Chapter 5
Asymmetric Synthesis Using Thioamides

Naoya Kumagai and Masakatsu Shibasaki

Abstract Following the preceding chapter in which synthesis and transformation of thioamides were introduced, this chapter provides an overview of state-of-the-art asymmetric catalysis to elicit the hidden reactivity of thioamide functionality, thereby engaging thioamide substrates in catalytic transformations to produce more elaborate thioamide compounds. The designed catalytic systems, comprising a soft Lewis acid and Brønsted base, chemoselectively activate thioamides in both a nucleophilic and electrophilic fashion, leading to a number of bimolecular reactions rendered catalytic and enantioselective. The last section showcases the synthetic application of these catalytic processes to demonstrate their practical utility.

Keywords C–C bond formation · Asymmetric catalysis · Enantioselective · Soft-soft interaction · Synthetic application

5.1 Introduction

As described in the preceding chapters, a thioamide is a readily accessible functional group that is widely utilized in organic synthesis. This chapter specifically focuses on enantioselective reactions featuring the thioamide functionality as a key functional group to drive the reaction of interest. Particular emphasis is placed on enantioselective catalysis, where the soft Lewis basic nature of the thioamide functionality dictates the catalyst design to achieve chemoselective interactions sufficient to promote the reaction in a highly stereoselective fashion. The inert reactivity of amides, the closest analog of thioamides, in these catalytic systems illustrates that these tailor-made catalytic systems for thioamides are highly chemoselective and compatible with common hard Lewis basic functionalities. Catalytic enantioselec-

N. Kumagai (✉) · M. Shibasaki (✉)
Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-Ku, Tokyo 141-0021, Japan
e-mail: nkumagai@bikaken.or.jp

M. Shibasaki
e-mail: mshibasa@bikaken.or.jp

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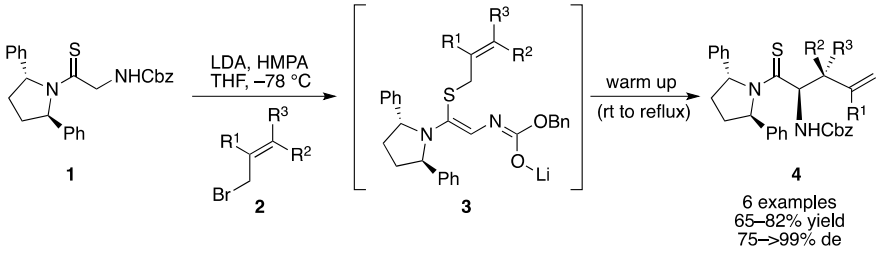
tive reactions offer a powerful strategy for producing value-added enantioenriched synthons, which are further leveraged by the capability of thioamides to undergo diverse functional group transformations [1]. Indeed, the catalytic enantioselective reactions introduced in this chapter are extensively utilized in enantioselective total syntheses of biologically active natural products as well as active pharmaceutical ingredients (APIs). These are briefly overviewed in the latter part of this chapter.

5.2 Enantioselective Reactions Using Thioamides

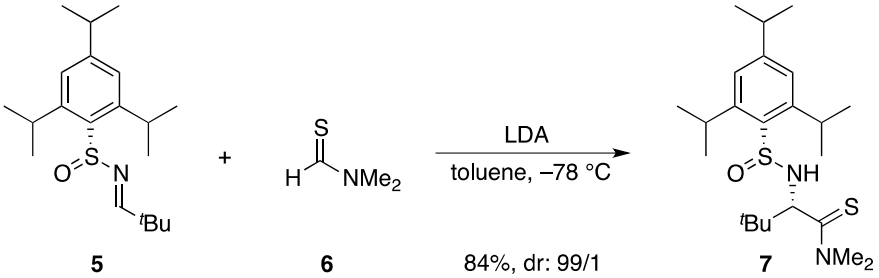
5.2.1 Auxiliary Approach

Surprisingly, enantioselective reactions utilizing thioamide compounds have not been extensively explored and only a few reaction settings are reported in the literature. Hruby et al. demonstrated a smooth chirality transfer of chirally decorated thioamide **1** to provide unnatural α-amino acid derivatives (Scheme 5.1) [2]. With (2*R*,5*R*)-2,5-diphenylpyrrolidine-appended thioacetamide **1** bearing an NHCbz group at the α-position as the substrate of choice, successive treatment with lithium diisopropylamide (LDA) and allylic bromides **2** at −78 °C in THF gives *S*-allylated intermediate **3**. Simply warming the reaction mixture to room temperature (then to THF reflux) leads to the breakdown of **3** to afford **4** with excellent control of the enantioselectivity via a thio-Claisen rearrangement. Dianion formation is proposed, and a slight excess of LDA (3.2 eq) is recommended. Facile transformation of **4** into the corresponding amide is achieved via the *S*-methylation/hydride reduction/Pinnick oxidation sequence.

Reeves et al. employed auxiliary appended *N*-sulfinyl aldimines **5** as electrophiles with a thiocarbamoyl anion generated from thioformamide **6** (Scheme 5.2) [3]. Although this reaction was principally developed for formamides, the conditions were equally effective for thioformamide **6**, potentially providing a range of unnatural α-amino acid derivatives.



Scheme 5.1 Thio-Claisen rearrangement of homochiral thioamide **1**

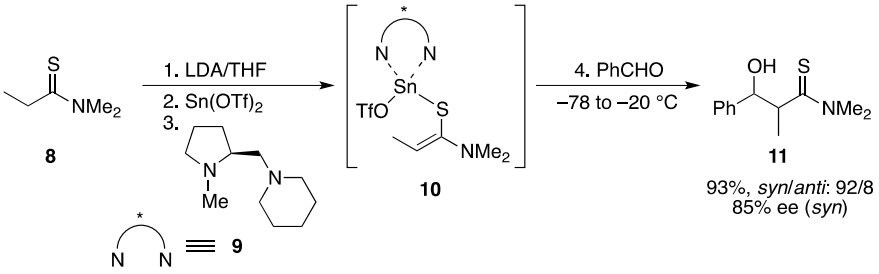


5 6 84%, dr: 99/1 7

Scheme 5.2 Addition of thiocarbamoyl anion generated from **6** to homochiral *N*-sulfinyl aldimine **5**

5.2.2 Chiral Lewis Acid Approach

The use of chiral Lewis acids obviates the additional procedures required for covalent linking and the removal of chiral molecular units. Chiral Lewis acid catalysis plays a pivotal role in this regard, where chiral Lewis acids interact with substrates and subsequent reactions proceed under a chiral environment to deliver enantioenriched products [4, 5]. Because thioamides belong to the carbonyl class of functional groups, enolization was attempted in diastereoselective aldol reactions by Yoshida et al. in 1980 [6, 7]. The observed diastereoselectivity suggested the in situ generation of *Z*-configured enolate, and these studies were followed by diastereoselective aldol reactions using *S*-silyl ketene *N*,*S*-acetals derived from thioamides [8–10]. It took nearly a decade to achieve an enantioselective version of the aldol reaction with strategic use of a chiral Lewis acid. Mukaiyama et al. reported the effectiveness of a chiral Sn(II) complex as a chiral Lewis acid to control the enantioselectivity of this important carbon-carbon bond-forming reaction (Scheme 5.3) [11]. The *Z*-enolate generated from thioamide **8** and LDA is successively treated with $Sn(OTf)_2$ and chiral diamine **9** to produce the Sn(II)-enolate of thioamide **10**, which is coupled with benzaldehyde to forge a carbon-carbon single bond with stereocontrol (85% ee) exerted by proximal chiral ligand **9**. Although this work pioneered the use of an external chiral element to drive enantioselectivity in thioamide reactions, stoichiometric amounts of bases and the chiral Sn(II) complex were essential. It took another two decades to witness that enantioselective thioamide reactions were rendered catalytic, as detailed in the following section.



Scheme 5.3 Enantioselective aldol reaction of thioamide **8** using stoichiometric amounts of base and chiral Lewis acid

5.3 Catalytic Enantioselective Reactions of Thioamides

5.3.1 Use of Thioamides as Pronucleophiles

Catalytic enantioselective reactions have gained popularity as a powerful tool in synthetic organic chemistry, as this class of reactions offers the most efficient means of producing enantioenriched high-value chiral building blocks. Given the well-established synthetic protocol of thioamides as well as the capability for diverse functional group transformation, chiral synthons bearing the thioamide functionality have particular utility in enantioselective syntheses of biologically active natural products and active pharmaceutical ingredients (APIs).

