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Cooperative Catalysis

Recent Advances in Direct Catalytic Asymmetric Transformations under Proton-Transfer Conditions

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asymmetric catalysis · atom economy · cooperative effects · proton transfer · tetrasubstituted stereogenic centers

Cooperative catalysis has proven to be a particularly powerful strategy for promoting stereoselective organic transformations under mild reaction conditions. The specific interactions between the catalyst components and substrates are precisely orchestrated to elicit high catalytic efficiency and excellent control of the stereochemical course. By harnessing the power of cooperativity, various sets of stereoselective reactions proceed under mild proton-transfer conditions with perfect atom economy. This Minireview summarizes our recent contributions to several C–N and C–C bond-forming reactions in this field and related transformations.

1. Introduction

Asymmetric catalysis has established its unwavering position as a truly efficient methodology for the construction of a wide variety of enantiomerically enriched carbon skeletons as well as for the enantioselective installation of requisite functional groups. Intensive efforts in this field have led to the emergence of numerous asymmetric catalysts, and now a number of reactions can be rendered asymmetric.[1] The huge demand and pressure for environmentally benign organic synthesis,[2] however, has gradually shifted the goal of synthetic methodology development from a basis oriented around high yield and selectivity to one oriented around atom economy;[3] conventional studies have pursued chemical processes that are high-yielding with high regio-, chemo-, and stereoselectivity, but without regard to the excessive use of reagents. The requirement of modern asymmetric catalysis in view of prospective practical applications is not only high chemical yield and selectivity but also minimal production of unwanted waste and co-products to achieve high overall efficiency, thereby meeting the criteria of environmentally benign organic synthesis and green chemistry.

The power of cooperative catalysis exerted by the precise placement of catalytically active functional groups is harnessed in a three-dimensional enzyme architecture, which allows for a number of vital enzymatic reactions under remarkably mild conditions.[4] For example, the proposed transition-state model of class II aldolase, a zinc-dependent aldolase, clearly illustrates the simultaneous activation of two distinct substrates. The enzyme catalyzes a direct asymmetric aldol reaction of dihydroxyacetone phosphate (DHAP) and various aldehydes under neutral conditions.[5] The proposed transition state (Figure 1) shows that the glutamate-73 residue in the proximity of Zn^{2+} functions as a Brønsted base for cooperative activation of the substrates (Figure 1). Inspired by this intriguing mechanism, our group has engaged in the development of asymmetric cooperative catalysts[6] that enable otherwise difficult transformations. This Minireview

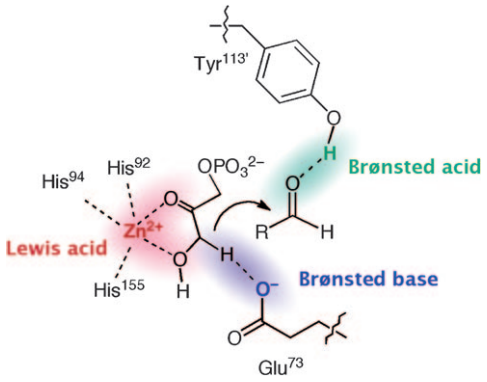

Figure 1. Cooperative activation of DHAP in class II aldolase.

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outlines our research over the last five years. The specific focus is the enantioselective construction of C–C and C–N bonds under proton-transfer conditions, in which the reaction proceeds by proton exchange of substrates, without generating any waste. The development of an asymmetric cooperative catalytic system, in which both electrophiles and nucleophiles are activated in concert, enables catalytic generation of active nucleophiles from pronucleophiles with otherwise low reactivity under mild conditions and subsequent enantioselective coupling with electrophiles, promoting the reaction with perfect atom economy. The designed cooperative catalysts can achieve a few formidable tasks: 1) a high level of stereocontrol with the highly coordinative substrates exhibiting multiple coordination modes (catalytic asymmetric amination), 2) high diastereo- and enantioselectivity that are difficult to achieve with other catalytic systems (*anti*-selective catalytic asymmetric nitroaldol reaction), and 3) exploitation of soft Lewis basic pronucleophiles with otherwise low reactivity for intermolecular direct catalytic asymmetric carbon–carbon bond-forming reactions.

2. Catalytic Asymmetric Amination

The stereoselective installation of nitrogen functionality has attracted growing attention, because nitrogen-containing substructures are a common structural motif in a wide variety of biologically active chiral compounds and therapeutics.[7] AS-3201 (Ranirestat, **1**), a therapeutic candidate as a novel aldose reductase inhibitor for diabetic neuropathy,[8] particularly attracted our interest owing to its high potency and intriguing architecture, in which a nitrogen atom is directly attached to a tetrasubstituted stereogenic carbon (Figure 2). The enantioselective synthesis of **1** relied on the optical resolution of racemic **3** using cinchonidine, whose recycling does not seem promising in this specific case,[8a] and a more practical synthetic strategy was in high demand. We envisioned that a catalytic asymmetric amination[9–13] of succinimide derivative **4** with azodicarboxylate[14] would provide key synthetic intermediate **2**. For prospective application to the amination reaction to produce a large quantity of **1**, the catalyst for this specific transformation needed to 1) be atom-economical, 2) exhibit high catalytic performance under ambient conditions with reliable reproducibility, and 3) be cost-effective. We first encountered remarkable difficulty in achieving high enantioselectivity in the asymmetric amination of **4**. Using known catalysts, either metal-based or organic, we obtained low enantioselectivity (less than 22% *ee*); probably because the highly coordinative nature of succinimide derivative **4**, which has multiple sites for both metal coordination and hydrogen bonding, leads it to display multiple coordination patterns and thus compromises the stereochemical course of the reaction. Therefore, we set out to devise a new catalytic system with a high level of enantioselectivity using this class of substrate. To avoid ligand dissociation and multiple coordination patterns of **4**, we initially focused on an asymmetric catalyst comprising a rare-earth metal (RE) and an amide-based

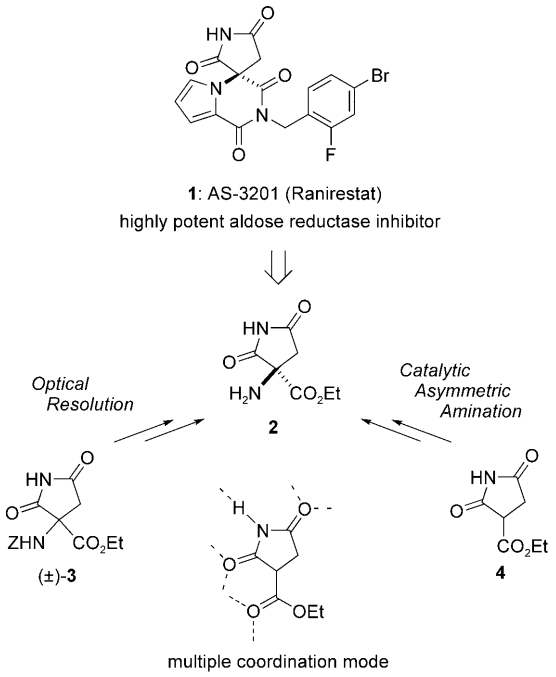
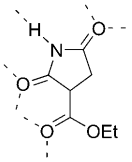


Figure 2. The structure of AS-3201 (Ranirestat) and its synthetic strategy.



