehydes 327 with pentafluorobenzene disulfide 328a in water (Scheme 138).^{206,207} A series of pentafluorophenyl thioesters 329 were synthesized from various alkyl and aryl aldehydes bearing electron-donating substituents in moderate to good yields; however, the aldehydes bearing electron-withdrawing groups failed to give the desired thioesters.

In 2005, Kageyama and Murata reported that a catalytic amount of 3-butyl-4-methylthiazolium bromide (XCVI) efficiently promoted the thioesterification of benzaldehyde derivatives 327 with octanethiol in the presence of azobenzene (Scheme 139).²⁰⁸ The corresponding *S*-octyl thiobenzoates 329 were obtained in good yields by trapping of the 2-benzoylthiazolium salts B with the thiol, which were generated

Scheme 138. Thioesterifications of Aldehydes with Pentafluorobenzene Disulfide



Scheme 139. Thioesterifications of Aldehydes with Octanethiol

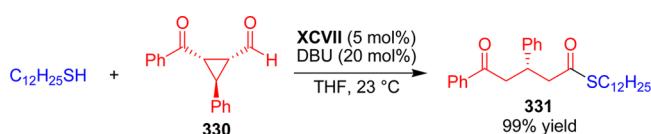


through the oxidation of the activated aldehydes A with azobenzene.

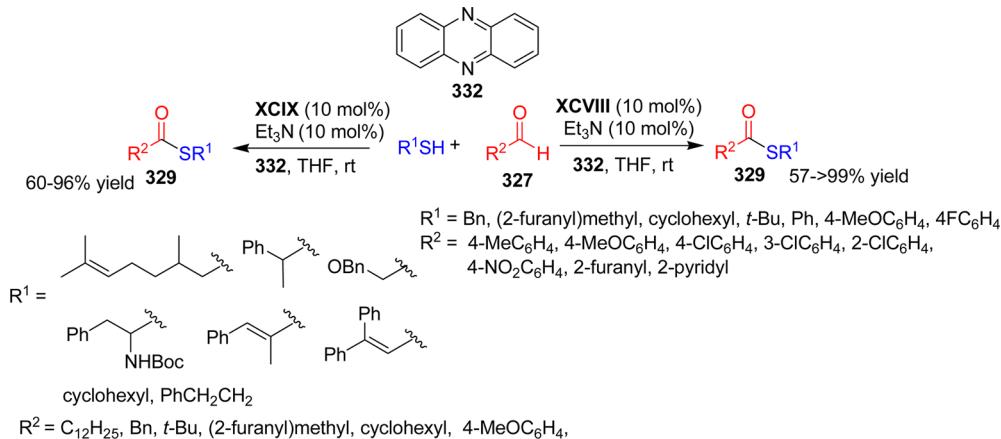
Sohn and Bode reported a NHC-catalyzed synthesis of enantiomerically enriched esters and thioesters via C–C bond-cleavage reaction (Scheme 140).²⁰⁹ The dodecylthiol reacted with the enantioenriched cyclopropane 330 in the presence of the NHC precatalyst XCIX and DBU to give an excellent yield of the thioester 331.

Takemoto's group developed a NHC-catalyzed thioesterification of aromatic and aliphatic aldehydes with a variety of thiols in the presence of a stoichiometric amount of an organic oxidant, that is, phenazine 332 (Scheme 141).²¹⁰ Two different NHC precatalysts XCIX and XCIX efficiently provided the corresponding thioesters 332 in moderate to high yields.

Scheme 140. NHC-Catalyzed Synthesis of Thioesters via a C–C Bond-Cleavage Reaction

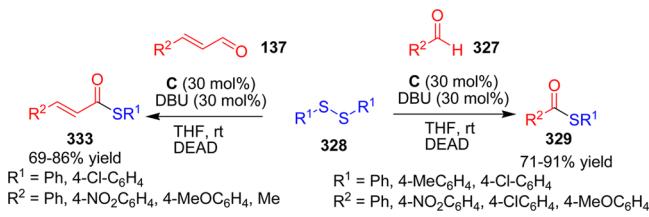


Scheme 141. Thioesterifications of Aldehydes with Thiols in the Presence of Phenazine as Oxidant



Yadav and Singh reported an efficient NHC-catalyzed thioesterification of aldehydes **327** and enals **137** with diaryl disulfides **328** (Scheme 142).²¹¹ Using NHC precatalyst C and

Scheme 142. Thioesterifications of Aldehydes and Enals with Disulfides in the Presence of DEAD as Oxidant



DEAD as oxidant, a variety of thioesters **329** and **333** were obtained in 69–91% yield. However, aliphatic aldehydes turned out to be unsuitable substrates for this transformation.

Very recently, Zhu and co-workers developed a tetraethylammonium bromide-catalyzed oxidative coupling of aldehydes or alcohols with thiophenols or disulfides.²¹² This protocol employed K2S2O8 as oxidant to afford a wide range of thioesters in high yields (75–91%).