As discussed in the previous section, however, catalytic turnover remained unrealized in enantioselective reactions of thioamides. Furthermore, the total efficiency of the reaction was deteriorated by the mandatory use of more than stoichiometric amounts of achiral activating reagents. In this context, Shibasaki et al. reported that thioamides exhibit enhanced reactivity in the presence of chiral Cu(I) complexes, which is rendered catalytic in terms of a chiral source and base for activation. The general concept is outlined in Fig. 5.1c; the Cu(I) complex is characterized by its soft Lewis acidic nature and tendency to interact with the soft Lewis basic thioamide functionality [12–14]. This strategy was inspired by research directed toward direct aldol chemistry [15–20], in which aldol acceptors (commonly aldehydes, electrophiles) and aldol donors (commonly aldehydes or ketones, pronucleophiles) are coupled in a truly catalytic fashion. To manifest this direct aldol scheme, chemoselective enolization of less acidic aldol donors in the presence of aldol acceptors (aldehydes) bearing highly acidic α-protons is essential. This mismatched acidity scale presents a large hurdle to achieve this rather simple reaction, severely limiting the scope of direct aldol reactions to relatively acidic aldol donors, e.g., aldehydes, ketones, and active methylene-type compounds (Fig. 5.1a) [21–24]. More commonly used carbonyl-type synthons, e.g., esters and amides, remain elusive as aldol donors in catalyst-driven reactions due to the reluctancy to enolize and generally lead to self-condensation of aldehydes (Fig. 5.1b). In this context, thioamides (Fig. 5.1c) are promising aldol

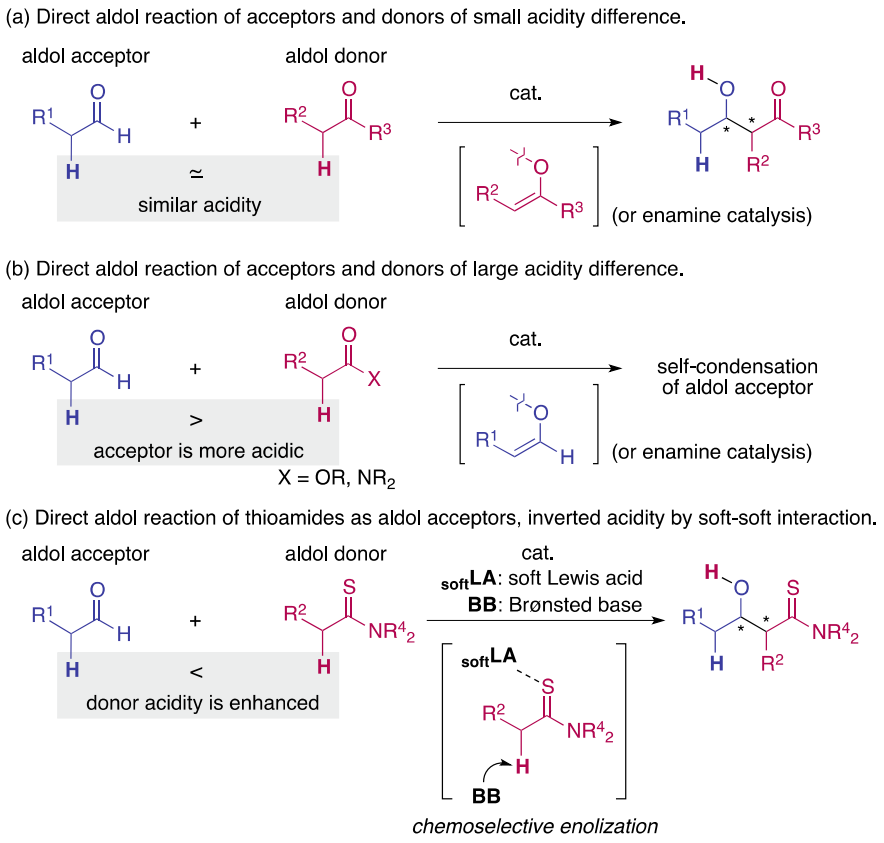
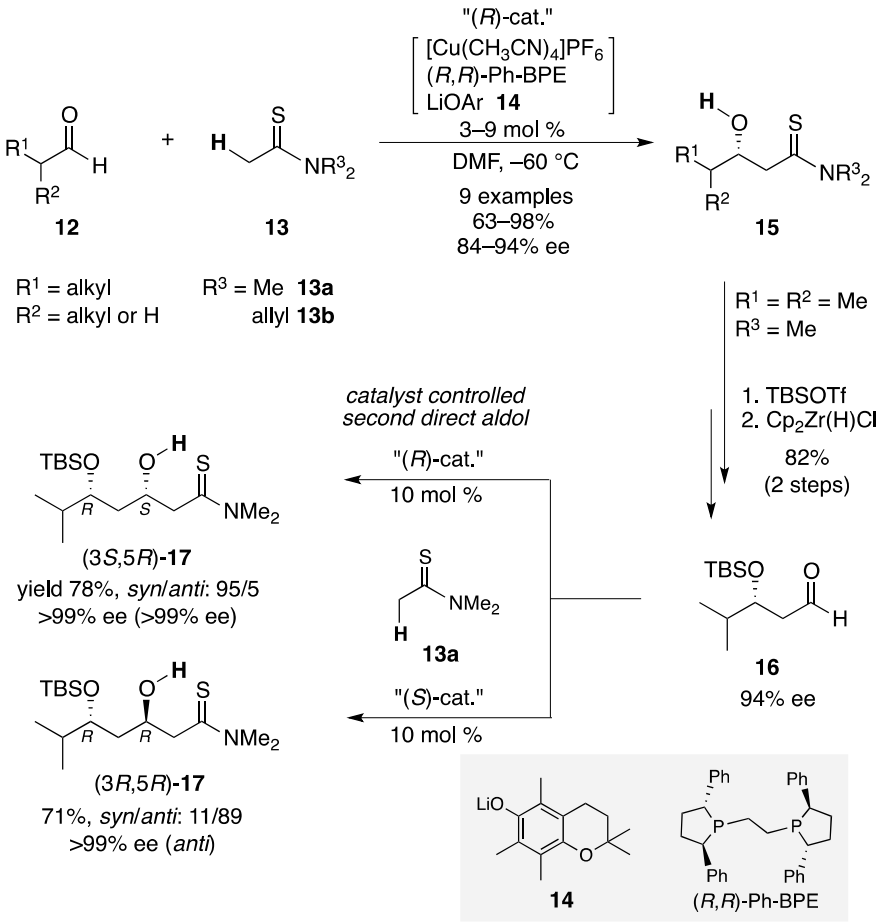


Fig. 5.1 Direct aldol reaction using various aldol donors

donors because (1) chemoselective activation of thioamides can be achieved by taking advantage of their soft Lewis basic nature; (2) excessive activation of hard Lewis basic aldehydes (aldol acceptors) can be avoided; (3) soft-soft interactions with a soft Lewis acidic catalyst can invert the enolization kinetics to enable the exclusive enolization of the thioamide; and (4) thioamides are in a carboxylic acid oxidation state and multifaceted transformations are possible after the enantioselective reactions. Based on this blueprint, a cooperative catalytic system comprising a soft Lewis acid and a Brønsted base was developed [4, 5, 13, 25–28], allowing for general and tractable direct aldol reactions for organic synthesis.

