Asymmetric Catalysis

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Multiple Catalysis with Two Chiral Units: An Additional Dimension for Asymmetric Synthesis

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asymmetric catalysis · multifunctional catalysis · multiple catalysis · organocatalysis · transition metals

Dedicated to K. C. Nicolaou on the occasion of his 65th birthday

This Minireview focuses on asymmetric reactions mediated by two distinct chiral catalysts (chiral multiple catalysis). Initially, this approach appears unconventional, but indeed it allows a fast multi-dimensional optimization and fine-tuning of the catalytic system required to perform a given transformation. Herein, this emerging concept is presented and its potential applications are highlighted.

1. Introduction: (Chiral) Multifunctional and Multiple Catalysis

A significant recognition of the importance of asymmetric catalysis[1] has surely been the 2001 Nobel Prize for Chemistry awarded to Sharpless, Knowles, and Noyori for their contributions in the field of metal-catalyzed reactions.[2] A year before, two pioneering papers by List, Lerner, and Barbas,[3a] and MacMillan and co-workers[3b] initiated the rediscovery of asymmetric organocatalysis,[3] which by now constitutes an established and complementary tool with respect to transition metal catalyzed asymmetric transformations. Both methodologies have been applied to the synthesis of biologically relevant chiral nonracemic molecules.[4] Several authors have also shown that these two alternative approaches can effectively cooperate with each other and their works have recently been reviewed.[5] Despite impressive advances, researchers are still eagerly looking for new asymmetric catalyzed reactions, since only a fraction of the known chemical transformations have an asymmetric version having a wide substrate scope. The one million dollar question, "what will asymmetric catalysis look like within the next decade?", would surely bring much debate and proposals, and the answer to it significant credit to the researchers who recognize, early on, a new and rising field.

To reach the goal described above, the identification of the best-performing catalyst is one of the most time- and resource-consuming tasks to be overcome. In addition to the classic "one catalyst one reaction" approach, more recent strategies can be pursued. A single molecule with two or more functional groups, each one having a different catalytic activity, is a multifunctional catalyst. If at least one of the subunits bearing the functional groups is chiral, then the molecule can be defined as a chiral multifunctional catalyst (Figure 1, left).[6] Examples of such structures can be found both in organocatalysis[7a–d] and transition-metal catalysis.[7e–g] A complementary strategy is multiple catalysis, that is the use of distinct noncovalently bound catalysts.[8] This review analyzes an apparently narrow aspect, albeit with enormous potential, of the latter: the multiple catalysis with two (or more) chiral units, or chiral multiple catalysis (Figure 1, right).[9]

Significant and successful applications of this concept can be found in the early 1990s[11] and a theoretical analysis can be

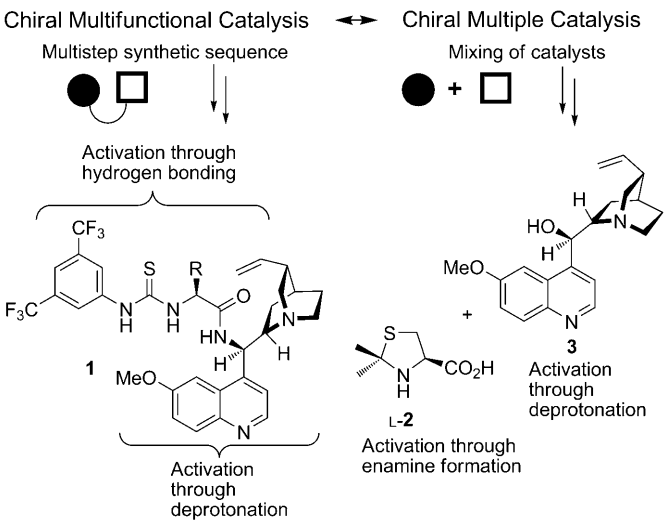

Figure 1. Example of multifunctional[10a] and multiple catalysis.[10b]

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traced back to the origin of asymmetric catalysis, when Kagan and co-workers described the nonlinear effects observed if different ratios of the same catalyst enantiomers are used together in a chemical transformation.[12] However, it was not until recently that a conspicuous number of examples reporting this strategy appeared in the literature. Our goal is to describe the several aspects of this concept and its synthetic applications through a choice of relevant examples. Although the authors did not always perform detailed mechanistic studies, we grouped the selected examples according to the most plausible mechanism of activation as indicated by the authors in their reports.[13]

1.1. Why Use Two Distinct Chiral Catalysts?

The main features associated with multiple catalysis and multifunctional catalysis are summarized in Figure 2. Probably, the most attractive aspect of multiple catalysis is that the subunits of the catalytic system (such as amines **2** and **3**, Figure 1) are brought together without covalent bonds between them and without chemical synthesis,[14] which is generally needed to prepare a multifunctional chiral catalyst. Expertise is not essential to realize that the preparation of the hybrid catalysts **1** requires substantially more effort than the simple mixing of widely available catalysts **2** and **3** (Figure 2a). With the multiple-catalysis approach, several new catalytic systems are easily accessed in a combinatorial way. A two-dimensional library of 10×12 different catalysts produces 120 catalytic systems. If both these classes of structures present stereoisomers, like the ones depicted in Figure 1 (secondary amines with one chiral center, cinchona alkaloids, which are commercially available as two quasienantiomers derived from quinine or quinidine), the library is enlarged along a third dimension to 480 members.

The improvement of the reaction yield and stereoselection can therefore be achieved by modifying not only the catalyst structure and other parameters, such as temperature and solvent, but also the catalyst configuration (Figure 2b). In this way, an additional feature of the catalytic system can be fine-tuned to the specific reaction. Furthermore, this approach appears attractive in light of the recent development of high-throughput screening methods, which in some cases allow determination of the enantiomeric excesses of up to 30000 samples per day.[14c] Thus multiple catalysis strategy, compared to multifunctional catalysis, can be advantageous because the synthetic efforts needed to prepare the often complex molecules employed as catalysts require the investment of a significant amount of time and resources. It is true that tremendous advances have been achieved in understanding the mechanism of several asymmetric transformations, but it is well accepted that the largest part of optimization of a new asymmetric reaction is empirical and dominated by a trial and error approach. An in-depth rationalization of the mechanism generally occurs a posteriori, only after identification of the best-performing catalysts. Thus, it has little predictive effectiveness.