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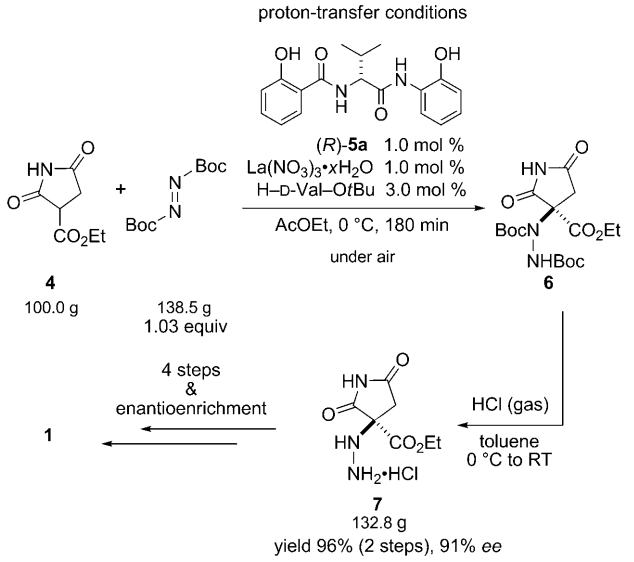
Naoya Kumagai was born in 1978 and raised in Ibaraki, Japan. After he received a Ph.D. in Pharmaceutical Sciences at the University of Tokyo in 2005 under the supervision of Prof. Masakatsu Shibasaki, he pursued postdoctoral study in the laboratory of Prof. Stuart L. Schreiber at Harvard University. He moved to Prof. Shibasaki's group at the University of Tokyo as an assistant professor in 2006. He is currently a senior researcher at the Institute of Microbial Chemistry, Tokyo. He received the Pharmaceutical Society of Japan Award for Young Scientists in 2010. His research is interested in the development of new methodology in asymmetric catalysis and its application to bioinspired dynamic processes.

Masakatsu Shibasaki received his Ph.D. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before conducting postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader and in 1986 took up a professorship at Hokkaido University before returning to the University of Tokyo as a professor in 1991. Currently, he is a director of the Institute of Microbial Chemistry, Tokyo. His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.

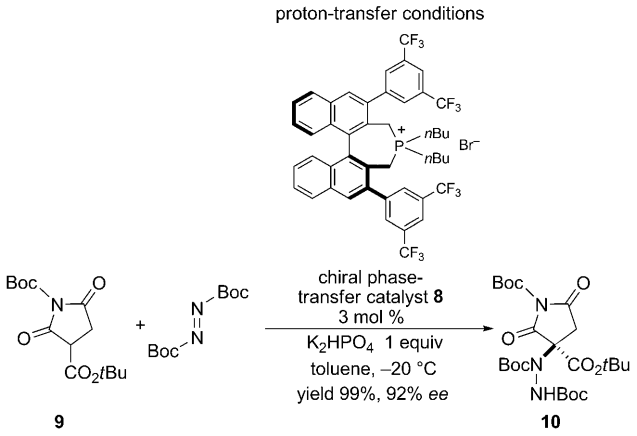
ligand,[15–17] where the high affinity of the amide functionality to the RE would avoid dissociation of **4**. Taking the high coordination number of RE metals into account, **4** could coordinate to REs surrounded by amide-based ligands, and the hydrogen bonding opportunities provided by the other ligands could cooperatively specify the coordination mode of **4**. An exquisite set of catalyst mixtures comprising an amide-based ligand (*R*)-**5a**,[18] $La(NO_3)_3{\cdot}xH_2O$ ($x = 3$–5),[19] and H-D-Val-O*t*Bu constituted a ternary complex, which proved a suitable catalyst to promote the catalytic asymmetric amination of **4** under proton-transfer conditions to give amination product **6**. Compound **6** was directly submitted to the subsequent deprotection of Boc groups under acidic conditions to deliver hydrazine hydrochloric salt **7** in 96% (two steps) and 91% *ee* (Scheme 1).[20] For comparison, a chiral



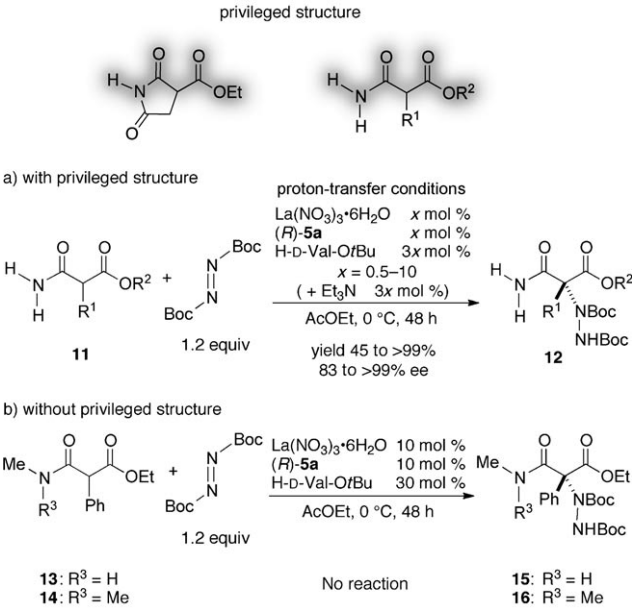
Scheme 1. Catalytic asymmetric amination of succinimide derivative **4**. Boc = *tert*-butoxycarbonyl.

phase-transfer catalyst **8** with a binaphthyl-based tetraalkyl phosphonium core structure was reported to promote the asymmetric amination of *N*-Boc-protected succinimide derivative **9** (Scheme 2).[13h,i] Owing to the high potency and prospective demand for AS-3201 (**1**), several alternative enantioselective synthetic routes were disclosed.[21] Our synthetic route is now under investigation for industrial production of **1** in the United States and Japan.