In 2009, Shibasaki et al. reported a direct catalytic enantioselective aldol reaction of thioamide based on the strategy discussed above (Scheme 5.4) [29]. Chiral bisphosphine ligand (*R*,*R*)-Ph-BPE is uniquely effective in combination with $[Cu(CH_3CN)_4]PF_6$, which activates thioacetamide **13** as the chiral soft Lewis acid and promotes enolization in combination with Li-phenoxide **14** (first-generation catalyst). **14** is relatively basic among phenoxide derivatives due to the electron-donating



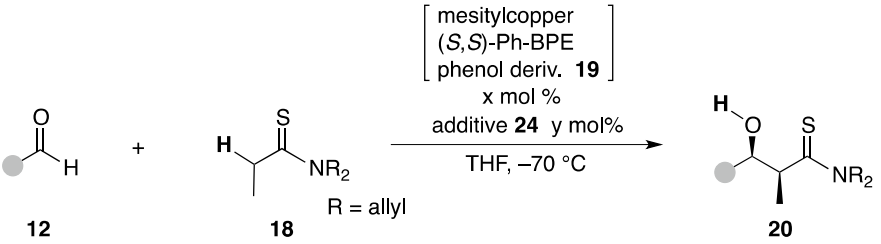
Scheme 5.4 Direct catalytic enantioselective aldol reaction thioacetamides **13** promoted by the soft Lewis acid/Brønsted base cooperative catalyst

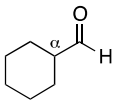
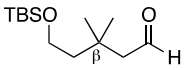
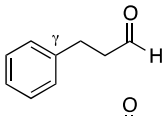
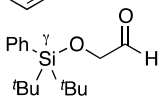
groups on the periphery of the phenol unit and a conformationally locked cyclic ether substructure, and the reaction proceeds at −60 °C in DMF with high enantioselectivity. Importantly, aldehydes bearing acidic α-protons deliver the desired aldol products in high yield, supporting effective suppression of the self-condensation of inherently more acidic aldehydes. Intriguingly, the highly catalyst-controlled enantioselectivity is confirmed by a sequential direct aldol reaction. After protecting the secondary alcohol of the aldol product **15** ($R^1 = R^2 = R^3 = Me$) as a TBS ether, exposure to Schwartz's reagent ($Cp_2Zr(H)Cl$) conveniently furnishes aldehyde **16**, which is subjected to the second direct aldol reaction with thioamide **13a**. The good *syn*- and *anti*-1,3-diol selectivity of product **17** resulting from the change in the sense of the chiral catalyst ((*S*)-cat denotes that the catalyst is prepared from (*S*,*S*)-Ph-BPE) con-

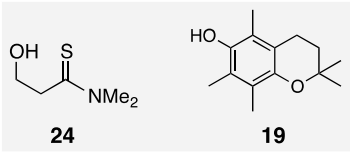
firms that the influence of the chiral environment of the Cu(I)-complex overrides the intrinsic chirality of **16**.

The synthetic utility of this direct aldol reaction is significantly expanded by incorporating thiopropionamide **18** as a viable pronucleophile. Given the privileged nature of the propionate unit in natural products, decent control of the stereoselectivity by direct aldol reactions enables expeditious access to a myriad of useful enantioenriched synthons. Initial attempts to control the stereoselectivity by simple extrapolation of the above-mentioned optimized conditions for thioacetamides **13** to the reactions of thiopropionamide **18** resulted in unexpectedly poor stereoselectivity [30]. Re-evaluation of the reaction conditions revealed that **18** is more reactive than **13**, likely due to higher enolization aptitude, and undergoes a rapid retro-aldol reaction, which is efficiently suppressed by changing the solvent from DMF to the less polar THF with a concomitant decrease in the reaction rate. The forward and reverse reaction rates are attenuated by the addition of hard Lewis basic phosphine oxide in a concentration-dependent manner, suggesting that the hard Lewis acidic Li cation perturbs the overall reaction rate and the equilibrium of the intermediate species. Based on this hypothesis, a Li-free catalyst was developed and proved to be a more active catalyst with the additional bonus of an easy-preparation protocol (Scheme 5.5) [31]. This second-generation catalyst was prepared by mixing mesitylcopper [32–34], (*S*,*S*)-Ph-BPE, and 2,2,5,7,8-pentamethylchromanol **19**, with the liberation of mesitylene (the opposite absolute configuration of product **20** was due to the *S*-catalyst) (Fig. 5.2). Initially in the catalytic cycle, the thus-formed phosphine-ligated Cu(I)-phenoxide **21** serves as the soft Lewis acid/Brønsted base cooperative catalyst to affect enolization of thioamides **18**. Subsequent addition of the Cu(I)-enolate **22** to aldehydes **12** affords Cu(I)-aldolate **23**, which functions as the cooperative catalyst to drive the following catalytic cycle (blue arrow), or abstracts a proton from **19** to regenerate Cu(I)-phenoxide **21**. Additionally, the identification of this more reactive catalyst revealed that erosion of the enantioselectivity due to the retro reaction (red arrow) becomes more obvious as the steric bulk is increased. To prevent reentry of the aldol products into the catalytic cycle (en route to a retro reaction), dummy product **24** was devised as an additive to competitively bind to the catalyst, thereby kinetically retarding the problematic retro reaction. Basically, when the aldehydes possess two methylene groups before branching, the steric hindrance has little effect and the aldol products are obtained in high *syn* and enantioselectivity, even after an extended reaction time (Scheme 5.5). In contrast, when the aldehyde branching occurs closer to the formyl group, enantioselectivity decreases as a function of the reaction time, which can be effectively suppressed by dummy product **24**. The unexpectedly close kinetics of the back and forth reactions is characteristic of direct aldol chemistry of thioamides. Diverse transformation of the thioamide moiety supports the synthetic utility of this direct aldol protocol [30].

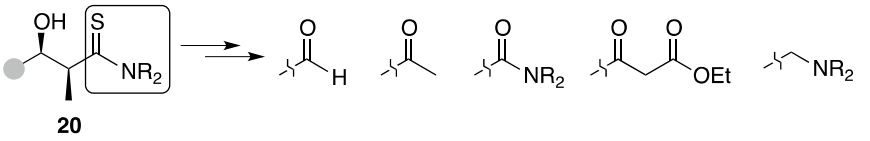
Intriguingly, α-vinyl thioacetamide pronucleophile **25** bearing an α-vinyl group exhibits different behavior (Scheme 5.6) [35]. The second-generation catalyst comprising mesitylcopper/(*R*,*R*)-Ph-BPE/phenol derivative **19** competently promotes the reaction, albeit with significantly eroded stereoselectivity. The structure of the phenol derivatives determines the stereoselectivity; while a less coordinative phenol deriva-



selected examples		cat. (x mol%)	additive 24 (y mol%)	time (h)	yield (%)	*syn*/*anti*	ee (%)
α-branch [**24** essential]		1	0	24	89	>20/1	90
		1	0	48	95	>20/1	72
		1	2	48	96	>20/1	95
β-branch [**24** essential]		3	0	48	99	3/1	20
		3	6	48	96	>20/1	89
γ-branch [**24** can be omitted]		3	0	48	>99	>20/1	94
		3	3	48	>99	>20/1	98
γ-branch [**24** can be omitted]		5	0	48	96	>20/1	97
		5	5	72	83	>20/1	97



functional group transformation



Scheme 5.5 Direct catalytic enantioselective aldol reaction of thiopropionamide **18**

tive, e.g., **19**, gives poor stereoselectivity, a more coordinative phenol derivative, e.g., *p*-methoxyphenol **26**, affords the aldol product in the expected absolute configuration with high stereoselectivity. The pendant vinyl group of **25** likely coordinates to Cu(I) at the stage of Cu(I)-enolate **29'**, which may lead to aldol addition via the less stereoselective open transition state **30'** (Fig. 5.3). By employing less coordinative **26** (catalyst **28**), undesired vinyl coordination is suppressed and the reaction via cyclic transition state **30** is operative from the enolate Cu(I)-enolate **29**. Indeed, the effect