For the above reason, an approach that permits the easy generation of libraries of catalytic systems is, at least in principle, advantageous with respect to any other method. Furthermore, it is well known that most asymmetric reactions, especially organocatalytic ones, suffer from poor substrate generality, and high stereoselectivity is achieved only in few specific cases.[3l] The stereocontrol exerted by a catalytic system is usually directly proportional to its complexity—as is the case for nature's enzymes—and, therefore, often inevitably associated with a narrow substrate scope (Figure 2c). So, if multifunctional catalysts possess what can be defined as an "entropic gain", since the two or more activating functionalities are brought close together in the same complex molecule, the use of chiral multiple catalysis provides a new feature, the "stereochemical resource". This feature permits generation of tailor-made catalytic systems potentially for any desired transformation (Figure 2a), without the need for lengthy chemical synthesis, thus ultimately allowing achievement of the goal of an efficient asymmetric synthesis. Finally, the screening of several structures by the multiple catalysis approach could be exploited as a "catalyst discovery strategy" to direct the synthesis of especially effective multifunctional catalysts by covalently linking the most effective pair of catalysts in a single molecule.

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Daniele M. Scarpino Schietroma was born in Rome, Italy, in 1986. He graduated in organic chemistry from the "Sapienza" Università di Roma in 2009 and he is now pursuing his PhD at the same institute, under the supervision of Dr. Bella, in the field of new asymmetric reactions.

Marco Bella obtained his PhD from the "Sapienza" Università di Roma (2000), and four days later moved to La Jolla, CA to join the group of K. C. Nicolaou as a postdoctoral fellow. After a second postdoctoral position at Aarhus University with K. A. Jørgensen, he returned back to his hometown as "Ricercatore" (2005) and tries, with a group of young but bright and motivated students, to do his best despite constant research budget cuts.

Figure 2. Comparison between multiple and multifunctional catalysis.

1.2. The Principal and Secondary Catalyst

When two chiral catalysts are simultaneously employed in a given asymmetric transformation, it is often observed that the sense of asymmetric induction essentially depends upon the configuration of only one of the two catalysts. To account for this behavior, we propose herein, the definition of a "principal" catalyst (or ligand) for the catalyst whose inversion of absolute configuration will, as well, invert the absolute configuration of the product; whereas the "secondary" catalyst (or ligand) is the chiral catalyst (or ligand) that only modulates the enantioselectivity without inverting the absolute configuration of the product. For example, in Figure 1, thiazolidine L-**2** is the principal catalyst and quinine **3** is the secondary catalyst (see Section 2.3).

2. Reactions Mediated by Two Chiral Nonracemic Organocatalysts

The success of asymmetric organocatalysts has also been greatly favored because of the mild experimental conditions required to perform the reactions. Additionally, impurities and traces of water are generally well tolerated because organocatalysts are among the most robust catalysts. The simultaneous use of two different chiral units is possible when one does not interfere with the activity of the other and is particularly useful when a synergistic effect is present. It should not be surprising that most of the examples, wherein two chiral catalysts successfully cooperate, belong to organocatalytic reactions.

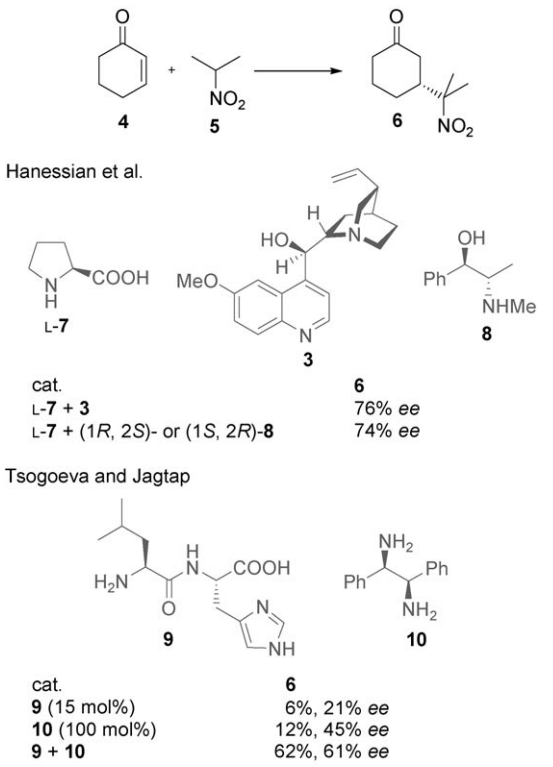
2.1. Early Examples

In 2000 Hanessian et al. described the addition of 2-nitropropane (**5**) to 2-cyclohexen-1-one (**4**) catalyzed by the amino acid L-proline (L-**7**) and a different amine as the secondary catalyst (Scheme 1). Although the best-performing secondary catalyst in terms of enantioselectivity is achiral 2,5-*trans*-dimethylpiperazine, significant enantioselectivity is also obtained with the chiral amines quinine (**3**) and ephedrine (**8**, Scheme 1).[15a]

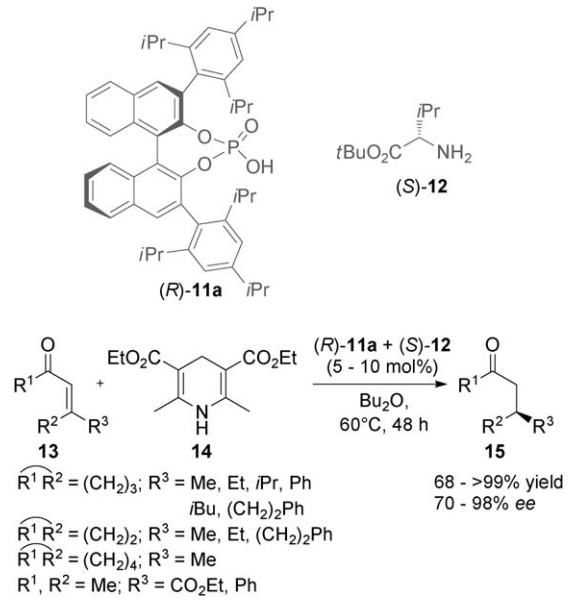
The same reaction was also performed some years later by Tsogoeva and Jagtap, and they employed the dipeptide H-Leu-His-OH (**9**) together with the chiral diamine **10**. The authors highlight the presence of a synergistic effect with respect to the use of a single catalyst (Scheme 1).[15b]

2.2. Activation through Both Iminium Ion Formation and an Acid

One of the easiest methods to assemble a new catalytic system is the reaction between chiral acids and bases. In the last few years such a strategy has become an alternative to Lewis acid activation. Asymmetric catalysis via iminium ion activation was pioneered by MacMillan and co-workers in 2000.[3b] Initially, stereocontrol was pursued by modifying only



Scheme 1. Addition of 2-nitropropane (**5**) to 2-cyclohexen-1-one (**4**) mediated by two different chiral catalysts.