The lanthanum-based ternary catalyst was revealed to exhibit superior performance in asymmetric amination of N-nonsubstituted α-alkoxycarbonylamides **11** not substituted at the nitrogen atom (Scheme 3), a relatively untouched class of pronucleophiles in asymmetric catalysis.[22,23] The highly coordinative nature of the primary amide as well as the acidic and kinetically labile NH proton compromise the efficient deprotonation of the α-CH proton to generate an active nucleophile and to control the subsequent nucleophilic addition. Studies of the substrate generally disclosed that the ternary catalyst recognized the α-alkoxycarbonylamide motif, including the *trans* NH proton, as a privileged structure, which



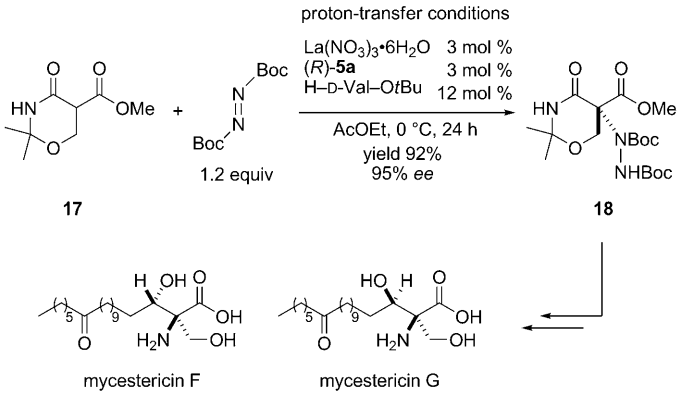
Scheme 2. Catalytic asymmetric amination of *N*-Boc-protected succinimide derivative **9**.



Scheme 3. Catalytic asymmetric amination of α-alkoxycarbonylamides **11**.

appears in both **4** and **11** (Scheme 3a).[24] Indeed, *N*-methyl and *N*,*N*-dimethyl α-alkoxycarbonylamides **13** and **14**, related substrates lacking the *trans* NH proton, failed to give the corresponding amination products, thus verifying the crucial nature of the *trans* NH proton in the present catalytic system (Scheme 3b). Extensive mechanistic elucidation through ^{1}H NMR spectroscopy, mass spectrometry, circular dichroism, and kinetic studies collectively suggested that the ternary catalyst components are in dynamic equilibrium between the associated and dissociated state with the latter predominant, and orchestrate to form an assembled transition state with substrates through metal coordination and hydrogen bonding. The large activation entropy observed in this catalysis is consistent with this assumption. Mechanistic investigation led to substantial improvement of the reaction efficiency with an Et_3N additive, allowing the reaction to proceed with catalyst

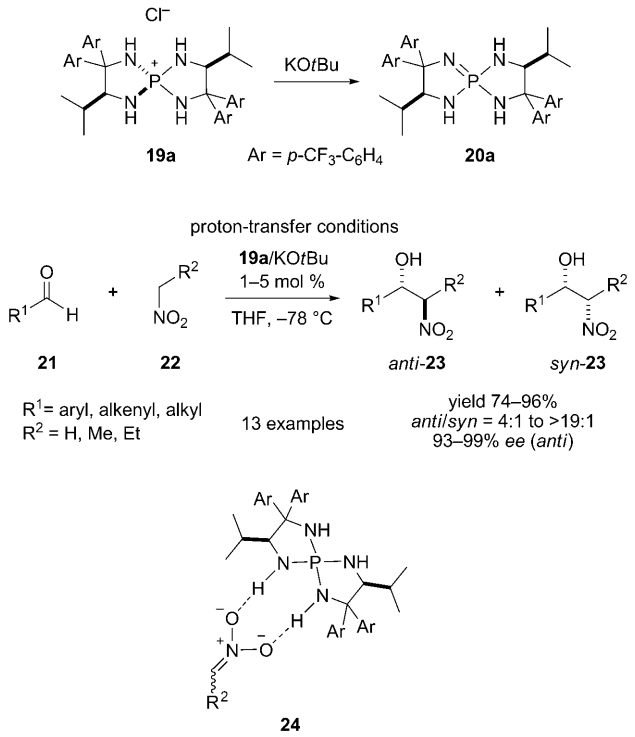
loadings as low as 0.5 mol%. A lactam-type substrate **17** retains the privileged motif and serves as a suitable substrate in the amination protocol (Scheme 4). The enantiomerically enriched amination product **18** bears a tetrasubstituted stereogenic center directly attached to ester and amide functionalities amenable to differential manipulation, thus allowing for a concise enantioselective synthesis of polar head groups of mycestericins F and G.[25,26]



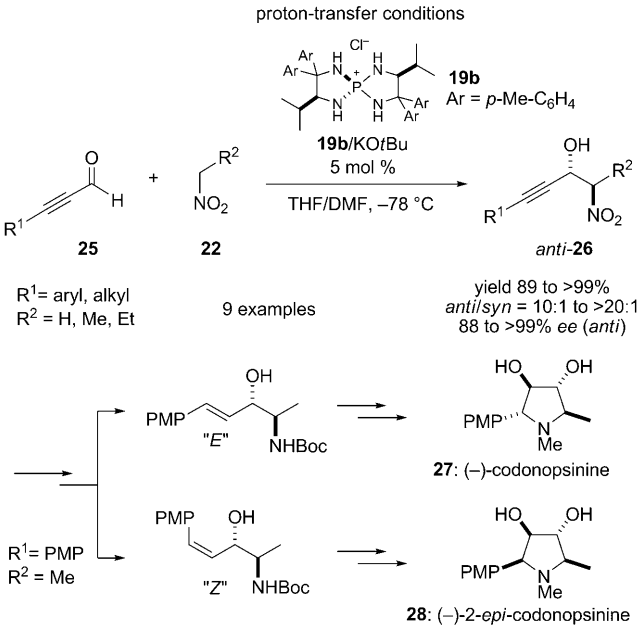
Scheme 4. A concise enantioselective synthesis of mycestericin F and G by catalytic asymmetric amination.