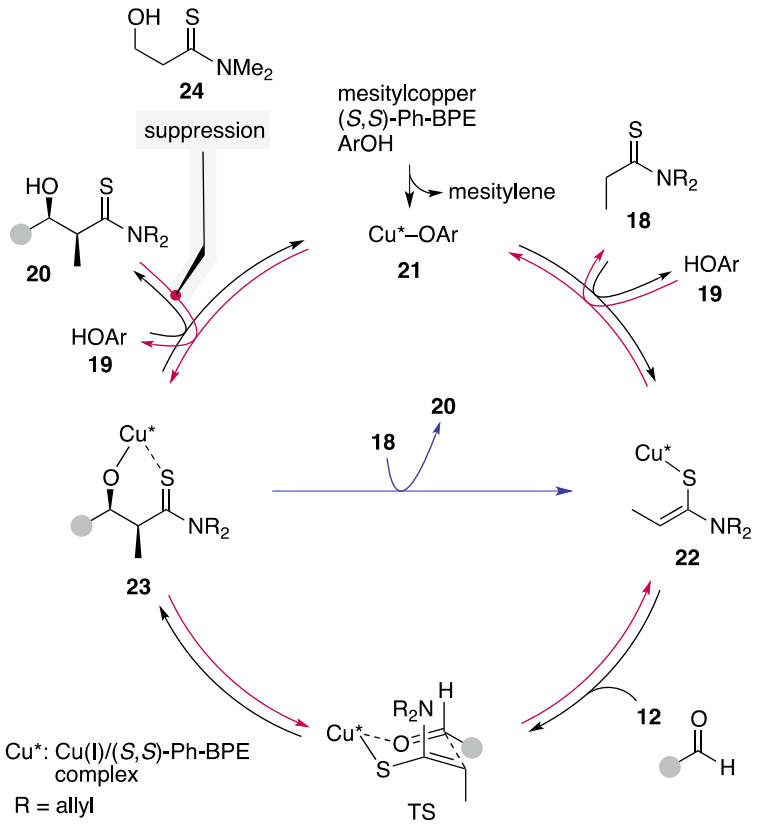
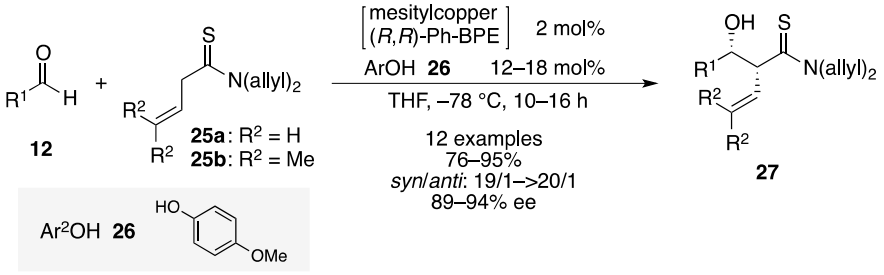


Fig. 5.2 Plausible catalytic cycle of aldol reaction using thiopropionamide **18**



Scheme 5.6 Direct catalytic enantioselective aldol reaction of α-vinylated thioacetamide **25**

of **26** is enhanced by increasing the loading, and the coordination of **26** with the vinyl group is likely competitive.

The diastereo- and enantioselective aldol reactions discussed above consistently give *syn*-products as the kinetic products, implying that an in situ-formed

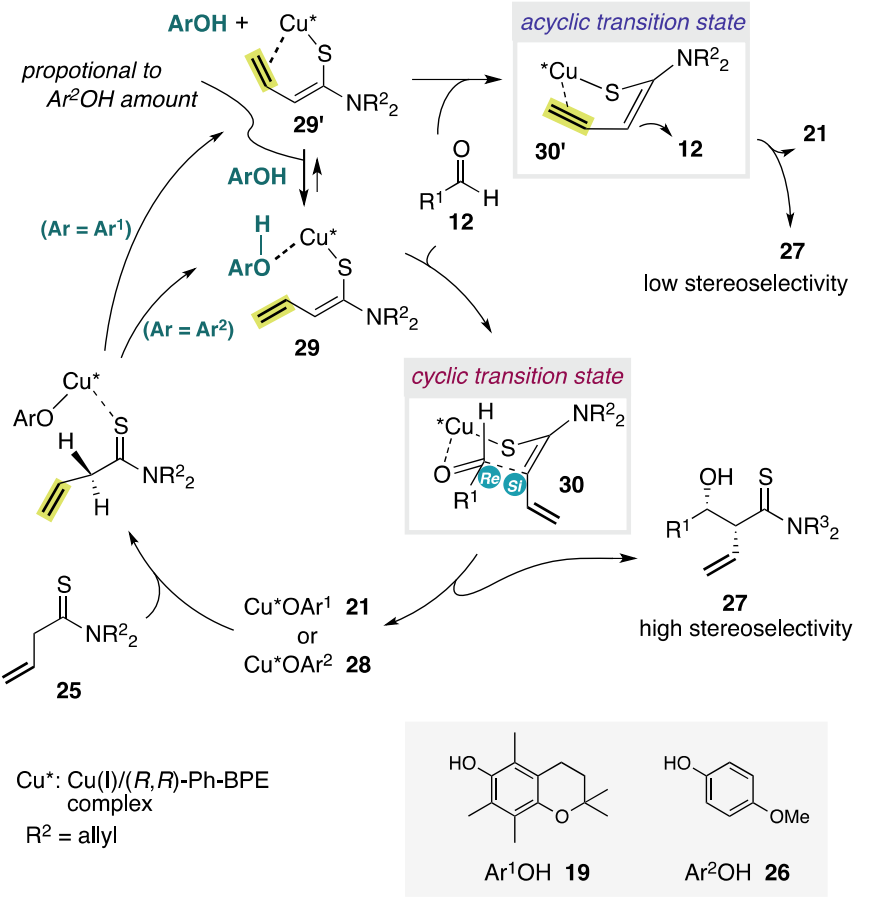
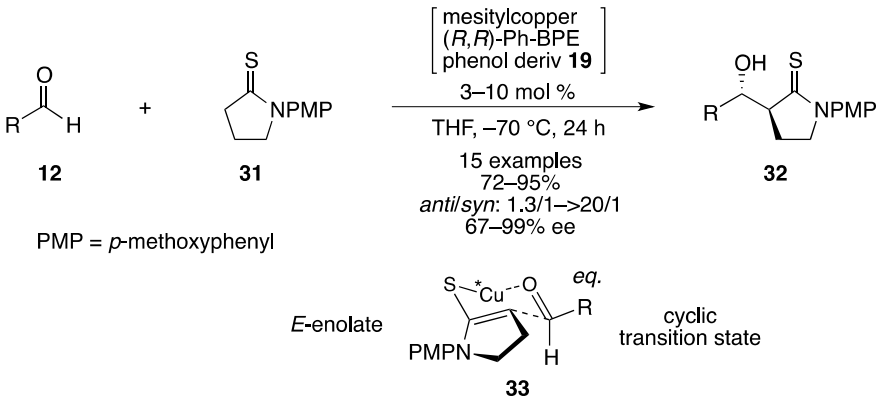


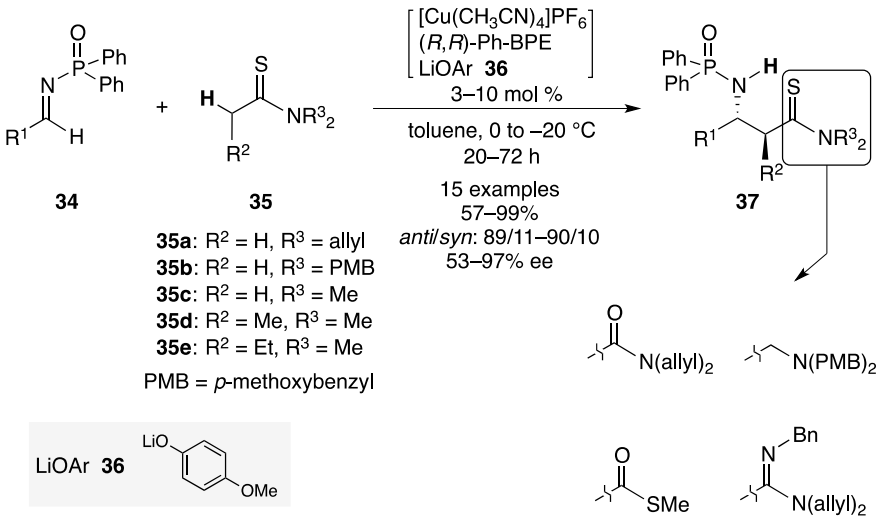
Fig. 5.3 Plausible catalytic cycle of aldol reaction using α-vinylated thioacetamide **25**

Z-configured enolate and cyclic transition state are involved. Although this stringent *Z*-selectivity is presumably due to the steric repulsion of two alkyl groups on the thioamide nitrogen and unlikely surpassed, the use of conformationally-restricted thiolactam pronucleophile **31** exclusively generates the *E*-configured enolate en route to *anti*-aldol products **32** via transition state model **33** (Scheme 5.7) [36]. Six-membered δ-valerothiolactam can also be utilized, although the stereoselectivity is decreased.