Scheme 2. Asymmetric reduction of α,β-unsaturated ketones **13** with Hantzsch ester **14**.

Table 1: Reaction of **13** ($R^1\widehat{R^2} = (CH_2)_2$; $R^3 = Me$) with the Hantzsch ester **14** (see Scheme 2).

Entry	Catalyst	Yield [%]	*ee* [%]
1[a]	(*S*)-**12** + TFA	66	54
2[b]	H^+ + (*R*)-**11a**	5	20
3[b]	(*S*)-**12** + (*R*)-**11a**	81	94
4[b]	(*S*)-**12** + (*S*)-**11a**	45	16

[a] Reaction run in 1,4-dioxane. [b] Reaction run in Bu_2O.

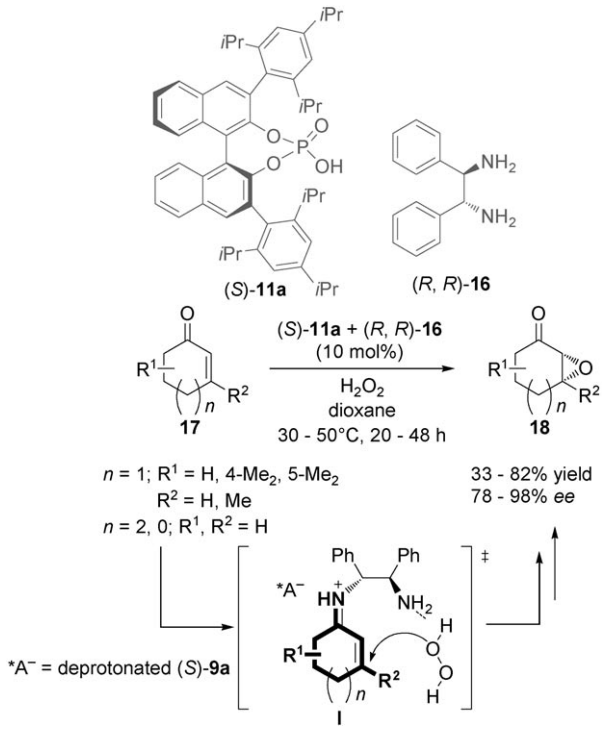
the chiral secondary amine structure. The presence of an acid additive is crucial for the catalytic activation, because the positively charged iminum ion is a better electrophile with respect to the imine. Later it was realized that anions in close proximity to the iminium ion can also effectively shield one of the two enantiotopic faces and therefore the stereocontrol can as well be achieved by means of chiral conjugated bases of acids. This strategy has been defined as asymmetric counter-ion-directed catalysis (ACDC).[16] If both species are chiral, a matched and a mismatched pair can be identified.

An important early example of this strategy was described in a paper that appeared in 2006, in which List and Martin presented a new class of catalytic salts, formed by the binaphthyl phosphoric acid (*R*)-TRIP [(*R*)-**11a**] and the amino acid (*S*)-**12**, that were suitable for the asymmetric reduction of α,β-unsaturated ketones **13** with the Hantzsch ester **14** (Scheme 2).[17] The acid (*R*)-**11a** or amino acid ester (*S*)-**12** are not efficient catalysts individually (Table 1, entries 1 and 2), but a strong synergistic effect is observed when they are employed together (entry 3). Additionally, the amino acid ester (principal catalyst) also shows a matched/mismatched relationship with the secondary catalyst: in fact, the use of (*S*)-**11a**, although not affecting the absolute configuration of the product, significantly decreases the enantioselectivity of the transformation (entry 4).

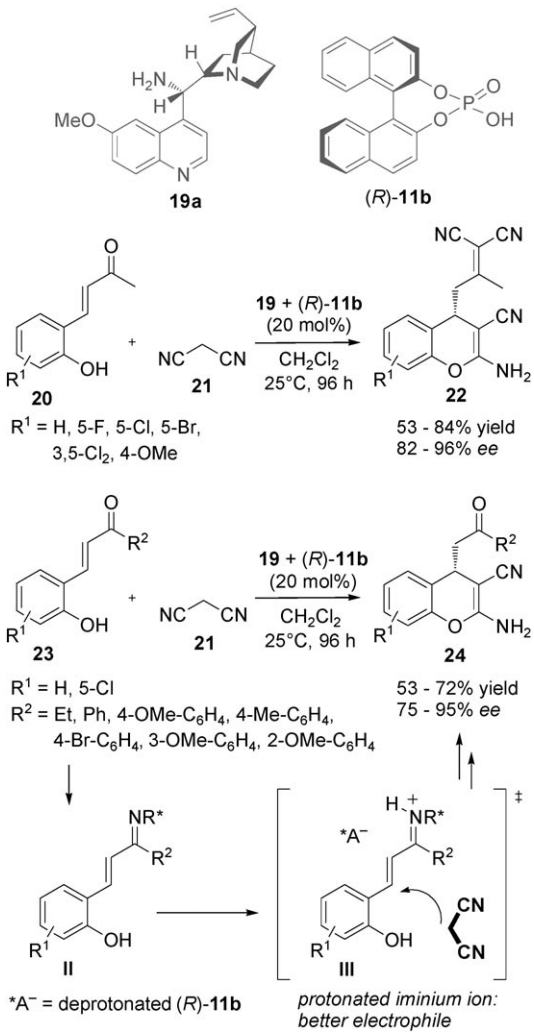
In another work, List et al. reported that (*S*)-**11a** is also suitable for the asymmetric epoxidation of cyclic enones **17** when used as the secondary catalyst along with the chiral diamine (*R*,*R*)-**16** (Scheme 3).In this reaction the principal catalyst, (*R*,*R*)-**16**, activates the electrophile **17** to thus forming the iminium ion **I**, which is subsequently attacked to afford the cyclic product **18**.[18]

The compound (*R*)-**11b**, which is structurally related to (*R*)-**11a**, was used by Xie and co-workers as a secondary catalyst in combination with the cinchona-alkaloid-derived primary amine **19a** (9-amino-9-deoxyepiquinine) to prepare the chromene derivatives **22** and **24** (Scheme 4), which belong to an important class of biologically active molecules.[19a] The desired products were obtained by means of the addition of malonitrile (**21**) to α,β-unsaturated carbonyl compounds **20** and **23**. Primary amine **19a** converts the substrates into the imine **II**, whereas the acid catalyst (*R*)-**11b** protonates the intermediate, thus forming the more electrophilic iminium ion **III** that when attacked by **21**, spontaneously cyclizes to give product **22** or **24**. The enantiomers of the secondary catalyst **11b** both gave similar results when used individually, but when employed as a racemate the enantioselection suffered a significant decrease (Table 2). Recently a similar catalytic system was employed for the asymmetric direct γ-alkylation of α-branched enals.[19b]

The self-assembled salt **26**, developed by Melchiorre et al., represents another application of ACDC in which both cation and anion are chiral. It is prepared by mixing the amine **19b** with the amino acid **25** (Scheme 5). The salt **26** is used to catalyze the Michael addition of different nucleophiles, such



Scheme 3. Catalytic asymmetric epoxidation of cyclic enones **17**.