3. anti-Selective Catalytic Asymmetric Nitroaldol (Henry) Reaction

The nitroaldol (Henry) reaction, which was first reported over 100 years ago,[27] offers one of the most useful and atom-economical methodologies to furnish both oxygen and nitrogen functionalities with concomitant C–C bond formation. The precise stereocontrol of generating 1,2-nitroalkanols has proved elusive, however, thus rendering the development of a catalytic enantio- and diastereoselective nitroaldol reaction a challenging objective. A *syn*-selective catalytic asymmetric nitroaldol reaction was first disclosed by our group in 1995,[28] followed by sporadic reports of successful catalysts by other groups.[29] However, catalyst-controlled production of optically enriched *anti*-1,2-nitroalkanols by the nitroaldol reaction was reported only recently.[30,31] In 2007 and 2008, three different classes of asymmetric catalyst appeared to address this longstanding task (see also Scheme 5, Scheme 7, and Scheme 8). An iminophosphorane-type asymmetric organocatalyst **20a**, generated in situ from the corresponding chiral tetraaminophosphonium chloride **19a** and KO*t*Bu, promoted the *anti*-selective nitroaldol reaction of aldehyde **21** and nitroalkane **22** in a highly enantioselective manner to afford *anti*-1,2-nitroalkanol **23** (Scheme 5).[32] Bidentate coordination of a nitronate nucleophile generated in situ is proposed (**24**), thus limiting the stereochemical course of the approaching aldehyde **22** and leading to the transition state favoring *anti*-diastereoselectivity. This catalytic system was successfully applied to the reaction with ynals **25**, thus providing a new entry to enantiomerically enriched β-nitropropargylic alcohols **26** (Scheme 6).[33] The transient propargylic alkoxide caused catalyst decomposition in THF solvent, which was



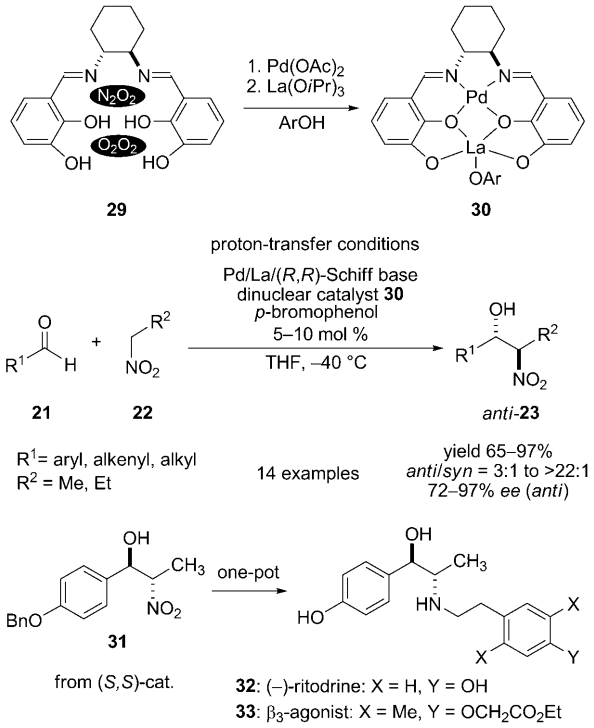
Scheme 5. The *anti*-selective catalytic asymmetric nitroaldol reaction promoted by iminophosphorane-type asymmetric organocatalyst **20a**.



Scheme 6. A concise enantioselective synthesis of (−)-codonopsinine and (−)-2-*epi*-codonopsinine by *anti*-selective catalytic asymmetric nitroaldol reaction. PMP = *p*-MeOC$_6$H$_4$.

circumvented by using a THF/DMF binary solvent system. The *Z*- and *E*-selective hydrogenation of the product enabled catalytic asymmetric synthesis of (−)-codonopsinin (**27**) and (−)-2-*epi*-codonopsinin (**28**), which have antibiotic and hypotensive activities.[34]

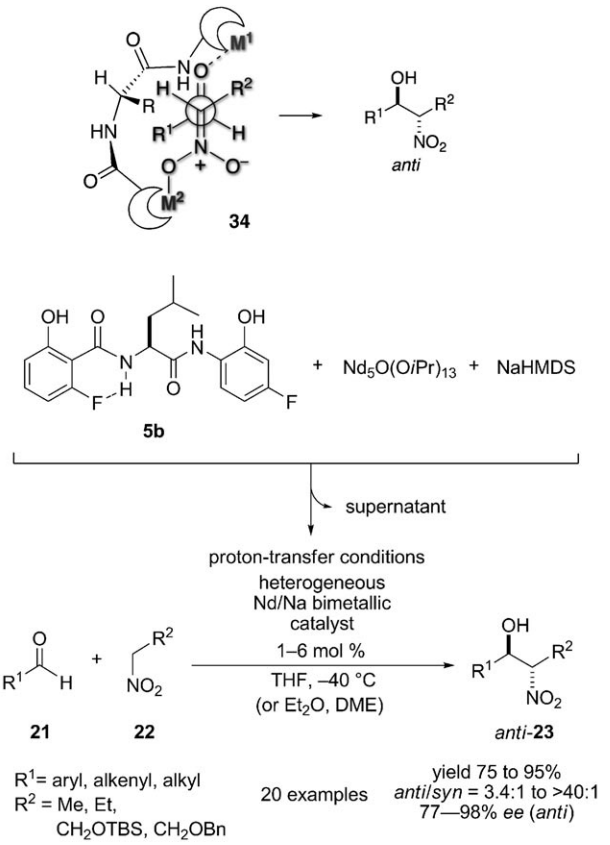
A dinucleating Schiff base **29** and its congeners recently emerged as useful ligands for incorporating two identical or different metal cations into the N_2O_2 inner cavity and the O_2O_2 outer cavity, thus generating a wide range of bimetallic asymmetric catalysts.[35,36] A palladium/lanthanum heterodinuclear catalyst **30** prepared from Schiff base **29**, $Pd(OAc)_2$, $La(OiPr)_3$, and *p*-bromophenol exhibited high *anti*-diastereoselectivity and enantioselectivity in the nitroaldol reaction (Scheme 7).[37] Considering that monometallic asymmetric



Scheme 7. The *anti*-selective catalytic asymmetric nitroaldol reaction promoted by Pd/La heterodinuclear catalyst **30**.

catalysts generally promote the nitroaldol reaction in a *syn*-selective manner, a bimetallic entity is likely key to attaining a transition state leading to *anti*-selectivity.[38] A one-pot transformation of nitroaldol product **31** derived from (*S*,*S*)-catalyst delivered (−)-ritodrine **32** and β_3-adorenoceptor agonist **33**.[39,40]

Another bimetallic catalyst proved to be effective for this valuable transformation. The amide-based ligand **5b** bearing an *m*-oriented phenolic hydroxy group was used as a platform for a bimetallic complex comprising a rare-earth metal and an alkali metal to activate aldehyde and nitroalkane independently, leading to the extended transition state **34** and finally to *anti* diastereoselectivity (Scheme 8).[41] Fluorine substituents on the aromatic ring are crucial for stereoselectivity, likely because the conformational restriction of flexible ligand **5b** through a C−H···F hydrogen bond is beneficial to formation of the extended transition state.[42] Intriguingly, the bimetallic complex of **5b** with $Nd_5O(OiPr)_{13}$ and NaHMDS is insoluble in THF and functions as a heterogeneous asymmetric catalyst to promote the *anti*-selective nitroaldol reaction of a wide