Expanding the scope of viable electrophilic partners further broadened the synthetic utility of the direct enolization of thioamide pronucleophiles. Aldimines are an obvious lateral extension from aldehyde electrophiles to achieve Mannich-type reactions, furnishing β-amino (thio)carbonyl products. In general, retro reactions are less prominent, particularly in the case of activated aldimines, e.g., *N*-diphenylphosphinoyl (Dpp) imines **34**, and the first-generation catalyst prepared from $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph-BPE/LiOAr **36** promotes the desired reaction with

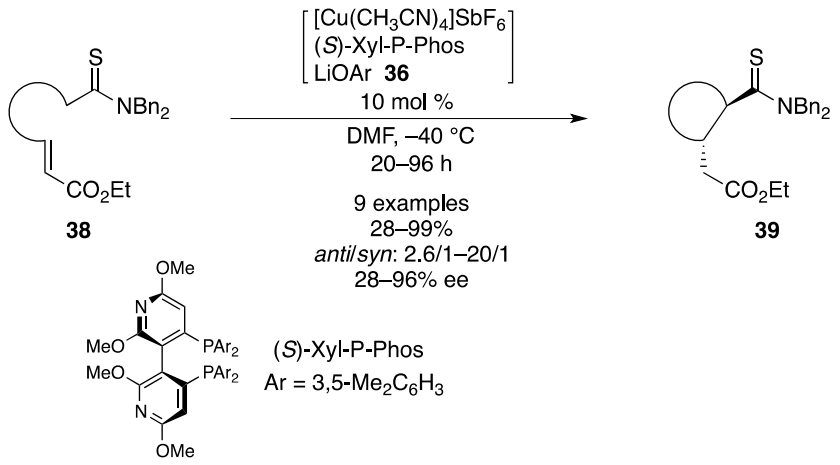


Scheme 5.7 Direct catalytic enantioselective aldol reaction of α-vinylated thioacetamide **31**

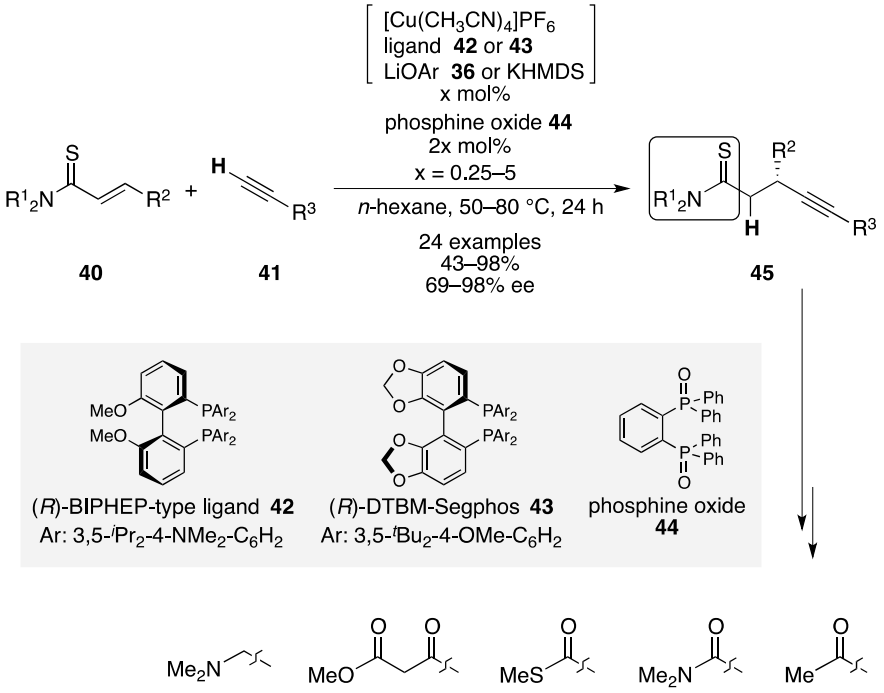


Scheme 5.8 Direct catalytic enantioselective Mannich-type reaction of *N*-diphenylphosphinoyl imines **34** and thioamides **35**

various thioamides **35** (Scheme 5.8) [37]. Most of the reported examples used thioacetamides **35a**–**c** for non-diastereoselective reactions with 3 mol% of catalyst, delivering the products **37** ($R^2 = H$) with generally high enantioselectivity. The reactions of thiopropionamide **35d** and thiobutyramide **35e** require higher catalyst loading (10 mol%), and enantioselectivity is significantly decreased. *anti*-Diastereoselection implies that a different transition state is operative from the *Z*-enolate due to the distinct coordination pattern of imine **34**. The diverse transformations of the thioamide moiety and easy removal of the Dpp group on the nitrogen highlight the synthetic utility of these enantioenriched products.



Scheme 5.9 Direct catalytic enantioselective intramolecular conjugate addition



Scheme 5.10 Direct catalytic enantioselective conjugate addition of terminal alkynes **41** to α,β-unsaturated thioamides **40**

Thioamide enolates have the capability to react in a conjugate-type addition manifold. Although the scope is relatively limited and only intramolecular reactions are attainable, this reaction is an important new entry for the collection of catalytic enantioselective reactions of thioamides. Contrasting with the aforementioned reactions, where Ph-BPE is uniquely effective as a chiral ligand in combination with a Cu(I) cation, a biaryl-type chiral bisphosphine ligand (*S*)-Xyl-P-Phos is optimal and can be applied to the first-generation catalyst format with $[Cu(CH_3CN)_4]SbF_6^-$ and LiOAr **36** (Scheme 5.9) [38]. 5-Exo-trigonal cyclization is generally higher yielding than a 6-exo-trigonal reaction, and stereoselectivity is relatively dependent on subtle differences in the substrate structures and functional groups. An intermolecular version was achieved by taking advantage of the dual activation strategy, as summarized in the following section.

5.3.2 Use of Thioamides as Electrophiles

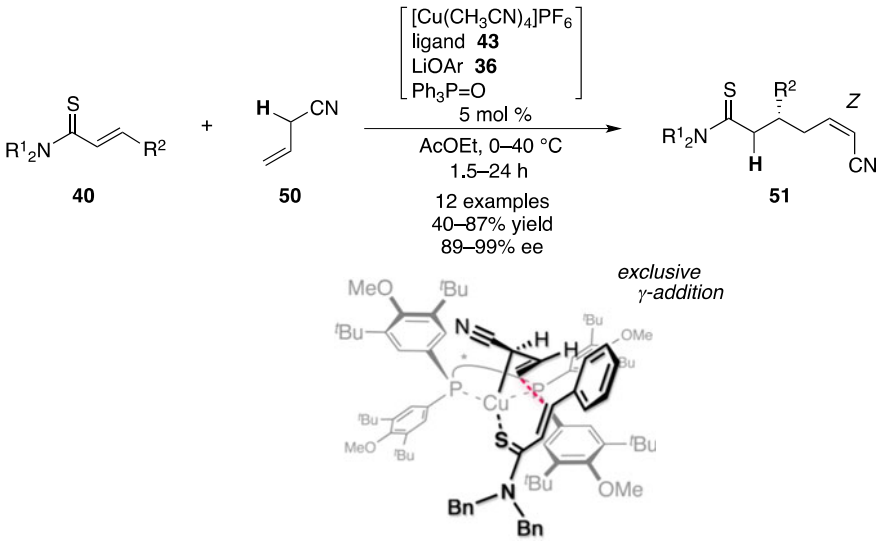
In addition to the utility of thioamides as pronucleophiles, conjugation of the thioamide functionality with a double bond provides moderately electron-deficient olefins as electrophiles that can be specifically activated by chiral soft Lewis acids with a soft-soft interaction. To make the best use of the cooperative catalytic system associated with a Brønsted base catalyst, the nucleophilic counterparts are in situ-generated to achieve perfect atom economy. Shibasaki et al. reported a direct catalytic enantioselective conjugate addition of soft Lewis basic terminal alkynes **41** to α,β-unsaturated thioamides **40**, where the soft Lewis acid Cu(I) complex exhibits dual functions to activate both the pronucleophile and the electrophile (Scheme 5.10) [39, 40]. The standard first-generation catalyst, $[Cu(CH_3CN)_4]PF_6$/chiral phosphine ligand/LiOAr **36**, acts to couple these two substrates in an enantioselective fashion, and more common biaryl-type ligands are optimal. Neither the Cu(I) complex nor LiOAr **36** can solely promote the reaction; these two catalytic elements cooperatively convert terminal alkyne **41** into the Cu(I)-alkynylide, the active nucleophile, while the vacant coordination site of Cu(I)-alkynylide directs nearby α,β-unsaturated thioamides **40** to forge a carbon-carbon bond. In general, the reaction of aromatic alkynes proceeds with high enantioselectivity using BIPHEP-type ligand **42**, but additional use of phosphine oxide **44** boosts the reaction rate to reach completion with 0.25–1 mol% of catalyst loading. The observed kinetic isotope effect (with deuterated **41**) indicates that Cu(I)-alkynylide formation is presumably the rate-determining step, which is accelerated by the enhanced basicity of LiOAr **36** through the coordination of hard Lewis basic phosphine oxide **44**. Silylated alkynes require more sterically demanding ligand **43** and the stronger KHMDS base to afford the corresponding products. In a competitive study using chalcone, a typical and inherently more electrophilic conjugate addition acceptor, α,β-unsaturated thioamides **40** exclusively react, confirming the highly chemoselective nature of the current catalytic system. As discussed in the previous section, mechanistic considerations raise the possibility that the reaction is promoted by a second-generation-type catalytic cycle. As delineated in Fig. 5.4,