3.6. Miscellaneous

Nguyen and co-workers developed an efficient procedure for the synthesis of various heterocycles such as benzimidazoles, 2,3-dihydroquinazolin-4(1*H*)-ones, quinazolin-4(3*H*)-ones, and benzothiazoles via autoxidation of benzylamines (Scheme 143).²¹³ Using acetic acid as catalyst, an efficient synthesis of

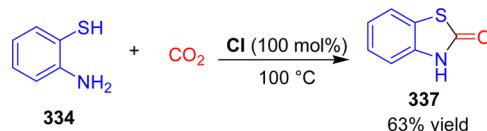
Scheme 143. Synthesis of Benzothiazoles via Autoxidation of Benzylamines



benzothiazoles **333** was realized by reacting benzylamines **335** with 2-aminothiophenol (**334**) in the presence of molecular oxygen. A Brønsted acid ($TsOH \cdot H_2O$)-catalyzed cyclization reaction of 2-aminothiophenols with β -diketones provided various 2-substituted benzothiazoles in good to excellent yields (51–92%) without using any oxidant.²¹⁴

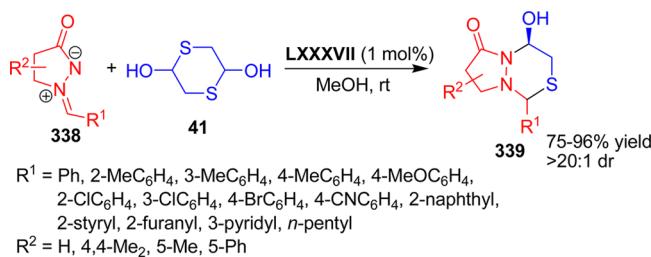
Liu and co-workers reported an efficient procedure for carbonylation of *o*-phenylenediamines with CO₂ catalyzed by the DBU-based ionic liquid **CI** under solvent and additive-free conditions to give a series of benzimidazolones.²¹⁵ The authors have also examined 2-aminothiophenol (**334**) in place of *o*-phenylenediamines to give benzothiazolone **337** in 63% yield (Scheme 144).

Scheme 144. DBU-Based Ionic Liquid-Mediated Synthesis of Benzothiazolone



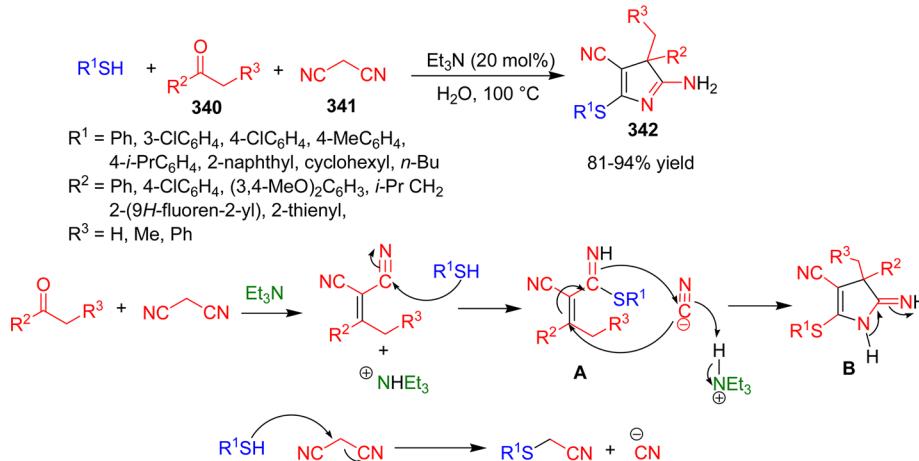
C.-J. Wang's group developed an unprecedented [3+3] cycloaddition of 1,4-dithiane-2,5-diol **41** with azomethine imines **338** catalyzed by DABCO LXXXVII (Scheme 145).²¹⁶ Only 1 mol % of DABCO afforded highly function-

Scheme 145. [3+3] Cycloaddition of 1,4-Dithiane-2,5-diol with Azomethine Imines



alized six-membered dinitrogen-fused heterocycles **339** in high yields with excellent diastereoselectivities from a variety of aryl, heteroaryl, as well as alkyl-substituted azomethine imines **338**. This transformation can be scaled up by using only 0.2 mol % of the catalyst.

Mukhopadhyay et al. reported an efficient one-pot multi-component synthesis of 3*H*-pyrroles via a triethylamine-mediated coupling of ketones, thiols, and malononitrile in aqueous medium (Scheme 146).²¹⁷ This transformation was proposed to be initiated by the tertiary amine promoted Knoevenagel condensation of ketones **340** with malononitrile **341** followed by the nucleophilic attack of thiols to the

Scheme 146. One-Pot Synthesis of 3*H*-Pyrroles via Triethylamine-Mediated Coupling of Ketones, Thiols, and Malononitrile

Knoevenagel adduct on the CN functionality to form intermediate A, which undergoes cheletropic addition with a cyanide ion (generated by nucleophilic attack of thiols on malononitrile) to give an amidine B species, that ultimately tautomerizes to yield an amino-3*H*-pyrrole 342.

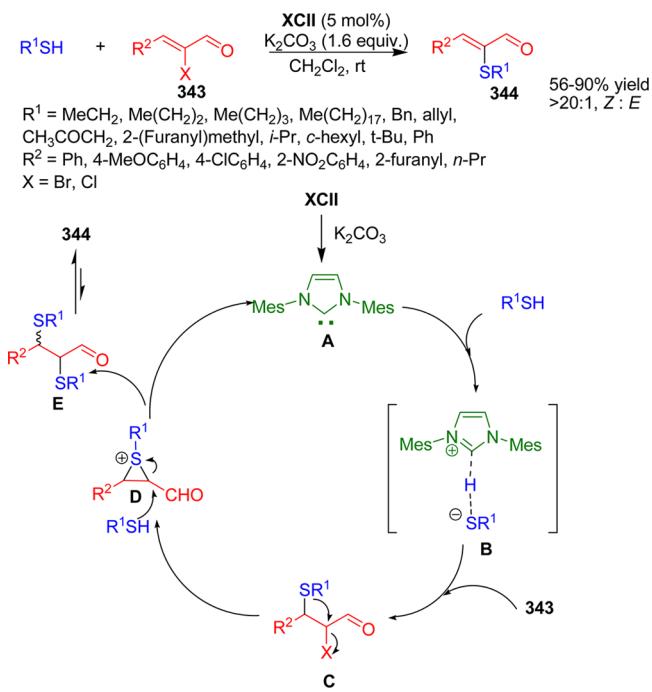
Recently, He and Dai reported an NHC-catalyzed formal cross-coupling reaction between α -haloenals and thiols (Scheme 147).²¹⁸ In the presence of 5 mol % NHC precursor

intramolecular sulfenylation via a 3-*exo-tert* attack to form the sulfonium ion intermediate D. This is followed by the attack of the second molecule of thiol resulting in the ring-opening of D and produces the bisulfenylated aldehyde E. The latter one undergoes a β -elimination to produce the desired product.