Scheme 4. Addition of malonitrile (**21**) to α,β-unsaturated carbonyl compounds **20** and **23** to provide chromene derivatives **22** and **24**, respectively.

as indoles,[20] oximes,[21] N-protected hydroxylamines,[22] and thiols.[23]

In a Friedel–Crafts-type alkylation reaction, simple enones **28** add to indoles **27** to afford β-indolyl derivatives **29** with high enantioselectivity (up to 96% *ee*) and the method has a broad substrate scope (Scheme 6a). The screening data indicate that the enantioselectivity depends mostly upon the amine, whereas the amino acid essentially influences the reactivity. Nevertheless, the counterion has a significant effect and the best performance was obtained with D-*N*-Boc phenylglycine (**25a**). The reaction proceeds smoothly and is not particularly affected by the substituent on the enone, whereas the methylation of the indole nitrogen atom decreases both the reactivity and enantioselectivity.

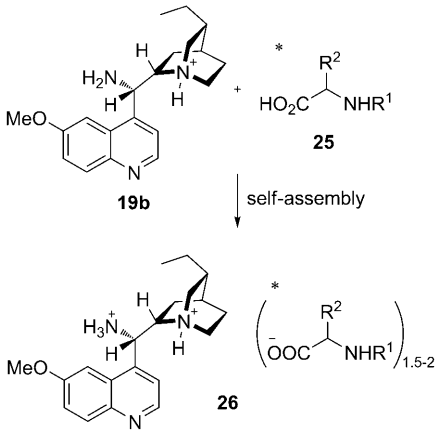
For the addition of hydroxylamines the authors suggest an orthogonal activation mode. The principal catalyst, the chiral primary amine **19b**, activates the enone **28** through the iminium ion formation to promote the addition of the hydroxylamine **30**. The resulting enamine attacks the nitrogen atom to give the substitution of a suitable leaving group, thus affording the desired chiral aziridine **31** in good yields and enantioselectivity (Scheme 6b).[22a] This procedure is direct, performs well with a wide range of simple enones, and is not only restricted to chalcones as in previously reported works.[24] This approach is successful even with 3-methyl-2-cyclohexen-1-one (**32**), which afforded the corresponding congested aziridine **33** bearing a quaternary stereocenter with moderate enantioselectivity (Scheme 6b). Very recently this procedure was improved to access both aziridine antipodes by employing the pseudoenantiomer of **26**.[22b] Melchiorre et al. also reported a new catalytic variant of the sulfa-Michael addition[25] of thiols **34** to α,β-unsaturated ketones **28** (Scheme 6c).[23]

Table 2: Reaction of **20** (R^1 = H) and **21** in THF (see Scheme 4).

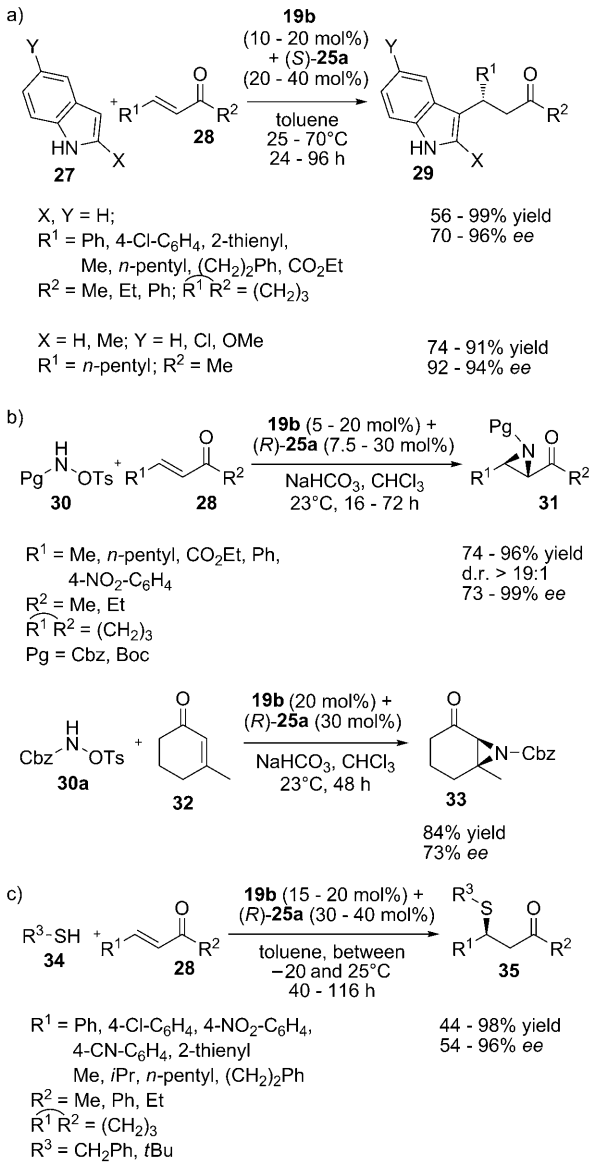
Entry	Catalyst	Yield [%]	*ee* [%]
1	**19** + (*R*)-**11b**	75	88
2	**19** + (*S*)-**11b**	69	87
3	**19** + *rac*-**11b**	76	27

A similar catalytic system was also exploited in an organocatalytic asymmetric vinylogous α-keto rearrangement via a semipinacol-type 1,2-carbon migration (**IV** in Scheme 7) that gave access to spirocyclic diketones **38** bearing an all-carbon quaternary stereocenter.[26]