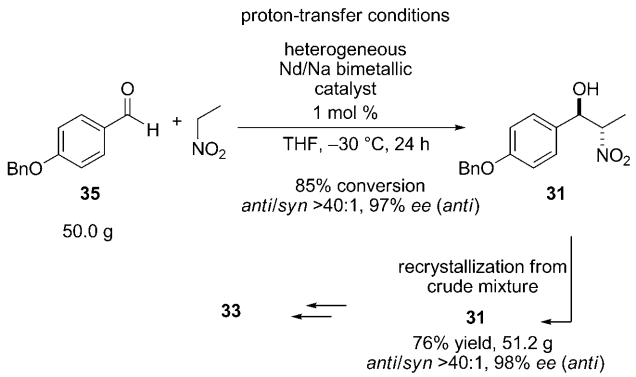


Scheme 8. The *anti*-selective catalytic asymmetric nitroaldol reaction promoted by heterogeneous Nd/Na catalyst. HMDS = hexamethyldisilazide, DME = 1,2-dimethoxyethane, TBS = *tert*-butyldimethylsilyl, Bn = benzyl.

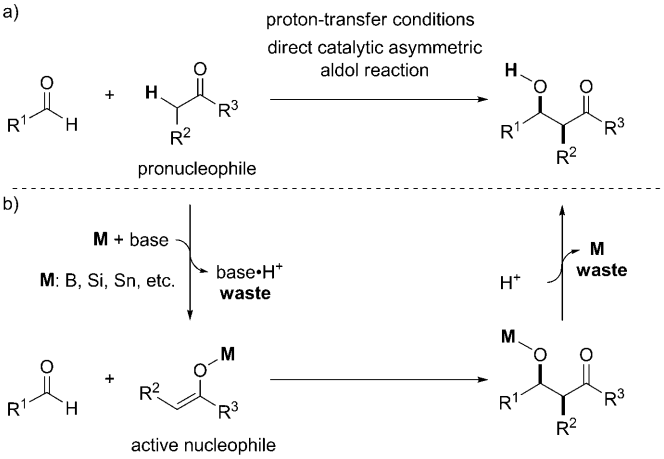
range of aldehydes and nitroalkanes. Inductively coupled plasma atomic emission spectrometry and X-ray fluorescence analysis revealed that the heterogeneous catalyst incorporates both Nd and Na cations to form a bimetallic polymeric entity with an approximate ratio **5b**/Nd/Na = 1:0.96:1.8.[43] The *anti*-nitroaldol protocol is operationally simple to perform on 50 g scale with 1 mol% of catalyst to give the desired *anti*-nitroaldol product **31** in 76% yield with 98% *ee* by recrystallization of the crude reaction mixture, which is a key intermediate in the enantioselective synthesis of **33** (Scheme 9).[39]

4. Direct Catalytic Asymmetric Addition of Soft Lewis Basic Carbon Pronucleophiles

Direct catalytic intermolecular asymmetric carbon–carbon bond-forming reactions, in which active carbon nucleophiles are catalytically generated in situ to engage in enantioselective addition to certain electrophiles, have gained increasing attention during the last decade, partially because of the considerable advances in direct catalytic asymmetric aldol reactions promoted by metal-based catalysts and organocatalysts (Scheme 10a).[44,45] The emergence of the direct catalytic asymmetric aldol reaction avoided the use of

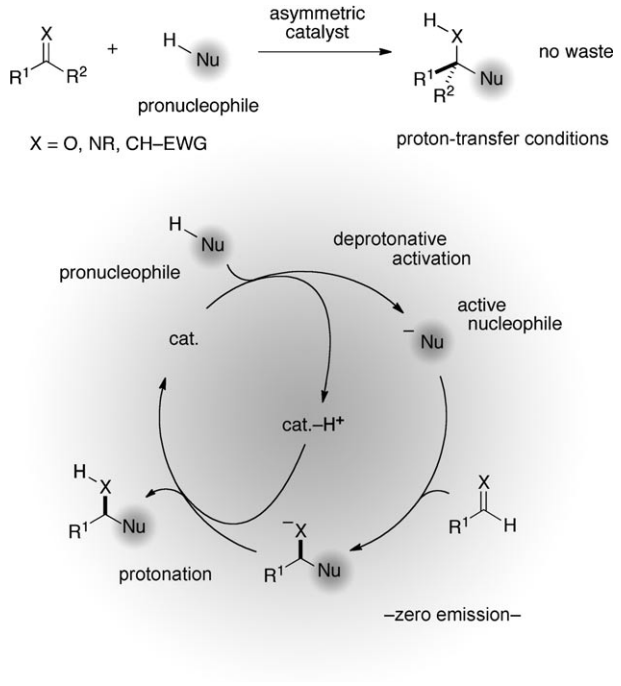


Scheme 9. A large-scale demonstration of catalytic asymmetric nitroaldol reaction promoted by heterogeneous Nd/Na heterodinuclear catalyst.



Scheme 10. a) Direct catalytic asymmetric aldol reaction and b) aldol reaction with preactivated nucleophile (enolate).

preformed metal enolate or enol silyl ethers that must be prepared in separate procedures with stoichiometric amounts of reagents (Scheme 10b). In principle, these direct reactions proceed in 100% atom economy under proton-transfer conditions, providing an ideal reaction system to produce enantiomerically enriched chiral building blocks without the formation of reagent-derived waste (Scheme 11). The initial step of the direct reaction is deprotonation of the pronucleophile by the catalyst to generate an active carbanion-type nucleophile; as a result, the acidity of the pronucleophile is a critical issue and severely limits the scope of applicable pronucleophiles in direct asymmetric reactions. Potential pronucleophiles with a high pK_a values not only mandate the use of a strong Brønsted base that can trigger undesirable side reactions, but they also retard the catalytic turnover through proton transfer, namely the protonation of an intermediary adduct with a protonated catalyst to regenerate the active catalyst. Therefore, an ingenious mechanistic trick to conquer the pK_a problem is required to broaden the scope of the direct catalytic asymmetric carbon–carbon bond-forming reaction. Recent extensive research in this area has reinforced the chemical toolbox for direct catalytic asym-



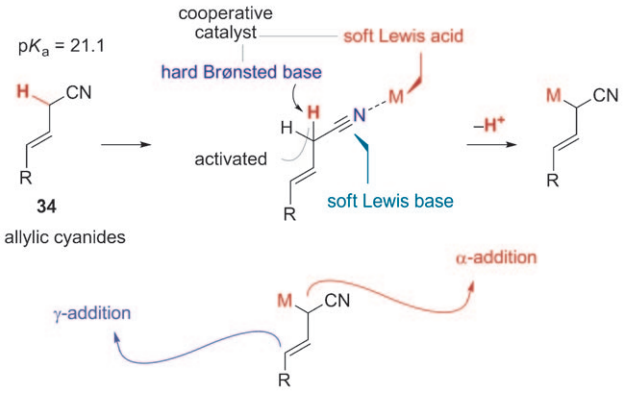
Scheme 11. Direct catalytic asymmetric reactions through proton transfer. EWG = electron-withdrawing group.

metric carbon–carbon bond-forming reactions, largely using carbon pronucleophiles with low pK_a values. This section highlights the use of carbon pronucleophiles with high pK_a values, which has received less attention, likely owing to reluctant deprotonative activation.