4. SUMMARY AND OUTLOOK

A rapid growth in the field of organocatalysis led to the development of a large number of valuable asymmetric and nonenantioselective carbon–carbon and carbon–heteroatom bond formation reactions. Among the various carbon–heteroatom bond formation reactions, the organocatalytic asymmetric C–S bond formations covered in this Review are at the forefront to providing valuable organosulfur compounds, as well as precursors for the synthesis of bioactive chiral entities. A wide range of chiral organocatalysts, such as Lewis bases, bifunctional Lewis base–Bronsted acids, Brønsted acids, secondary as well as tertiary amines, etc., are found to catalyze the simple C–S bond formations via sulfa-Michael, desymmetrization, 1,2-, 1,6-, and γ -additions, α -sulfonylation reactions, etc., with a high level of stereoselectivity. These chiral organocatalysts also facilitated various domino reactions, involving C–S bond formation as a key step, thus providing valuable chiral thiochromanes, benzothiopyrans, and tetrahydrothiophene derivatives. As is evident from our literature survey, chiral organocatalysts have emerged as powerful activators for the construction of new C–S bonds, and the high efficiency of these organocatalysts used in 0.1–20 mol % loading can be seen in a large number of reactions with a wide substrate scope, as well as from the excellent results in terms of product yields and stereoselectivities. In the majority of cases, a low loading (≤ 5 mol %) of a chiral organocatalyst is required to achieve high efficiency.

Small organic molecules, either commercially available or derived from readily available sources, are also act as efficient catalysts to promote nonenantioselective C–S bond formations such as sulfa-Michael reactions, the ring-opening of epoxides and aziridines, α -sulfonylation reactions, etc. The advantages of these achiral organocatalysts are they are easily available, they are cheap, show high selectivity, and can be used under solvent-free conditions as well as in water as a reaction medium. Many supported achiral organocatalysts have also been applied to catalyze C–S bond formations, and these catalysts were easily recycled without losing the catalytic potential.

Scheme 147. NHC-Catalyzed Formal Cross-Coupling Reaction between α -Haloenals and Thiols

XCII and potassium carbonate, various thiols coupled with α -haloenals to provide an efficient access to α -thioenals in 53–91% yield with excellent Z-selectivity ($>20:1$). The proposed mechanism for this new cross-coupling reaction involves the generation of NHC A from XCII and K_2CO_3 , which deprotonates the thiol thereby forming the sulfide anion/azolium ion complex B. The conjugate addition of thiol leads to the generation of intermediate C, which undergoes an

We can see a loophole in the utility of organocatalysts for C–S bond formations in substitution reactions such as cross-coupling and direct substitution. Most of these reactions require metal catalysts or stoichiometric amounts of base. Now the need of the hour is to devote more effort for the development of metal-free organocatalytic C–S bond formations through these substitution reactions. At the present stage, we believe that the design and development of new organocatalysts showing new modes of action will make the C–S bond formation even more practical and handy for the synthesis of valuable sulfur-containing molecules.

AUTHOR INFORMATION

Corresponding Author

*Tel.: +49 241 809 4676. Fax: +49 241 809 2127. E-mail: enders@rwth-aachen.de.

Notes

The authors declare no competing financial interest.

Biographies



Pankaj Chauhan was born in 1984 in Bindal, a small village in the Shimla District of Himachal Pradesh, India. He obtained his B.Sc. from Himachal Pradesh University, Shimla in 2004 and M.Sc. Chemistry from Guru Nanak Dev University, Amritsar, India in 2007. He completed his Ph.D. under the supervision of Prof. Swapandeep Singh Chimni from Guru Nanak Dev University, Amritsar, India, in 2012, and after that he worked as a research associate in the same research group until March 2013. Since April 2013 he is working as a postdoctoral fellow in the research group of Professor Dieter Enders at RWTH Aachen University, Germany. His research interests include the synthesis and application of chiral bifunctional organocatalysts as well as NHC-organocatalysts for asymmetric domino reactions and organofluorine chemistry.



Suruchi Mahajan was born in 1985 in Gurdaspur, India. She completed her M.Sc. Chemistry (Hons. School) from Guru Nanak Dev University, India in 2007. In 2013 she completed her Ph.D. under the supervision of Prof. Rakesh Kumar Mahajan from Guru Nanak Dev University, Amritsar, India. Currently she is working as a postdoctoral fellow in the research group of Professor Dieter Enders at RWTH Aachen University, Germany. Her research interests include the enantioselective organocascade reactions as well as the synthesis of new surfactants and their interactional studies with drugs.



Dieter Enders was born in 1946 in Butzbach, Germany, studied chemistry at the Justus Liebig University Giessen, and completed his Ph.D. under the supervision of Professor D. Seebach in 1974. After postdoctoral research at Harvard University with Professor E. J. Corey, he returned to Giessen and obtained 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 RWTH Aachen University. His research interests are asymmetric synthesis, the synthesis of biologically active compounds, and organocatalysis. He has been the recipient of many awards, such as the Leibniz Prize (Deutsche Forschungsgemeinschaft), the Yamada Prize (Japan), the Max Planck Research Award (Max Planck Gesellschaft and Alexander von Humboldt Foundation), the Emil Fischer Medal (Gesellschaft Deutscher Chemiker), the Arthur C. Cope Senior Scholars Award (American Chemical Society), the Robert Robinson Award (Royal Society of Chemistry), the ERC Advanced Grant (European Union), and more recently the Karl Ziegler Lecture, Max Planck Institut für Kohlenforschung, Mülheim. He is a member of the German Academy of Sciences Leopoldina, a corresponding member of the Academy of Sciences at Göttingen, and a member of the Senate of the German Research Foundation.