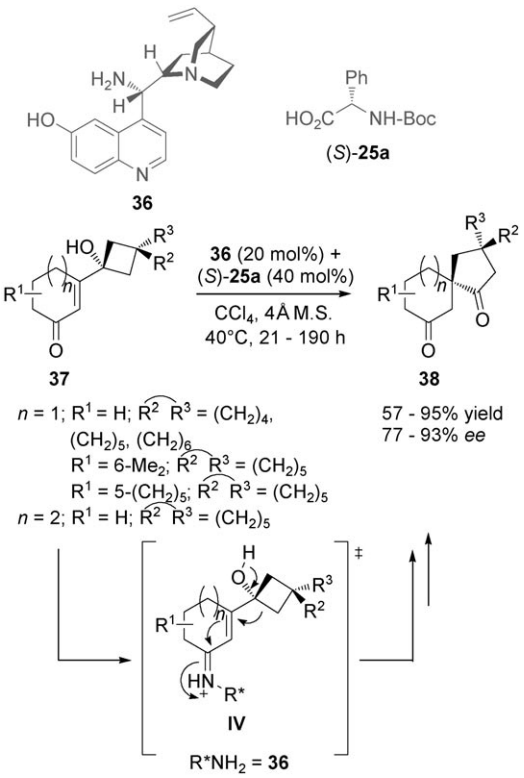
The proline derivative (*S*)-**39** [(*S*)-α,α-diphenylprolinyl trimethylsilyl ether] is used in combination with the chiral acid (*S*)-**40** to form the catalytic salt **V**, which is employed to promote the asymmetric oxa-Michael reaction of α,β-unsaturated aldehydes **41** with salicylaldehydes **42** with a subsequent intramolecular aldol condensation (Scheme 8).[27] The



Scheme 5. Self-assembling catalytic salt **26. 25a**: R^1 = Boc, R^2 = Ph; Boc = *tert*-butoxycarbonyl.



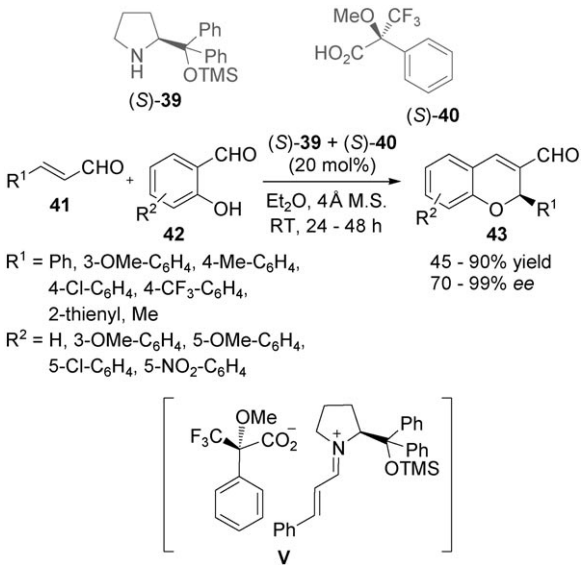
Scheme 6. Enantioselective addition of a) indoles **27**, b) N-protected hydroxylamines **30**, and c) thiols **34** to enones. Cbz = benzyloxycarbonyl, Pg = protecting group, Ts = 4-toluenesulfonyl.



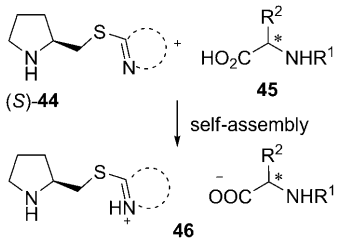
Scheme 7. Organocatalytic asymmetric vinylogous α-keto rearrangement via a semipinacol-type 1,2-carbon migration. M.S. = molecular sieves.

authors again point out the presence of a synergistic effect of the two catalysts influencing the enantioselectivity of this transformation.

Once established that the pyrrolidine motif was useful for the activation of carbonyl compounds, many derivatives that are not commercially available, but can be synthesized quite easily, have been developed to catalyze a wide range of



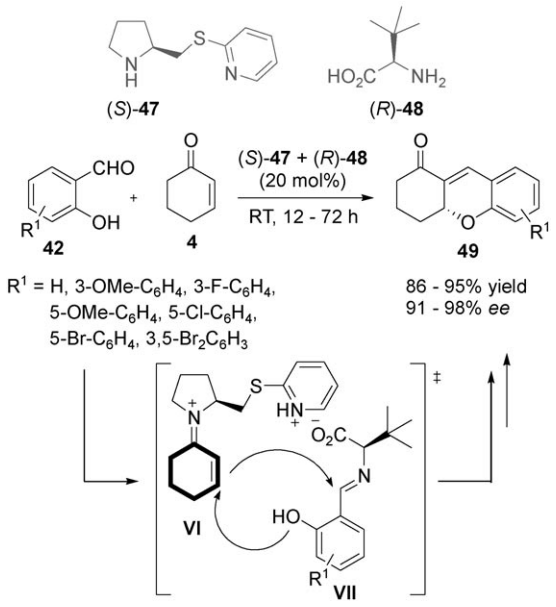
Scheme 8. Asymmetric oxa-Michael reaction of α,β-unsaturated aldehydes **41** and salicylaldehydes **42**. TMS = trimethylsilyl.



Scheme 9. Self-assembled catalyst having a pyrrolidine motif.

Michael reactions.[28] These catalysts may contain functional groups that are able to interact with groups present both on the substrate and on the secondary catalyst to create a self-assembled catalyst such as **46** (Scheme 9).

Recently, bifunctional catalysts assembled from a pyrrolidine and simple amino acids have been developed. In particular, Xu et al. have presented a catalytic system formed by two molecules [(*S*)-**47** and (*R*)-**48**; Scheme 10)] that both possess an amine moiety suitable to activate the substrates via the iminium **VI** and enamine **VII** catalysis, respectively. In this way, the salicyl aldehydes **42** react with 2-cyclohexen-1-one (**4**) to obtain differently substituted tetrahydroxanthenones **49** in good yield and enantioselectivity.[29] The absolute configuration of the products is determined by the principal catalyst (*S*)-**47** and the configuration of the amino acid **48** has a minor role; both catalysts are necessary to achieve high yield and enantioselectivity (Table 3).