4.1. Direct Catalytic Asymmetric Addition of Carbon Pronucleophiles Producing Tetrasubstituted Stereogenic Centers

The stereoselective construction of a tetrasubstituted stereogenic center with concomitant catalytic carbon–carbon bond formation is a challenging objective in modern synthetic organic chemistry.[46] Catalytic asymmetric hydrogenation, the most advanced asymmetric catalysis in terms of mechanistic details and practical application, cannot access this class of compounds. The development of this useful transformation by a direct catalytic asymmetric reaction poses a particular difficulty; in addition to the catalytic generation of active nucleophiles in situ, the catalyst must overcome the high activation barrier of a highly congested transition state to produce a tetrasubstituted carbon center. In this context, nitrile-based pronucleophiles[47] are promising because 1) the soft Lewis basic character of nitrile functionality allows for chemoselective activation by a soft Lewis acidic catalyst, thus increasing the acidity of the intrinsically high-pK_a α-proton of nitriles;[48] 2) their unique linear topology poses minimal steric bias, making them well-suited to the highly congested transition state to produce a tetrasubstituted stereogenic center; 3) nitriles are readily available and sufficiently stable to allow easy handling; and 4) they can be viewed as masked carboxylic acid derivatives or amines, which promise diverse

transformation of the reaction product. Recently, allylic cyanides **34**,[49] which bear an olefinic function that lowers the pK_a of the α-proton and is amenable to further transformation of the product, proved their utility as pronucleophiles in direct catalytic asymmetric carbon–carbon formation promoted by a soft Lewis acid/hard Brønsted base catalyst (Scheme 12). In this catalyst design, the soft Lewis

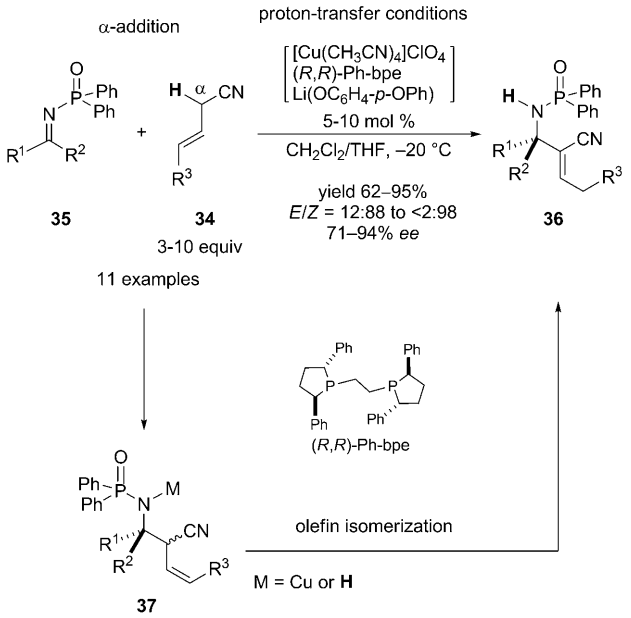


Scheme 12. Catalytic generation of an active carbon nucleophile from allylic cyanides **34** through a soft Lewis acid/hard Brønsted base cooperative catalyst.

acid and hard Brønsted base functioned cooperatively;[6] allylic cyanides **34** are chemoselectively activated by a soft Lewis acid through a soft–soft interaction to enhance the acidity of the α-proton of **34**, which is deprotonated by a hard Brønsted base. Another advantage of **34** is its ability to undergo ambident nucleophilic addition; **34** undergoes α-addition and γ-addition depending on the electrophile chosen, displaying a divergent reaction pattern.

4.1.1. Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines

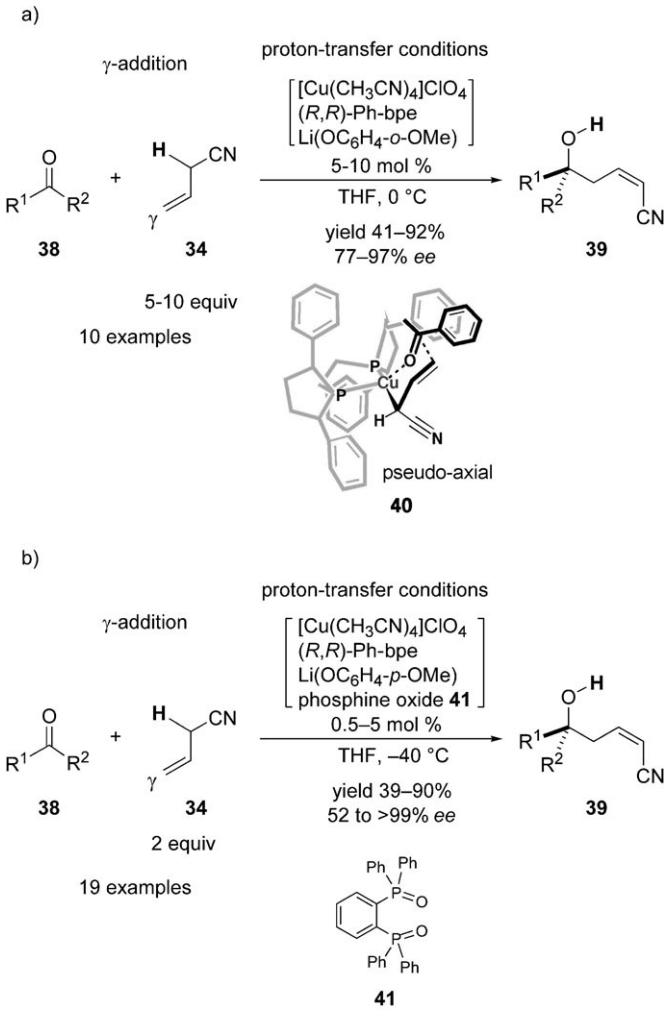
Enantioselective addition of certain carbon nucleophiles to ketoimines allows for efficient access to enantioenriched α-tertiary amines. Although intensive investigation disclosed a number of catalytic systems that realize the transformation in a highly enantioselective manner, almost all of them utilized highly nucleophilic organometallic nucleophiles, likely in order to compensate for the high activation barrier in the reaction with low-reactivity and sterically demanding ketoimines.[50] These methodologies required the generation of active organometallic nucleophiles in a separate operation using more than stoichiometric amounts of metallic reagents and bases, which significantly decreases the overall atom economy. Transformations that proceeded under proton-transfer conditions were limited to the reaction using a specialized pronucleophile such as hydrogen cyanide[51] or highly reactive ketoimines.[52] This specific transformation revealed the utility of allylic cyanides **34** as carbon pronucleophiles in direct catalytic asymmetric reaction. In the direct addition of allylic cyanides **34** to *N*-diphenylphosphinoyl (*N*-Dpp) ketoimines **35**,[53] a soft Lewis acid/hard Brønsted base cooperative catalyst comprising a cationic copper complex $[Cu(CH_3CN)_4]ClO_4$, a bisphosphine ligand (*R*,*R*)-Ph-bpe, and $Li(OC_6H_4$-*p*-OPh) was identified to effect catalytic generation of the active carbon nucleophile and subsequent enantioselective addition to **35** (Scheme 13).[54–56] The reaction proceeded at −20 °C with exclusive α-addition, thus affording α,β-unsaturated nitrile **36** via olefin isomerization of intermediary adduct **37**.