ACKNOWLEDGMENTS

The support by the European Research Council (ERC Advanced Grant “DOMINOCAT”) is gratefully acknowledged.

ABBREVIATIONS

Å	angstrom
Ac	acetyl
APCIMS	atmospheric pressure chemical ionization mass spectroscopy
AIBN	azobis-isobutyronitrile
BEMP	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Bn	benzyl
Bz	benzoyl
Boc	<i>tert</i> -butyloxycarbonyl
CPME	cyclopentyl methyl ether

DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DKR	dynamic kinetic resolution
DEAD	diethyl azo-dicarboxylate
DMS	dimethyl sulfide
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoramide
ICPOES	inductively coupled plasma/optical emission spectroscopy
IBX	2-iodoxybenzoic acid
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
MTBE	methyl <i>tert</i> -butyl ether
MS	molecular sieves
NOESY	nuclear Overhauser effect spectroscopy
PS	polystyrene
PVA	poly(vinyl alcohol)
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBAF	tetrabutylammonium fluoride
THP	tetrahydropyranyl
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TES	triethylsilyl
TIPS	triisopropylsilyl

REFERENCES

- (1) Frausto da Silva, J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, 2001.
- (2) (a) Nudelman, A. *The Chemistry of Optically Active Sulfur Compounds*; Gordon and Breach: New York, 1984. (b) *Sulphur-Containing Drugs and Related Organic Compounds*; Damani, L. A., Ed.; Wiley: New York, 1989. (c) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582.
- (3) <http://www.genengnews.com/insight-and-intelligenceand153/top-20-best-selling-drugs-of-2012/77899775/?page=2>.
- (4) Parry, R. J. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Eds.; Pergamon Press: Oxford, 1999; Vol. 1, p 825.
- (5) Fennell, T. R.; Friedman, M. A. *Comparison of Acrylamide Metabolism in Humans and Rodents, Chemistry and Safety of Acrylamide in Food Advances in Experimental Medicine and Biology*; Springer: New York, 2005; Vol. 561, pp 109–116.
- (6) (a) Adolph, S.; Jung, V.; Rattke, J.; Pohnert, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2806. (b) Sylvia, F. *Chem. Unserer Zeit* **2005**, *39*, 233.
- (7) (a) Weiss, C. J.; Marks, T. J. *J. Am. Chem. Soc.* **2010**, *132*, 10533. (b) Ananikov, V. P.; Orlov, N. V.; Zalesskiy, I. P.; Beletskaya, S. S.; Khrustalev, V. N.; Morokuma, K.; Musaev, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6637. (c) Giuseppe, A. D.; Castarlenas, R.; Pérez-Torrente, J. J.; Crucianelli, M.; Polo, V.; Sancho, R.; Lahoz, F. J.; Oro, L. A. *J. Am. Chem. Soc.* **2012**, *134*, 8171.
- (8) For reviews on transition metal-catalyzed C–S bond formations, see: (a) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (b) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205. (c) Lyons, T. W.; Sanford. *Chem. Rev.* **2010**, *110*, 1147. (d) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (e) Postigo, A. *RSC Adv.* **2011**, *1*, 14. (f) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (g) Liu, W.; Zhao, X. *Synthesis* **2013**, 2051.
- (9) For leading books, see: (a) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (b) Bichler, P.; Love, J. A. *Top. Organomet. Chem.* **2010**, *31*, 39.
- (10) For selected reviews on asymmetric organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Special issue: *Asymmetric Organocatalysis*. *Acc. Chem. Res.* **2004**, *37*, 487. (d) Special issue: *Organic Catalysis*. *Adv. Synth. Catal.* **2004**, *346*, 1007. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (f) Special issue: *Organocatalysis*. *ChemCatChem* **2012**, *4*, 885. (g) Chauhan, P.; Chimni, S. S. *Beilstein J. Org. Chem.* **2012**, *8*, 2132. (h) Scheffler, U.; Mahrwald, R. *Chem.—Eur. J.* **2013**, *43*, 14346. (i) Goudedranche, S.; Raimondi, W.; Bugaut, X.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Synthesis* **2013**, *45*, 1909. (j) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. For reviews on nonasymmetric organocatalysis, see: (k) Renzi, P.; Bella, M. *Chem. Commun.* **2012**, 6881. (l) Ren, Q.; Wang, J. *Asian J. Org. Chem.* **2013**, *2*, 542.
- (11) For books on asymmetric organocatalysis, see: (a) Berkessel, A.; Gröger, H. *Metal Free Organic Catalysis in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2004. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (c) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (d) List, B. *Asymmetric Organocatalysis*; Springer: New York, 2009. (e) Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*; RSC Publishing: UK, 2012. (f) Dalko, P. I. *Comprehensive Stereo-selective Organocatalysis*; Wiley-VCH: Weinheim, 2013; Vols. 1–3.
- (12) For reviews on the application of asymmetric organocatalysis for the synthesis of natural products and medicinally useful compounds, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (b) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138. (c) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774.
- (13) Enders, D.; Lüttgen, K.; Narine, A. *Synthesis* **2007**, 959.
- (14) For selected reviews on bifunctional Lewis-base–Brønsted acid organocatalysis, see: (a) Connon, S. *J. Chem.—Eur. J.* **2006**, *12*, 5418. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Connon, S. *J. Chem. Commun.* **2008**, 2499. (e) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785. (f) Bhadury, P. S.; Song, B.-A.; Yang, S.; Hu, D.-Y.; Xue, W. *Curr. Org. Synth.* **2009**, *6*, 380. (g) Chauhan, P.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 737.
- (15) For selected reviews on Lewis-base organocatalysis, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Gawronski, J.; Wascinska, N.; Gajewry, J. *Chem. Rev.* **2008**, *108*, 5227. (c) Palomo, C.; Oiarbide, M.; Loópez, R. *Chem. Soc. Rev.* **2009**, *38*, 632.
- (16) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2181.
- (17) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.
- (18) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 195.
- (19) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547.
- (20) (a) Mukaiyama, T.; Ikegawa, A.; Suzuki, K. *Chem. Lett.* **1981**, *10*, 165. (b) Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277. (c) Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Chem. Lett.* **1982**, *11*, 899.
- (21) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071.
- (22) Hodge, P.; Khoshdel, E.; Waterhouse, J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2327.
- (23) Gawronski, J.; Gawronska, K.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1981**, 307.
- (24) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157.
- (25) Skarzewski, J.; Zielińska-Blajet, M.; Turowska-Tyrk, I. *Tetrahedron: Asymmetry* **2001**, *12*, 1923.
- (26) Zielińska-Blajet, M.; Kowalczyk, R.; Skarzewski, J. *Tetrahedron* **2005**, *61*, 5235.
- (27) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338.
- (28) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603.
- (29) Li, H.; Zu, L.; Wang, J.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 3145.