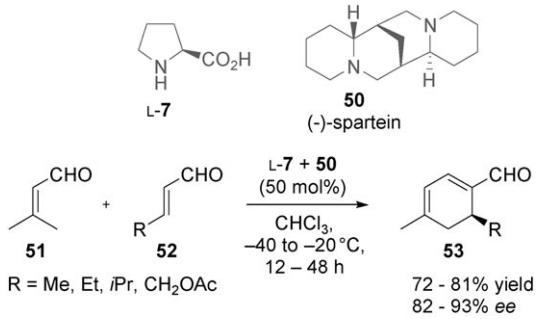
Scheme 10. Reaction of salicyl aldehydes **42** with **4** to obtain differently substituted tetrahydroxanthenones **49**.

2.3. Activation through Both Enamine Formation and a Base

As previously described, in the enamine activation by chiral secondary amines acids are generally employed as co-catalysts.[30] Recently, some researchers have shown that a base additive could also be beneficial. In particular, tertiary amines enhance the nucleophilic character of the enamine by deprotonation and effectively shield one of the enantiotopic faces of the intermediate, thus improving the stereoselectivity. Hong et al. report one of the early examples of this strategy employing L-proline (L-**7**) and (−)-sparteine (**50**) in the organocatalytic Robinson condensation of α,β-unsaturated aldehydes to obtain a precursor for the total synthesis of the natural substance (+)-palitantine (Scheme 11).[31]

Table 3: Reaction of salicyl aldehyde **42** ($R^1 = H$) and **4** (see Scheme 10).

Entry	Catalyst	Solvent	Yield [%]	*ee* [%]
1	(*R*)-**48**	1,4-dioxane	trace	–
2	(*S*)-**47**	1,4-dioxane	48	60
3	(*S*)-**47** + (*R*)-**48**	1,4-dioxane	>99	88
4	(*S*)-**47** + (*S*)-**48**	CH_3CN	3	84
5	(*S*)-**47** + (*R*)-**48**	CH_3CN	37	86

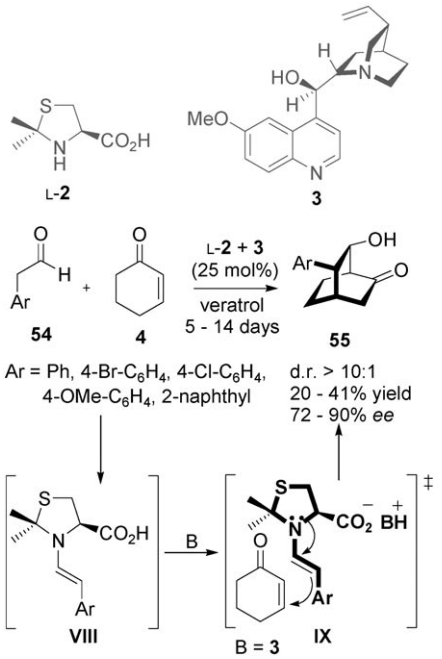


Scheme 11. Organocatalytic Robinson condensation of α,β-unsaturated aldehydes.

Likewise, Bella et al. report a formal [4 + 2] cycloaddition of substituted arylacetaldehydes **54** and 2-cyclohexen-1-one (**4**) that is promoted by the thiazolidine L-**2** and quinine **3** via enamine formation (**VIII**) and spontaneous intramolecular aldol reaction (**IX**; Scheme 12).[10b] The stereoselection depends upon the secondary amine L-**2**, whereas the secondary catalyst is involved in the enhancement of the nucleophilicity of the derived enamine, probably through deprotonation of the carboxylic group. There is a synergistic effect in the contemporary use of the two catalysts **L-2** and **3** because neither of them is able to efficiently promote the reaction alone (Table 4).

2.4. Activation through Both Iminium and Enamine Formation

Kotsuki et al. describe an organocatalytic Robinson annulation mediated by the diamine (*S*,*S*)-**56** and the dicarboxylic acid (*S*,*S*)-**57** (Scheme 13).[32] The diamine (*S*,*S*)-**56** is the principal catalyst and promotes the addition of the aldehydes **58** to the α,β-unsaturated ketones **59** by means of a double activation of both substrates (aldehyde **58** via enamine and ketone **59** via iminium ion **X**), and the cyclization



Scheme 12. Formal [4+2] cycloaddition of substituted arylacetaldehydes **54** and **4**.

Table 4: Reaction of **54** (Ar = Ph) and **4** (see Scheme 12).

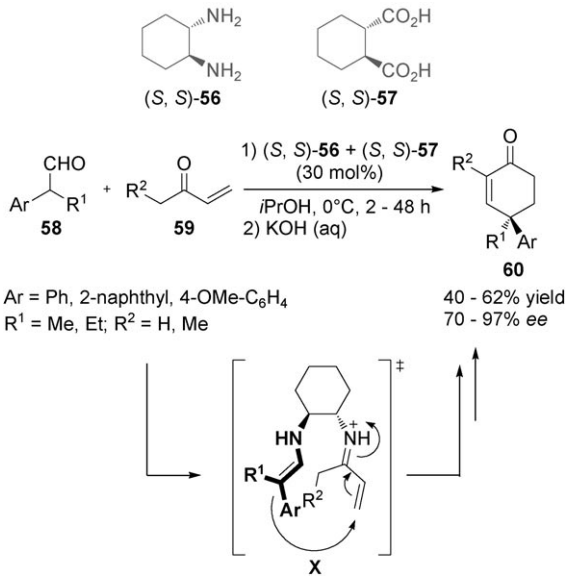
Entry	Catalyst	Solvent	d.r.	Yield [%]	*ee* [%][a]
1	L-**2**	toluene	–	n.r.	–
2	3	toluene	–	n.r.	–
3	L-**2**/Li salt	toluene	1:1.2	23	−63
4	L-**2**+**3**	veratrol[b]	<1:10	41	−87

[a] A negative *ee* value indicates formation of the enantiomer. [a] 1,2-dimethoxy benzene. n.r. = no reaction.

spontaneously occurs after the hydrolysis of the intermediates.

2.5. Activation through Both Iminium Ion/Enamine Formation and Hydrogen Bonding

The possibility of combining the advantages of multifunctional catalysis with the simplicity of the self-assembled catalyst approach has turned out to be an attractive feature. The salt obtained from thioureido cinchona alkaloid derivative **62a** and an amino acid is an example of this approach. This catalytic system is used by Zhao and Mandal in the direct addition of carbonyl compounds **63** to nitroalkenes **64**, a reaction chosen as a model to point out the advantages of this strategy (Scheme 14),[33] that is, exploiting two orthogonal activation modes: hydrogen bonding and enamine catalysis. The reaction proceeds smoothly with a wide range of substrates, thanks to the versatility of a modularly designed catalytic system wherein the amino acid, (*S*)-**61** or L-**7**, activates the carbonyl compound, and the thiourea **62a** interacts with the nitro group of the Michael acceptor through hydrogen bonding (transition-state **XI**). The absolute configuration of the products depends on the amino acid used, which can therefore be considered the principal catalyst. The authors also highlight that amino acid derivatives lacking the carboxylic moiety fail to react, probably because they are unable to interact with the secondary catalyst and form the self-assembled structure.