Scheme 13. Direct catalytic asymmetric addition of allylic cyanides **34** to *N*-Dpp ketoimines. bpe = 1,2-bis(2,5-diphenylphospholano)ethane.

4.1.2. Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketones

In contrast to the α-addition observed in the reaction of allylic cyanides **34** with ketoimines **35**, the analogous direct reaction with ketone **38** in a similar catalytic system displayed γ-addition to deliver the corresponding tertiary alcohol **39** bearing a characteristic *Z*-configured olefin (Scheme 14a).[57] The different regioselectivity and *Z*-olefin formation was explained by assuming a six-membered transition state **40** in which the nitrile group occupied a pseudo-axial position to avoid steric hindrance with the (*R*,*R*)-Ph-bpe ligand. The protocol for the direct catalytic asymmetric addition of carbon pronucleophiles to ketones in proton-transfer conditions is rare[58,59] and provides a useful chemical tool for catalytic enantioselective production of synthetically versatile tertiary alcohols.[60] The protocol was further advanced by using the hard Lewis basic bisphosphine oxide **41**,[61] which gave a ternary cooperative catalytic system of a soft Lewis acid/hard Brønsted base/hard Lewis base (Scheme 14b).[62] Detailed mechanistic studies indicated that the third component, bisphosphine oxide **41**, preferentially coordinated to the Li cation to enhance the Brønsted basicity of $Li(OC_6H_4$-*p*-OMe),[63] boosting the reaction by remarkably facilitating the rate-determining deprotonation process. With the ternary

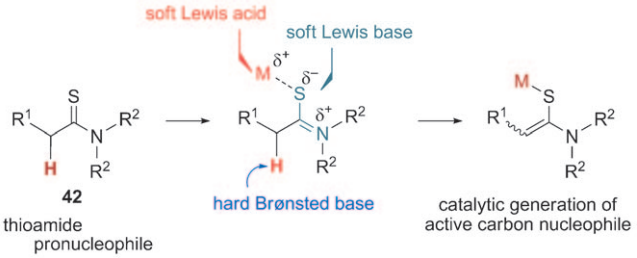


Scheme 14. Direct catalytic asymmetric addition of allylic cyanide **34** to ketones.

catalytic system, the substrate scope was broadened with minimal catalyst loading of 0.5 mol%. The obvious ambident nature of the allylic cyanide pronucleophile **34** delineated in Scheme 13 and Scheme 14 highlights its synthetic utility.

4.2. Direct Catalytic Asymmetric Addition of Thioamide Pronucleophiles

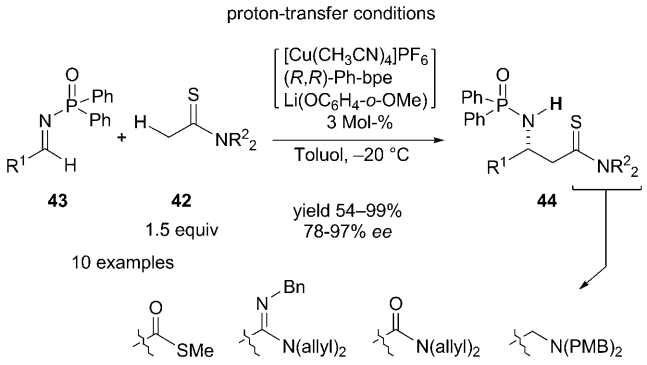
The use of carbonyl-based pronucleophiles in the carboxylic oxidation state is a longstanding problem in direct catalytic asymmetric intermolecular carbon–carbon bond-forming reactions. The inherent low acidity of the α-proton of this class of compounds hampers the deprotonative generation of the corresponding enolates, the initial trigger of the reaction.[64] The chemoselective activation strategy through a soft-soft interaction described above was extrapolated to the activation of thioamides **42**, carbonyl-based pronucleophiles that display soft Lewis basic character at the sulfur atom. Although thioamides are recognized as a particularly useful functional group for the synthesis of a wide variety of heterocyclic compounds,[65] only sporadic studies have been conducted on the use of thioamides as pronucleophiles.[66] The enantioselective aldol reaction of thioamides **42** was pioneered by Mukaiyama in 1989,[67] but the generation of the thioamide required stoichiometric amounts of strong base. The catalytic generation of thioamide enolate is manifested by the soft Lewis acid/hard Brønsted base cooperative catalyst, in which the sulfur atom of the thioamide chemoselectively coordinates to a soft Lewis acid to enhance the acidity of the α-proton; hence, facile deprotonation is possible under mild basic conditions to generate thioamide enolate (Scheme 15). The divergent functional group transformation of the thioamide functionality highlights the synthetic versatility of the reaction product derived from the thioamide pronucleophile.



Scheme 15. Catalytic generation of an active carbon nucleophile from thioamides **42** through a soft Lewis acid/hard Brønsted base cooperative catalyst.