- (30) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089.
- (31) Rana, N. K.; Unhale, R.; Singh, V. K. *Tetrahedron Lett.* **2012**, *53*, 2121.
- (32) Yoshida, M.; Ohno, Y.; Hara, S. *Tetrahedron Lett.* **2010**, *51*, 5134.
- (33) Meciarová, M.; Toma, S.; Kotrusz, P. *Org. Biomol. Chem.* **2006**, *4*, 1420.
- (34) Kumar, A.; Akanksha. *Tetrahedron* **2007**, *63*, 11086.
- (35) Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2010**, *352*, 2137.
- (36) Moccia, M.; Fini, F.; Scagnetti, M.; Adamo, M. F. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6893.
- (37) Athawale, V.; Manjrekar, N. *Tetrahedron Lett.* **2001**, *42*, 4541.
- (38) Fredriksen, K. A.; Kristensen, T. E.; Hansen, T. *Beilstein J. Org. Chem.* **2012**, *8*, 1126.
- (39) Zhao, F.; Zhang, W.; Yang, Y.; Pan, Y.; Chen, W.; Liu, H.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2011**, *353*, 2624.
- (40) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. *Org. Lett.* **2012**, *14*, 1090.
- (41) Su, Y.; Ling, J.-B.; Zhang, S.; Xu, P.-F. *J. Org. Chem.* **2013**, *78*, 11053.
- (42) Yao, L.; Liu, K.; Tao, H.-Y.; Qiu, G.-F.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2013**, 6078.
- (43) Gao, Y.; Ren, Q.; Wu, H.; Li, M.; Wang, J. *Chem. Commun.* **2010**, 9232.
- (44) Meninno, S.; Croce, G.; Lattanzi, A. *Org. Lett.* **2013**, *15*, 3436.
- (45) Jin, Z.; Xu, J.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *47*, 12354.
- (46) Pracejus, H.; Wilke, F.-W.; Hanemann, K. *J. Prakt. Chem.* **1977**, *319*, 219.
- (47) Keniya, J.; Natu, A. A.; Gogte, V. N. *Chem. Ind. (Chichester, U.K.)* **1986**, 243.
- (48) Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. *J. Chem. Soc., Chem. Commun.* **1991**, 485.
- (49) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641.
- (50) Cho, B.; Tan, C.-H.; Wong, M. W. *J. Org. Chem.* **2012**, *77*, 6553.
- (51) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, *14*, 363.
- (52) Dong, X.-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* **2011**, *13*, 4426.
- (53) Fang, X.; Li, J.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448.
- (54) Duan, S.-W.; Li, Y.; Liu, Y.-Y.; Zou, Y.-Q.; Shi, D.-Q.; Xiao, W. *Chem. Commun.* **2012**, 5160.
- (55) Huang, Y.; Zheng, C.; Chai, Z.; Zhao, G. *Adv. Synth. Catal.* **2014**, *356*, 579.
- (56) Dodd, R.; Mandal, T.; Zhao, C.-G. *Tetrahedron Lett.* **2008**, *49*, 1899.
- (57) Choudhury, A. R.; Mukherjee, S. *Adv. Synth. Catal.* **2013**, 355, 1989.
- (58) Dai, L.; Yang, H.; Niu, J.; Chen, F.-E. *Synlett* **2012**, 314.
- (59) Lin, S.; Leow, D.; Huang, K.-W.; Tan, C.-H. *Chem.—Asian J.* **2009**, *4*, 1741.
- (60) Rana, N. K.; Singh, V. K. *Org. Lett.* **2011**, *13*, 6520.
- (61) Unhale, R. A.; Rana, N. K.; Singh, V. K. *Tetrahedron Lett.* **2013**, *54*, 1911.
- (62) Breman, A. C.; Smits, J. M. M.; de Gelder, R.; van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *Synlett* **2012**, 2195.
- (63) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036.
- (64) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418.
- (65) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 1292.
- (66) Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882.
- (67) Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *ChemCatChem* **2014**, *6*, 649.
- (68) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2012**, 7238.
- (69) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Adv. Synth. Catal.* **2012**, *354*, 1141.
- (70) For selected reviews on nitroalkenes, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Ballini, R.; Araújo, N.; Gil, M. V.; Román, E.; Serrano, J. A. *Chem. Rev.* **2013**, *113*, 3493.
- (71) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
- (72) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823.
- (73) Li, H.; Wang, J.; Zu, L.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 2585.
- (74) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754.
- (75) Kimmel, K. L.; Robak, M. T.; Thomas, S.; Lee, M.; Ellman, J. A. *Tetrahedron* **2012**, *68*, 2704.
- (76) Palacio, C.; Connon, S. *J. Chem. Commun.* **2012**, 2849.
- (77) Uraguchi, D.; Kinoshita, N.; Nakashima, D.; Ooi, T. *Chem. Sci.* **2012**, *3*, 3161.
- (78) Kowalczyk, R.; Nowak, A. E.; Skarzewski, J. *Tetrahedron: Asymmetry* **2013**, *24*, 505.
- (79) Yang, W.; Du, D.-M. *Org. Biomol. Chem.* **2012**, *10*, 6876.
- (80) Pei, Q.-L.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2013**, *69*, 5367.
- (81) Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946.
- (82) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177.
- (83) Du, Z.; Zhou, C.; Gao, Y.; Ren, Q.; Zhang, K.; Cheng, H.; Wang, W.; Wang, J. *Org. Biomol. Chem.* **2012**, *10*, 36.
- (84) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379.
- (85) Yang, W.; Yang, Y.; Du, D.-M. *Org. Lett.* **2013**, *15*, 1190.
- (86) Yu, C.; Zhang, Y.; Song, A.; Ji, Y.; Wang, W. *Chem.—Eur. J.* **2011**, *17*, 770.
- (87) Dodd, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, E. R. T. *Adv. Synth. Catal.* **2008**, *350*, 537.
- (88) Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *Adv. Synth. Catal.* **2013**, *355*, 1053.
- (89) For selected reviews on organocatalytic transformations involving sulfones, see: (a) Zhu, Q.; Lu, Y. *Aust. J. Chem.* **2009**, *62*, 951. (b) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668. (c) Alba, A.-N. R.; Companyó, X.; Ríos, R. *Chem. Soc. Rev.* **2010**, *39*, 2018.
- (90) Enders, D.; Hoffman, K. *Eur. J. Org. Chem.* **2009**, 1665.
- (91) Fang, X.; Dong, X.-Q.; Liu, Y.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2013**, *45*, 4509.
- (92) For selected reviews on secondary amine catalysis, see: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Melchiorre, P.; Marigo, M.; Carloni, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (c) Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2009**, 2178. (d) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, 632. (e) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.
- (93) For an excellent review on iminium ion activation, see: Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
- (94) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710.
- (95) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.
- (96) Ríos, R.; Sundén, H.; Ibrahim, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 8547.
- (97) Ríos, R.; Sundén, H.; Ibrahim, I.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 8679.
- (98) Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *Chem.—Asian J.* **2013**, *8*, 2204.
- (99) Zhao, G.-L.; Vesely, J.; Ríos, R.; Ibrahim, I.; Sundén, H.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 237.