Scheme 13. Organocatalytic Robinson annulation.

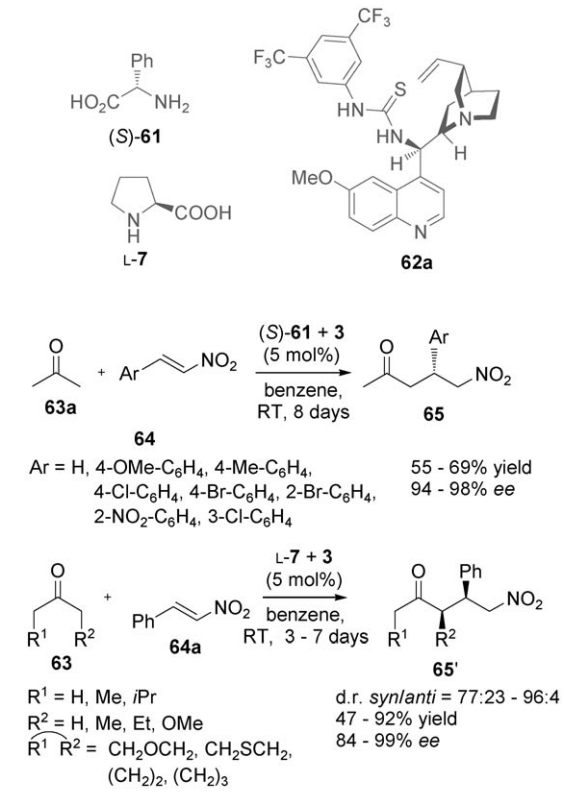
For the same reaction Xu and co-workers employ (*S*)-**66** as the principal catalyst, a molecule characterized by the presence of a pyrrolidine moiety and an imidazolyl moiety, with the latter being able to form an ion pair with the carboxylic group belonging to the secondary catalyst (thioureido acid (*R*)-**62b** or (*R*)-**62c**; Scheme 15).[34] A recurrent feature of this work, as of others previously mentioned, is a synergistic effect of the two modules and the possibility of matched/mismatched ion pairs of the catalysts. The same approach was also used to catalyze the addition of cyclic ketones **69** to nitrodienes **70** (Scheme 15).[35]

Two catalysts were also employed for the allylic–allylic alkylation of Morita–Baylis–Hillman carbonates **74** with α,α-dicyanoalkenes **73** and **76** (Scheme 16).[36] The enantioselectivity depends on the dimeric cinchona alkaloid derivative **72**, whereas the acid additive (*S*)-**11c** is necessary to improve the yield and the enantioselectivity of the reaction which proceeds through the transition-state **XII.**

3. Reactions Mediated by Two Chiral Nonracemic Metal Catalysts or Ligands

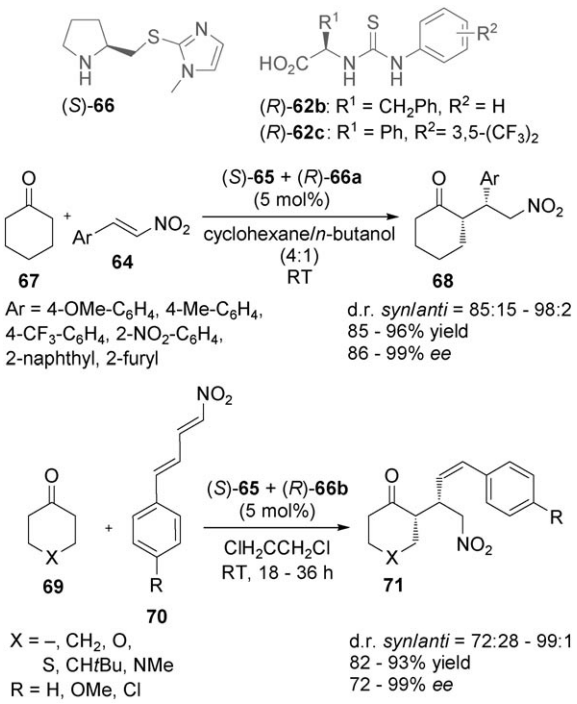
The use of two different metal catalysts is possible when the relative stability of each complex prevents cross-exchange between their ligands. With respect to mixing two purely organic catalysts, this strategy is less common and so far only limited examples are present in the literature.

As mentioned in the introduction, a catalytic system built by two separate chiral binding sites for the electrophilic and nucleophilic partners of a given reaction, in this case an

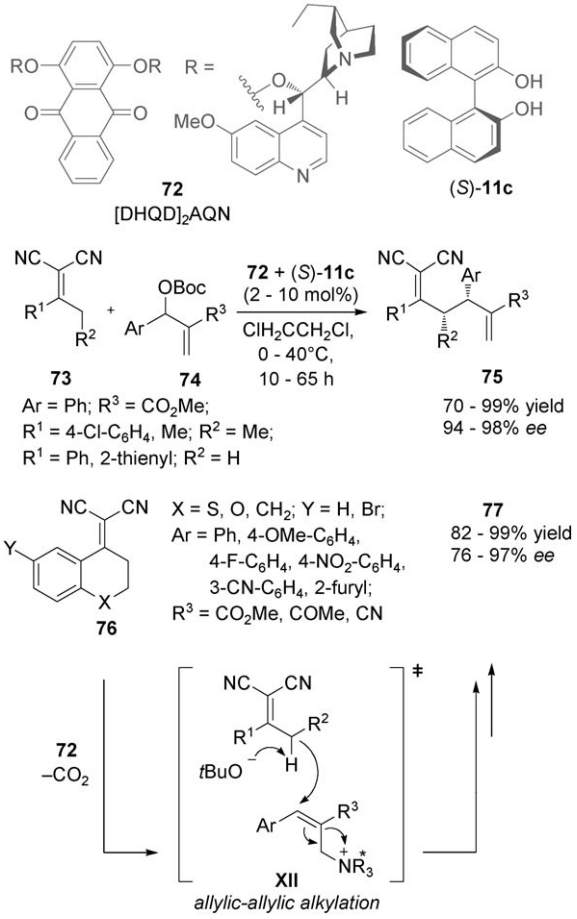


Scheme 14. Direct addition of carbonyl compounds **63** to nitroalkenes **64**.