4.2.1. Direct Catalytic Asymmetric Mannich-type Reaction of Thioamides

The direct catalytic asymmetric Mannich-type reaction has gained increasing attention as an atom-economical protocol for the production of enantioenriched β-amino carbonyl entities.[68] Pronucleophiles with low pK_a values such as ketones and aldehydes are successfully implemented in this useful transformation by both metal-based catalysts and organocatalysts. The use of carboxylate-derived pronucleophiles broadens the scope of this transformation, and in this regard the direct catalytic asymmetric Mannich-type reaction of trifluoroethyl thioester provides a partially successful example (45% *ee*).[69] The first example of the catalytic generation of thioamide enolate is demonstrated in this transformation, using the soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[Cu(CH_3CN)_4]PF_6$, a (*R*,*R*)-Ph-bpe, and $Li(OC_6H_4$-*o*-OMe).[70] Under mildly basic conditions, the thioamide enolate is generated with the aid of the soft Lewis acid Cu^I bearing a chiral bisphosphine ligand. The thus-formed chiral Cu thioamide enolate engages in enantioselective carbon–carbon bond formation with *N*-Dpp aldimine **43**,[53] affording Mannich product **44** under proton-transfer conditions (Scheme 16). An *anti*-diastereoselectivity is observed in the reaction using propionic acid-derived thioamide as the pronucleophile. Divergent transformation of the thioamide functionality into thioester, amidine, amide, and amine highlights the synthetic utility of the protocol.[70] Quite recently, amides were disclosed to function as pronucleophiles in the Mannich-type reaction with *N*-tosyl imines

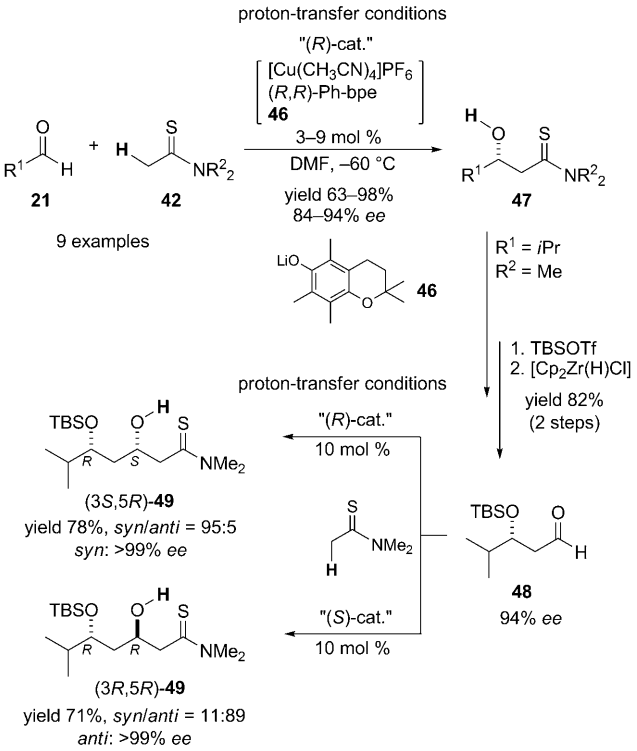


Scheme 16. Catalytic asymmetric Mannich-type reaction of thioamides **42**. PMB = *p*-methoxybenzyl.

with a catalyst composed of iPr$_3$SiOTf/Et$_3$N, which is partially extended to an enantioselective version (69% *ee*) in the presence of a catalytic amount of CuOTf/tol-binap catalyst (OTf = SO_3CF_3, binap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl).[71]

4.2.2. Direct Catalytic Asymmetric Aldol Reaction of Thioamides

The aldol reaction is a well-known and ubiquitous reaction both in biochemical transformations and in chemical synthesis, and it has been a primary target of direct catalytic asymmetric reactions.[45] Similar to Mannich-type reactions, ketones and aldehydes, which are apt to be converted to the corresponding enolates under mildly basic conditions, are first implemented as pronucleophiles in the direct aldol reaction.[44] Less acidic aldol donor substrates in the carboxylic acid oxidation state are reluctant to generate active enolates under catalytic conditions and usually require preactivation in a separate operation.[64] Carboxylate derivatives bearing a strong electron-withdrawing group[72] or a vinyl group at the α-position facilitate the enolization process and serve as effective pronucleophiles in the direct aldol reaction,[64c] although the substrate structure is limited. Recent advances in this field found the direct catalytic asymmetric aldol reaction of thiazolidinethione promoted by Ni/chiral bisoxazoline catalyst with the aid of more than stoichiometric amounts of base and silylating reagent.[64e] An *N*-Boc activated amide enables direct catalytic aldol reaction by a barium aryloxide catalyst through intramolecular transfer of a *tert*-butoxycarbonyl group to a newly formed secondary alcohol, albeit with limited enantioselectivity (33% *ee*).[64b] In this context, the direct catalytic asymmetric aldol reaction of carboxylate-derived pronucleophiles is in high demand, and thioamide pronucleophiles **42** have established their utility by harnessing a specific soft–soft interaction. The catalytic generation of thioamide enolates and their integration into the subsequent addition to aldehydes **21** was achieved by the soft Lewis acid/hard Brønsted base cooperative catalyst comprising [Cu(CH$_3$CN)$_4$]PF$_6$, (*R*,*R*)-Ph-bpe, and Li aryloxide **46**, affording enantioenriched β-hydroxythioamides **47** (Scheme 17).[73] The Lewis basic solvent DMF was essential to drive the catalytic cycle, presumably by accelerating the proton exchange of a metastable Cu aldolate.



Scheme 17. Catalytic asymmetric aldol reaction of thioamides **42** and its application to stereoselective synthesis of 1,3-diols. Cp = C_5H_5.

Enhanced basicity of Li aryloxide **46**, which has electron-donating substituents and a conformationally rigid cyclic ether, exhibits particular effectiveness in this reaction as a hard Brønsted base to deprotonate activated thioamide **42**. Aliphatic aldehydes bearing a more acidic α-proton can be used, and no self-condensation was observed, thus verifying the highly chemoselective nature of the present direct aldol reaction. A facile reduction of the thioamide functionality gave aldehyde **48**, which was subjected to a second direct aldol reaction with either the (*R*)- or (*S*)-catalyst to give *syn* and *anti*-diols **49**, respectively, showcasing the highly catalyst-controlled stereoselectivity of the direct aldol reaction. This iterative direct aldol methodology led to the stereoselective construction of 1,3-polyol arrays, a widespread structural motif in natural products.[74,75]

5. Conclusion

In the last three decades, the arsenal of chemical tools has been substantially reinforced by the huge collection of asymmetric catalysts, which allows for efficient production of a wide variety of enantioenriched compounds. In view of sustainable chemistry, asymmetric catalysis is a central methodology that continues to attract growing attention. Another issue that requires particular attention is overall reaction efficiency, that is, pursuit of atom-economy of the reaction to avoid the excessive use of reagents and minimize the production of unwanted waste. The sophisticated syner-

gism of the two concepts of asymmetric catalysis and atom-economy will significantly advance synthetic chemistry, making it more amenable to truly efficient production of requisite chemical entities.

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