- (100) Baricordi, N.; Benetti, S.; De Risi, C.; Fogagnolo, M.; Pollini, G. P.; Zanirato, V. *Lett. Org. Chem.* **2009**, *6*, 593.
- (101) Tang, J.; Xu, D. Q.; Xia, A. B.; Wang, Y. F.; Jiang, J. R.; Luo, S. P.; Xu, Z. Y. *Adv. Synth. Catal.* **2010**, *352*, 2121.
- (102) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986.
- (103) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2009**, *50*, 2946.
- (104) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833.
- (105) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816.
- (106) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403.
- (107) For reviews on primary amine organocatalysts, see: (a) Chen, Y.-C. *Synlett* **2008**, *13*, 1919. (b) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (c) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.
- (108) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49.
- (109) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892.
- (110) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934.
- (111) For selected reviews, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (d) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626. (e) Xiao-Hua, C.; Hui, G.; Bing, X. *Eur. J. Chem.* **2012**, *3*, 258.
- (112) Ingle, G. K.; Mormino, M. G.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4822.
- (113) Fang, X.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 327.
- (114) Wang, H.-Y.; Zhang, J.-X.; Cao, D.-D.; Zhao, G. *ACS Catal.* **2013**, *3*, 2218.
- (115) Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439.
- (116) Pei, Q.-L.; Sun, H.-W.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 7849.
- (117) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568.
- (118) Lu, N.; Meng, L.; Chen, D.; Zhang, G. *J. Mol. Catal. A: Chem.* **2011**, *339*, 99.
- (119) Fujiwara, Y.; Sun, J.; Fu, G. C. *Chem. Sci.* **2011**, *2*, 2196.
- (120) For reviews on the organocatalytic asymmetric reactions of Morita–Baylis–Hillman carbonates, see: (a) Rios, R. *Catal. Sci. Technol.* **2012**, *2*, 267. (b) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101.
- (121) Lin, A.; Mao, H.; Zhu, X.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal.* **2011**, *353*, 3301.
- (122) For reviews on stereoselective desymmetrization of meso-anhydrides, see: (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131. (b) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683. (c) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327. (d) Docampo, Z. R.; Connolly, S. J. *ChemCatChem* **2012**, *4*, 151.
- (123) Honjo, T.; Sano, S.; Shiro, M.; Nagao, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5838.
- (124) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connolly, S. J. *J. Org. Chem.* **2008**, *73*, 6409.
- (125) Peschiulli, A.; Procuranti, B.; O'Connor, C. J.; Connolly, S. J. *Nat. Chem.* **2010**, *2*, 380.
- (126) Schmitt, E.; Schiffers, I.; Bolm, C. *Tetrahedron* **2010**, *66*, 6349.
- (127) Yang, H.-J.; Xiong, F.-J.; Chen, X.-F.; Chen, F.-E. *Eur. J. Org. Chem.* **2013**, 4495.
- (128) For reviews on azlactones in asymmetric transformations, see: (a) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755. (b) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *107*, 5471.
- (129) Rodriguez-Docampo, Z.; Quigley, C.; Tallon, S.; Connolly, S. J. *J. Org. Chem.* **2012**, *77*, 2407.
- (130) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224.
- (131) Palacio, C.; Connolly, S. J. *Eur. J. Org. Chem.* **2013**, 5398.
- (132) Geng, Z.-C.; Li, N.; Chen, J.; Huang, X.-F.; Wu, B.; Liu, G.-G.; Wang, X.-W. *Chem. Commun.* **2012**, *4713*.
- (133) For reviews, see: (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (b) Padwa, A.; Murphree, S. S. *ARKIVOC* **2006**, *6*. (c) D'hooghe, S. M.; Catak, S.; Eum, H.; Waroquier, M.; Speybroeck, V. V.; Kimpe, N. D.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643. (d) Wang, P.-A. *Beilstein J. Org. Chem.* **2013**, *9*, 1677.
- (134) Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2007**, *18*, 443.
- (135) Wang, Z.; Sun, X.; Ye, S.; Wang, W.; Wang, B.; Wu, J. *Tetrahedron: Asymmetry* **2008**, *19*, 964.
- (136) Lattanzi, A.; Sala, G. D. *Eur. J. Org. Chem.* **2009**, 1845.
- (137) Sala, G. D.; Lattanzi, A. *Org. Lett.* **2009**, *11*, 3330.
- (138) Sala, G. D. *Tetrahedron* **2013**, *69*, 50.
- (139) Larson, S. E.; Baso, J. C.; Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186.
- (140) Zhang, Y.; Kee, C. W.; Lee, R.; Fu, X.; Soh, J. Y.-T.; Loh, E. M. F.; Huang, K.-W.; Tan, C.-H. *Chem. Commun.* **2011**, 3897.
- (141) Cao, Y.-M.; Zhang, F.-T.; Shen, F.-F.; Wang, R. *Chem.—Eur. J.* **2013**, *19*, 9476.
- (142) For selected reviews of enantioselective ring-opening reactions of meso-epoxides, see: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Schneider, C. *Synthesis* **2006**, 3919. (c) Matsunaga, S. *Compr. Chirality* **2012**, *5*, 534.
- (143) Wang, Z.; Law, W. K.; Sun, J. *Org. Lett.* **2013**, *15*, 5964.
- (144) (a) Burkhardt, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227.
- (145) For selected examples: (a) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2483. (b) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699. (c) Loy, R. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 2786. (d) Zhao, W.; Wang, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6209. (e) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2027.
- (146) Wang, Z.; Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6685.
- (147) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem.—Eur. J.* **2005**, *11*, 5689.
- (148) Fang, L.; Lin, A.; Hu, H.; Zhu, C. *Chem.—Eur. J.* **2009**, *15*, 7039.
- (149) Lin, A.; Fang, L.; Zhu, X.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal.* **2011**, *353*, 545.
- (150) Fang, L.; Lin, A.; Shi, Y.; Cheng, Y.; Zhu, C. *Tetrahedron Lett.* **2014**, *55*, 387.
- (151) Polaske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2742.
- (152) Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 11531.
- (153) Li, X.; Liu, C.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2012**, *14*, 4374.
- (154) Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett.* **2012**, *14*, 4670.
- (155) Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett.* **2014**, *16*, 672.
- (156) Hatcher, J. M.; Kohler, M. C.; Colart, D. M. *Org. Lett.* **2011**, *13*, 3810.
- (157) For an excellent review on asymmetric organocatalysis via enamine activation, see: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