cycle A, the first-generation catalyst promotes the reaction from the top to cyclic transition state **47** in a clockwise manner, though the subsequent Cu(I)-thioamide enolate species **48** warrants deeper inspection. **48** contains two characteristic units, a soft Lewis acidic Cu(I) cation with a vacant coordination site and a Brønsted basic thioamide enolate unit, implying that **48** potentially acquires the requisite functionality as the cooperative catalyst in this specific reaction. The second-generation catalytic system, without LiOAr **36**, avoids quenching **48** by in situ-generated ArOH **26** and directly promotes the following catalytic cycle. Indeed, the simplified catalytic system, mesitylcopper and ligand **42**, is a competent catalyst to promote the reaction via the efficient proton exchange mechanism shown in **49**, incorporating the next terminal alkyne into the catalytic cycle with simultaneous liberation of product **45**. The thioamide moiety of the product is successfully transformed into a variety of functional groups for further synthetic elaboration (Scheme 5.10).

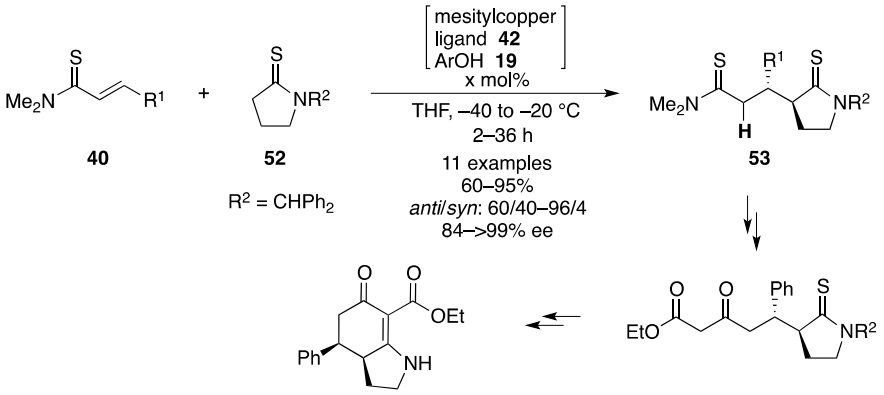
The powerful dual activation mechanism is also emulated in the reaction using allyl cyanide **50** as a soft Lewis basic pronucleophile (Scheme 5.11) [41]. While the α-proton of **50** is not sufficiently acidic to catalytically generate the corresponding carbanion under mild basic conditions, the combined use of a soft Lewis acid and suitable Brønsted base efficiently renders this elusive task. A similar type of first-generation catalyst promotes the coupling reaction of **50** with α,β-unsaturated thioamides **40**, which are activated in near proximity of the Cu(I)-cyanocarbanion in an asymmetric environment of ligand **43**. The exclusive formation of γ-adduct **51** is intriguing, because the Cu(I) complex binds to the α-position of **50** and the γ-carbon approaches the β-position of the coordinated **40** in a cyclic transition state. The beneficial effect of triphenylphosphine oxide is likely due to the enhanced Brønsted basicity of LiOAr, which accelerates the reaction.

Further application of this strategy enables the intermolecular version of conjugate addition, which is not manifested in the ester-thioamide combination outlined in Scheme 5.9. The coexistence of a saturated thioamide (pronucleophile) and α,β-unsaturated thioamides **40** in the context of a soft Lewis acid/Brønsted base cooperative catalytic system provides a dual activation mechanism to render intermolecular conjugate addition in an enantio- and diastereoselective fashion (Scheme 5.12) [42]. The second-generation catalyst prepared from mesitylcopper/ligand **42**/2,2,5,7,8-pentamethylchromanol **19** performed best to couple *N*-benzhydryl—protected thiobutyrolactam **52** and α,β-unsaturated thioamides **40**. The reaction favors *anti*-diastereoselectivity, while valerothiolactam gives the *syn*-adduct with a different chiral phosphine ligand. Sequential transformation of the thiolactam and thioamide moieties enables the productive transformation of enantioenriched products, as demonstrated by the construction of an optically active azabicyclo[4.3.0] skeleton.

In addition to the dual activation strategy discussed above, the activation of α,β-unsaturated thioamides **40** proved sufficiently powerful to produce enantioenriched chiral building blocks by taking advantage of the specific soft-soft interaction. In general, α,β-unsaturated carboxylic acid derivatives suffer from intrinsically low electrophilicity toward nucleophilic reaction partners, while enals and enones readily furnish the corresponding conjugate addition products. Therefore, the development of



Scheme 5.11 Direct catalytic enantioselective addition of allyl cyanide **50** to α,β-unsaturated thioamides **40**



Scheme 5.12 Direct catalytic enantioselective conjugate addition of thiolactam **52** to α,β-unsaturated thioamides **40**

catalytic enantioselective reactions of α,β-unsaturated thioamides **40**, i.e., carboxylic acid derivatives, contributes to reinforce the chemists' toolbox for producing enantioenriched specialty chemicals. Indeed, relatively active pronucleophiles serve as suitable substrates for soft Lewis acid/Brønsted base cooperative catalysis. Thiophenol **54** is a pronucleophile in this category, and a second-generation catalyst comprising mesitylcopper/ligand **43** without the phenol component, the simplest catalytic system shown in Fig. 5.4, was effective (Scheme 5.13) [43]. Thereby, the intermediate Cu(I)-thioamide enolate functions as a cooperative catalyst to deprotonate **54** to pro-