- (158) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.
- (159) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.
- (160) Armstrong, A.; Challinor, L.; Moir, J. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5369.
- (161) Armstrong, A.; Deacon, N.; Donald, C. *Synlett* **2011**, 2347.
- (162) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547.
- (163) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856.
- (164) Wang, X.; Yang, T.; Cheng, X.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 12860.
- (165) Vinogradova, E. V.; Müller, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3125.
- (166) Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun.* **2014**, 2508.
- (167) Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192.
- (168) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468.
- (169) Li, L.; Li, Z.; Huang, D.; Wang, H.; Shi, Y. *RSC Adv.* **2013**, *3*, 4523.
- (170) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308.
- (171) (a) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419. (b) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140.
- (c) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 3655.
- (172) Wang, X.-N.; Shen, L.-T.; Ye, S. *Chem. Commun.* **2011**, *47*, 8388.
- (173) Zhang, W.-J.; Wei, D.-H.; Tang, M.-S. *J. Org. Chem.* **2013**, *78*, 11849.
- (174) Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 5200.
- (175) Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12943.
- (176) Gelat, F.; Jayashankaran, J.; Lohier, J.-F.; Gaumont, A.-C.; Perrio, S. *Org. Lett.* **2011**, *13*, 3170.
- (177) Caston, L. F.; Wanzer, C. C. *J. Am. Chem. Soc.* **1951**, *73*, 142.
- (178) Li, M.; Huang, J.; Zhan, W. *React. Funct. Polym.* **2001**, *47*, 71.
- (179) Ménand, M.; Dalla, V. *Synlett* **2005**, 95.
- (180) Kotrusz, P.; Toma, Š. *Molecules* **2006**, *11*, 197.
- (181) Tamami, B.; Fadavi, A.; Tamami, M. *Iran. Polymer J.* **2006**, *15*, 799.
- (182) Lanari, D.; Ballini, R.; Bonollo, S.; Palmieri, A.; Pizzoa, F.; Vaccaro, L. *Green Chem.* **2011**, *13*, 3181.
- (183) Bonollo, S.; Lanari, D.; Longo, J. M.; Vaccaro, L. *Green Chem.* **2012**, *14*, 164.
- (184) Sarkar, A.; Roy, S. R.; Chakraborti, A. K. *Chem. Commun.* **2011**, *47*, 4538.
- (185) Azizi, N.; Saki, E.; Edrisi, M. C. R. *Chimica* **2011**, *14*, 973.
- (186) Fini, F.; Nagabelli, M.; Adamo, M. F. A. *Adv. Synth. Catal.* **2010**, *352*, 3163.
- (187) Bruschi, S.; Moccia, M.; Adamo, M. F. A. *Tetrahedron Lett.* **2011**, *52*, 3602.
- (188) Albanese, D.; Landini, D.; Penso, M. *Synthesis* **1994**, 34.
- (189) Chandrasekhar, S.; Reddy, C. R.; Babu, B. N.; Chandrashekhar, G. *Tetrahedron Lett.* **2002**, *43*, 3801.
- (190) Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726.
- (191) Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* **2003**, *67*, 5295.
- (192) Fringuelli, F.; Pizzo, F.; Tortoli, S.; Vaccaro, L. *Tetrahedron Lett.* **2003**, *44*, 6785.
- (193) Wu, J.; Xia, H.-G. *Green Chem.* **2005**, *7*, 708.
- (194) Wu, J.; Sun, X.; Li, Y. *Eur. J. Org. Chem.* **2005**, 4271.