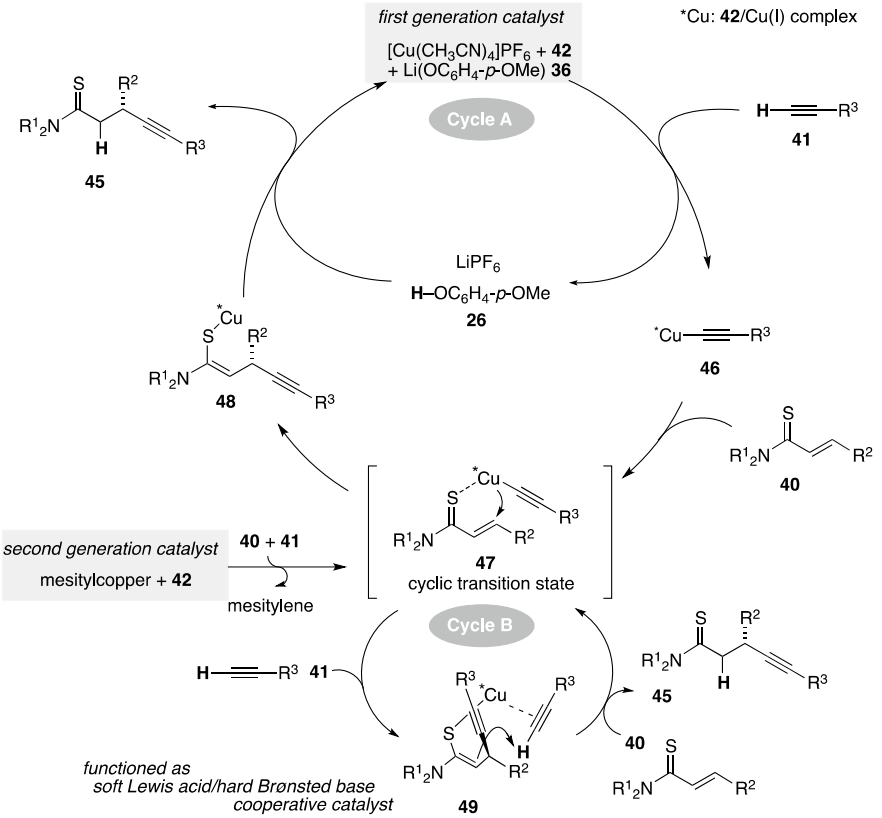
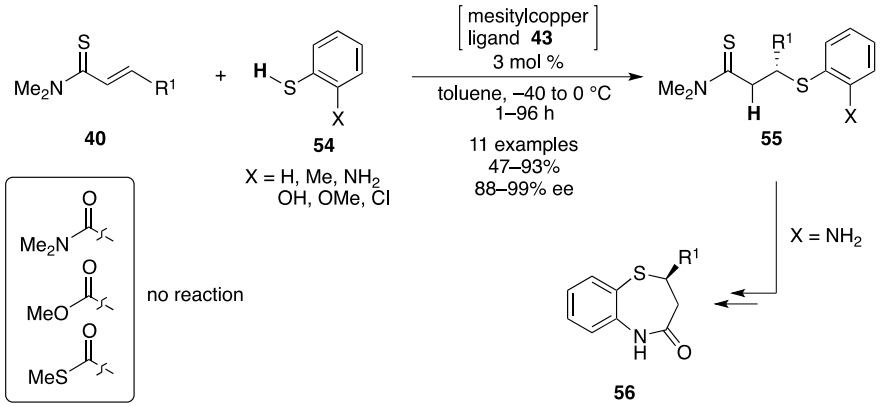


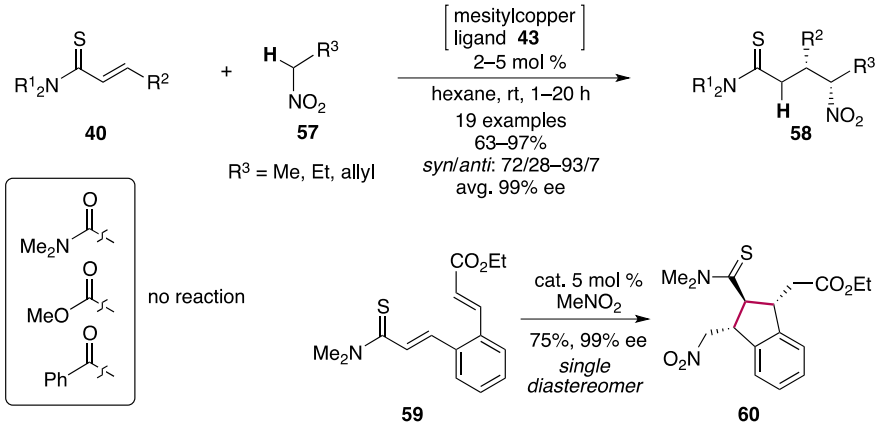
Fig. 5.4 Plausible reaction mechanisms operating in the first-generation and second-generation catalytic systems

mote the catalysis. Free amino and phenol functionalities on the thiophenol are tolerated, presumably due to the significantly higher nucleophilicity of the thiolate anion. The inertness of structurally related unsaturated olefins bearing amide, ester, and thioesters underscores the significance of the specific soft-soft interaction between the thioamide and the Cu(I) complex. The product derived from 2-aminothiophenol is particularly useful in terms of medicinal chemistry; alkylative activation of the thioamide moiety of **55** gives rise to the construction of 1,5-benzothiazepine skeleton **56**, a privileged core structure of pharmaceuticals. Successful incorporation of 2-mercaptoethanol is also noteworthy, affording the corresponding product bearing a pendant 2-hydroxyethyl group with high enantioselectivity. The identical catalytic system can be directly applied to the conjugate addition of nitroalkanes **57** (Scheme 5.14) [44]. The reaction can be run conveniently at room temperature and with excellent enantioselectivity. In most cases, 4-nitrobut-1-ene is used, affording the product with a synthetically useful allyl group (R^3 = allyl). Similarly, the catalytic system is exclusive for thioamide activation, which is advantageous in terms of

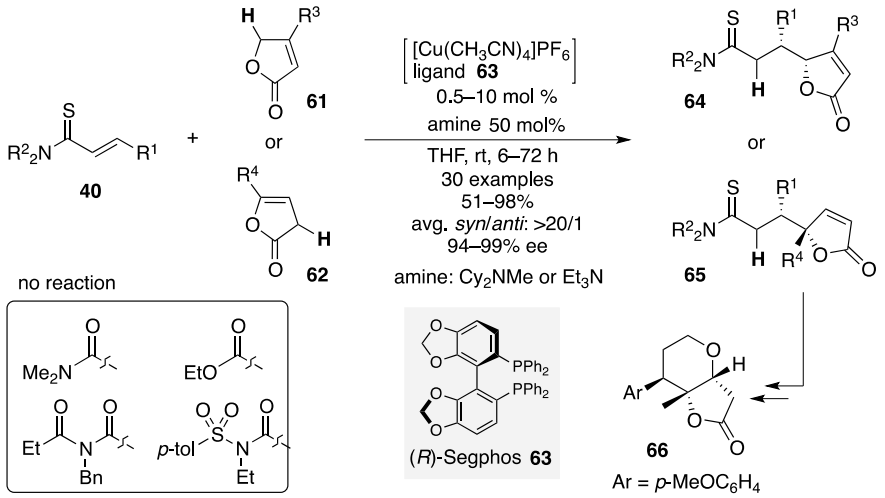


Scheme 5.13 Direct catalytic enantioselective conjugate addition of thiophenols **54** to α,β-unsaturated thioamides **40**

functional group tolerance for more complicated substrates. Intriguingly, for the specific case of α,β-unsaturated thioamide **59** installed with α,β-unsaturated ester, initial nitroalkane addition proceeds at the β-position of thioamide, and the intermediate Cu(I)-thioamide enolate undergoes subsequent intramolecular conjugate addition to the α,β-unsaturated ester, furnishing trisubstituted indane **60** as a single diastereomer in 99% ee. Butenolides **61** and α-angelica lactones **62** are another class of compatible pronucleophiles for α,β-unsaturated thioamides **40**, where slightly modified first-generation catalysts with sterically less congested chiral ligand **63** effectively afford the corresponding optically active compounds as densely functionalized chiral building blocks (Scheme 5.15) [45]. Although LiOAr bases are competent to promote this reaction in a highly stereoselective manner, conversion remains moderate even after an extended reaction time. Considering the enolization-prone property of these pronucleophiles, a substoichiometric amount of inexpensive tertiary amines can be used instead of LiOAr bases, leading to the optimized conditions shown in Scheme 5.15. Diastereoselectivity and enantioselectivity are uniformly high in all cases examined, and the convenient room temperature protocol is advantageous. As opposed to the α,β-unsaturated amide and ester, the corresponding imide and sulfonimide fail to promote the reaction under the cooperative catalysis. Of note, consecutive tri- and tetrasubstituted stereogenic centers are constructed in the reaction of α-angelica lactones **62**, whose product **65** can be transformed into bicyclic compound **66** as a single diastereomer via a reduction/intramolecular conjugate addition sequence.