- (195) Fringuelli, F.; Pizzo, F.; Vittoriani, C.; Vaccaro, L. *Eur. J. Org. Chem.* **2006**, 1231.
- (196) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315.
- (197) Ranu, B. C.; Mandal, T.; Banerjee, S.; Dey, S. S. *Aust. J. Chem.* **2007**, *60*, 278.
- (198) Bandgar, B. P.; Joshi, N. S.; Kamble, V. T.; Sawant, S. S. *Aust. J. Chem.* **2008**, *61*, 231.
- (199) Shailaja, M.; Manjula, A.; Rao, B. V. *Synth. Commun.* **2010**, *40*, 3629.
- (200) Singh, A. K.; Chawla, R.; Yadav, L. D. S. *Tetrahedron Lett.* **2013**, *54*, 5099.
- (201) Yang, Q.; Yin, Z.; Yang, M.; Peng, Y. *Chin. J. Chem.* **2011**, *29*, 79.
- (202) Chen, D.-D.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2008**, *73*, 5578.
- (203) Li, L.; Li, Z.; Wang, Q. *Synlett* **2009**, 1830.
- (204) Dubey, R.; Polaske, N. W.; Nichol, G. S.; Olenyuk, B. *Tetrahedron Lett.* **2009**, *50*, 4310.
- (205) Enders, D.; Rembiak, A.; Liebich, J. X. *Synthesis* **2011**, 281.
- (206) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Commun.* **2002**, 1082.
- (207) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem.—Eur. J.* **2005**, *11*, 719.
- (208) Kageyama, Y.; Murata, S. *J. Org. Chem.* **2005**, *70*, 3140.
- (209) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021.
- (210) Uno, T.; Inokuma, T.; Takemoto, Y. *Chem. Commun.* **2012**, *48*, 1901.
- (211) Singh, S.; Yadav, L. D. S. *Tetrahedron Lett.* **2012**, *53*, 5136.
- (212) Zhu, X.; Shi, Y.; Mao, H.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2013**, *355*, 3558.
- (213) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Green Chem.* **2013**, *15*, 2713.
- (214) Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *Org. Lett.* **2014**, *16*, 764.
- (215) Yu, B.; Zhang, H.; Zhao, Y.; Chen, S.; Xu, J.; Hao, L.; Liu, Z. *ACS Catal.* **2013**, *3*, 2076.
- (216) Fang, X.; Li, J.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 5554.
- (217) Das, P.; Ray, S.; Mukhopadhyay, C. *Org. Lett.* **2013**, *15*, 5622.
- (218) He, L.; Guo, H.; Li, Y.-Z.; Du, G.-F.; Dai, B. *Chem. Commun.* **2014**, *50*, 3719.
- (219) Zhao, B.-L.; Du, D.-M. *Org. Biomol. Chem.* **2014**, *12*, 1585.
- (220) Qian, H.; Sun, J. *Asian J. Org. Chem.* **2014**, *3*, 387.
- (221) Kowalczyk, R.; Wierzba, A. J.; Boratyński, P. J.; Bąkowicz, J. *Tetrahedron* **2014**, *70*, 5834.
- (222) Akagawa, K.; Nishi, N.; Sen, J.; Kudo, K. *Org. Biomol. Chem.* **2014**, *12*, 3581.
- (223) Bera, K.; Namboothiri, I. N. N. *Org. Biomol. Chem.* **2014**, *12*, 6425.
- (224) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915.
- (225) Zhao, B.-L.; Du, D.-M. *RSC Adv.* **2014**, *4*, 27346.
- (226) Nakamura, S.; Ohara, M.; Koyari, M.; Hyodo, K.; Nabisaheb, N. R.; Funahashi, Y. *Org. Lett.* **2014**, DOI: dx.doi.org/10.1021/o1501990t.
- (227) Keshari, T.; Yadav, V. K.; Srivastava, V. P.; Yadav, L. D. S. *Green Chem.* **2014**, *16*, 3986.
- (228) Hans, M.; Delaude, L.; Rodriguez, J.; Coquerel, Y. *J. Org. Chem.* **2014**, *79*, 2758.

NOTE ADDED IN PROOF

After the submission of this review, some new papers appeared in the literature on organocatalytic C-S bond formations.^{219–228}