Scheme 5.14 Direct catalytic enantioselective conjugate addition of nitroalkanes **57** to α,β-unsaturated thioamides **40**



Scheme 5.15 Direct catalytic enantioselective conjugate addition of butenolides **61** or α-angelica lactones **62** to α,β-unsaturated thioamides **40**

5.4 Utility in Enantioselective Synthesis of Natural Products and Biologically Active Compounds

As overviewed in Sect. 5.5.3, thioamides serve as useful starting materials for catalytic enantioselective reactions as both pronucleophiles and electrophiles, producing diverse sets of chiral building blocks bearing suitable functional handles for further elaboration. This chapter illustrates the collection of biologically active nat-

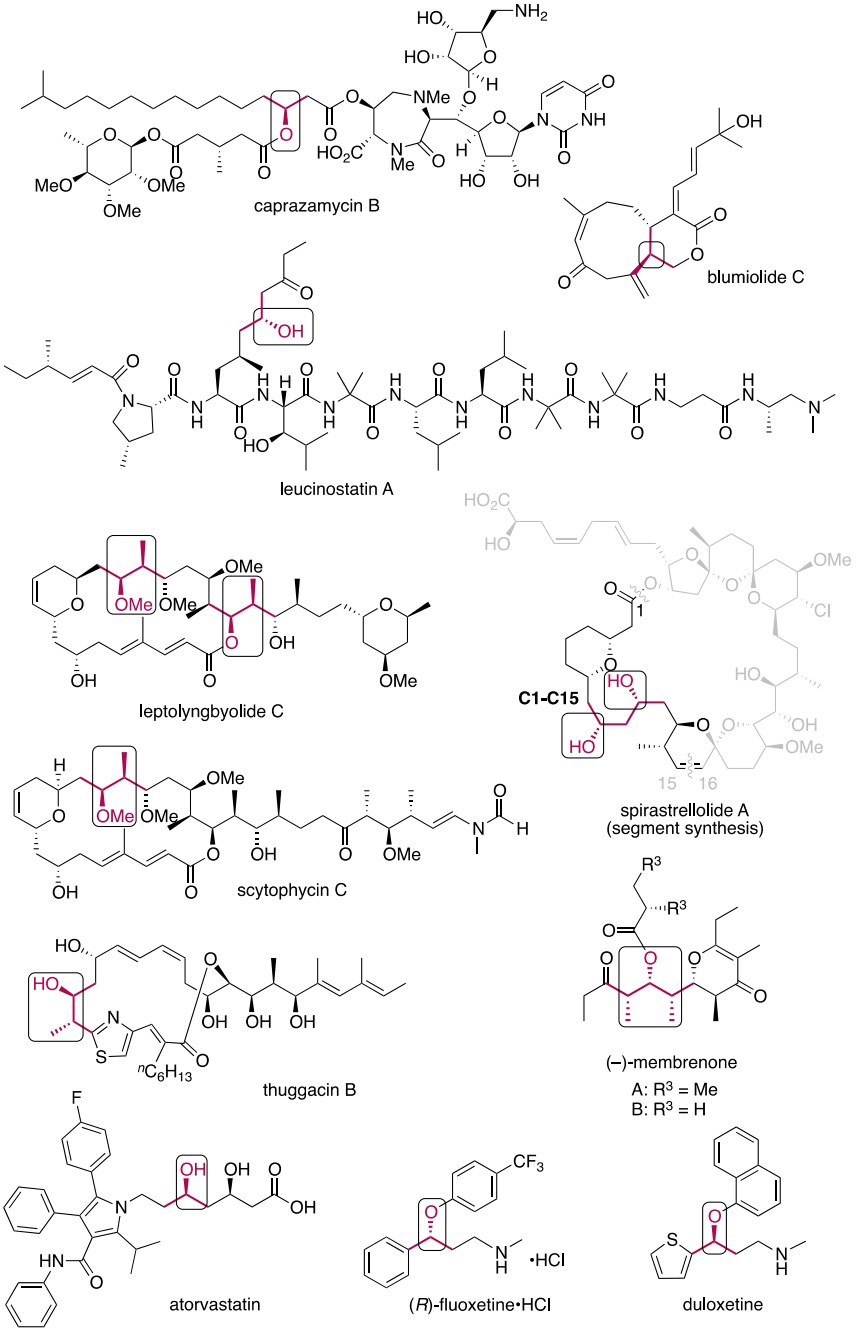


Fig. 5.5 Natural products and APIs synthesized by direct catalytic asymmetric aldol reaction of thioamides

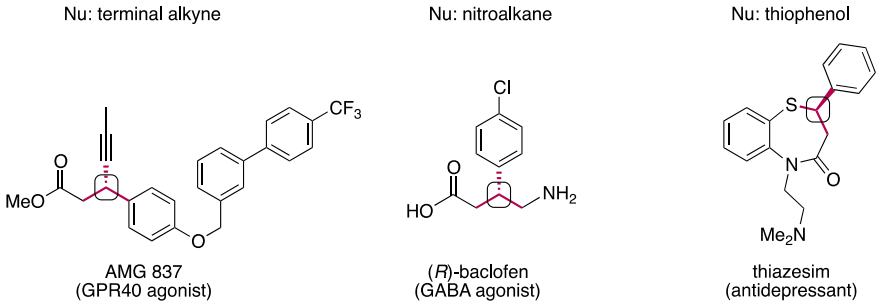


Fig. 5.6 APIs synthesized by catalytic asymmetric reactions of α,β-unsaturated thioamides as electrophiles

ural products as well as APIs that can be accessed by synthetic strategies based on the enantioselective catalysis of thioamides.

As the Evans aldol strategy gained unparalleled popularity in the synthetic chemistry community [46–48], aldol products unquestionably contain the necessary structural elements for synthesizing complicated synthetic targets. Reliable stereocontrol is also an issue for streamlined stereoselective synthesis without nonproductive stereoinversion processes. One drawback of the Evans aldol strategy is the stoichiometric use of chiral materials and bases to promote the reaction, which can be avoided by the direct aldol strategy empowered by the unique properties of the thioamide functionality and cooperative catalysis. As demonstrated by Shibasaki et al., the thioamide aldol reaction can be applied to a number of enantioselective syntheses (Fig. 5.5). Thioacetamide pronucleophiles are used in the natural products caprazamycine B (anti-tuberculosis) [49, 50], leucinostatin A (anti-tumor) [51, 52], spirastrellolide (anti-tumor, segment synthesis of C1–C15) [53], as well as APIs atorvastatin (anti-hypercholesterolemia) [54, 55], fluoxetine (antidepressant) [56], and duloxetine (antidepressant) [57]. Thiopropionamide pronucleophiles are even more effective for constructing propionate units and introducing a methyl group at the stereogenic center with precise stereocontrol, allowing for streamlined synthesis of leptolyngbyolide B (cytotoxin) [58], scytophycin C (anti-tumor) [59], thuggacin B [60], and membrenone A and B [61], the last of which showcases the iterative aldol strategy to construct consecutive propionate units in a highly stereoselective fashion. The enantioenriched product derived from α-vinylated thioacetamide is particularly useful for constructing a cyclic architecture, e.g., blumiolide C [35], where the pendant vinyl group serves as a handle for ring-closing metathesis. Besides their role as pronucleophiles, α,β-unsaturated thioamides offer additional utility as electrophiles to accept various nucleophiles under stringent stereocontrol (Fig. 5.6). APIs bearing a β-branched carboxylic acid units are suitable synthetic targets, as demonstrated by the synthesis of AMG 837 (GPR40 agonist) [39, 40, 62] and baclofen (GABA agonist) [44] by the catalytic enantioselective addition of a terminal alkyne and a nitroalkane, respectively. 2-Aminothiophenol addition is quite useful for rapidly con-

structing the 1,5-benzothiazepine ring system as exemplified by the enantioselective synthesis of thiazesim (antidepressant) [43].

5.5 Future Outlook

Thioamides comprise a very attractive class of compounds with distinctive chemical properties, e.g., soft Lewis basicity, that can be effectively exploited for chemoselective activation. Chemoselectivity is a fundamental, but sometimes overwhelming, factor for determining the overall efficiency of synthetic processes; high chemoselectivity promises orthogonal reactivity in an ensemble of multiple functional groups, and functional groups that are inert but become active solely in the presence of a specific trigger are highly useful in many synthetic processes. Thioamides are such a functional group, where a soft Lewis acid complex serves as a key to unlock hidden reactivity to render catalytic reactions in a highly enantioselective fashion. This favorable property is further leveraged by the easy preparation and the capability for multifaceted transformation. The synthetic demonstrations illustrated in the previous section showcases the utility of the stereocontrolled construction of molecules of interest. Further sophistication of catalytic systems will allow these catalytic processes to be functional in future pilot plant syntheses of high-value specialty chemicals.

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