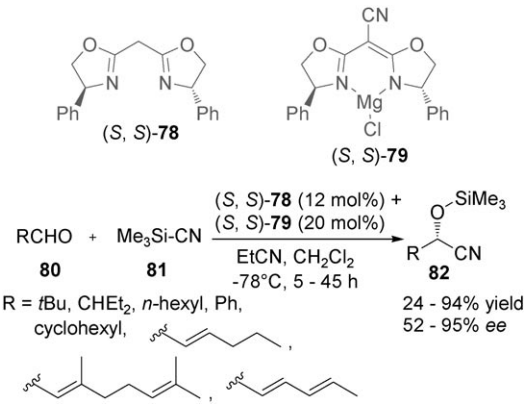
aldehyde and a cyanide donor, was already employed by Corey and Wang for the synthesis of enantioenriched cyanohydrins in 1993.[11] The two chiral units were bis(oxazoline) (*S*,*S*)-**78** and bis(oxazoline) magnesium complex (*S*,*S*)-**79** (Scheme 17). When employed alone, (*S*,*S*)-**79** gave good conversion but moderate enantioselectivity (65% *ee*, Table 5, entry 1), whereas (*S*,*S*)-**78** gave little conversion and completely racemic products (entry 2). On the contrary, a strong synergistic effect was observed if the homochiral compounds (*S*,*S*)-**79** and (*S*,*S*)-**78** were employed together, thus achieving 94% *ee* (entry 3). The use of (*R*,*R*)-**78** led to poor selectivity (38% *ee*, entry 4). According to the authors, these experiments show that the highly stereoselective formation of product **82** is due to the activation of the aldehyde by



Scheme 15. Addition of cyclic ketones **67** and **69** to nitroalkenes **64** and nitrodienes **70**, respectively.



Scheme 16. Allylic–allylic alkylation of Morita–Baylis–Hillman carbonates **74** with α,α-dicyanoalkenes **73** and **76**.



Scheme 17. Synergistic effect in the addition of Me_3SiCN (**81**) to aldehydes **80** mediated by two chiral units.

Table 5: Effect of the catalyst combination on the addition of Me_3SiCN (**81**) to aldehyde **80** (R = cyclohexyl; see Scheme 17).

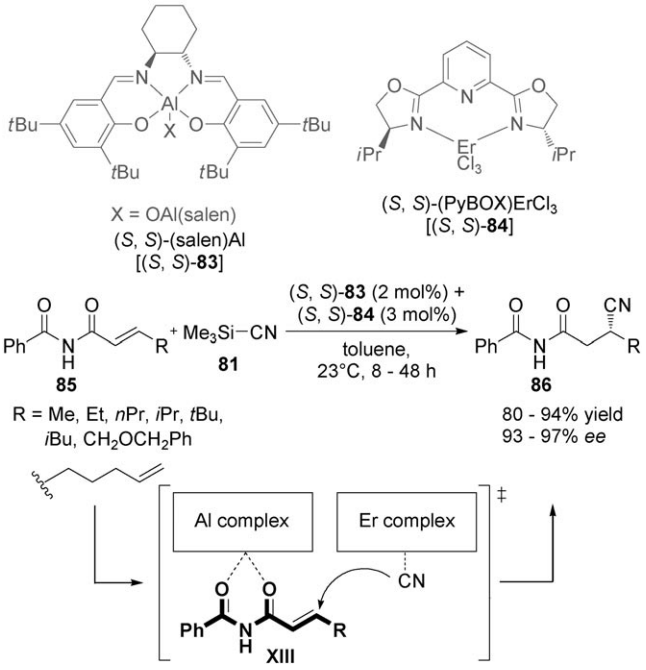
Entry	Catalyst	Yield [%]	*ee* [%]
1	(*S*,*S*)-**79**	85	65
2	(*S*,*S*)-**78**	n.d.[a]	0
3	(*S*,*S*)-**78** + (*S*,*S*)-**79**	95	94
4	(*R*,*R*)-**78** + (*S*,*S*)-**79**	90	38

[a] n.d. = not determined.

coordination to the Mg complex (*S*,*S*)-**79** that then reacts with an activated source of "chiral" cyanide ion derived from interaction with (*S*,*S*)-**78**.

3.1. Two Distinct Metal Complexes

Catalytic systems comprising a chiral ligand and two distinct metals (hetero-bimetallic complexes) are largely exploited to mediate diverse asymmetric reactions and this area has already been reviewed.[6a,c] The catalysis by two distinct metals, each one coordinated by its own chiral ligand, is a general design principle. It is clear that the success of such an approach relies on the possibility of avoiding ligand exchange between the two complexes. The (salen)Al complex **83** and PyBOX lanthanide **84** were simultaneously employed by Jacobsen and co-workers to mediate the asymmetric conjugate addition of cyanide to unsaturated imides **85** via the transition-state **XIII** (Scheme 18).[37] Minimal conversion was observed by employing either **83** or **84** (Table 6, entries 1, 2), whereas the combination of their *S*,*S* stereoisomers led to adduct **86** in almost quantitative yield and high enantioselectivity (96% *ee*, entry 3). The aluminum complex can be seen as the principal catalyst and when used with (*R*,*R*)-**84** as secondary catalyst, there was a small amount of catalytic activity (lower conversion after 3.5 h, 20% versus 87%) but especially decreased enantioselectivity (72% *ee*, entry 4). An intermediate value of enantioselectivity was achieved when a racemic mixture of the secondary catalysts **84** was used. The authors defined this approach as cooperative dual metal catalysis and, according to them, no other related reaction had



Scheme 18. Cooperative dual metal catalysis for the enantioselective Michael addition of cyanide to imides **85**.

Table 6: Effect of the catalyst combination on the enantioselective Michael addition of cyanide to imide **85** (R = *n*Pr; see Scheme 18).

Entry	Catalyst	Conv.[a]	Conv.[b]	*ee* [%]
1	(*S*,*S*)-**83**	–	< 3	n.d.[c]
2	(*S*,*S*)-**84**	–	< 3	16
3	(*S*,*S*)-**83** + (*S*,*S*)-**84**	87	99	96
4	(*S*,*S*)-**83** + (*R*,*R*)-**84**	20	99	72

[a] After 3 hours. [b] After 24 hours. [c] n.d. = not determined.

appeared within this category prior to the publication of their manuscript.

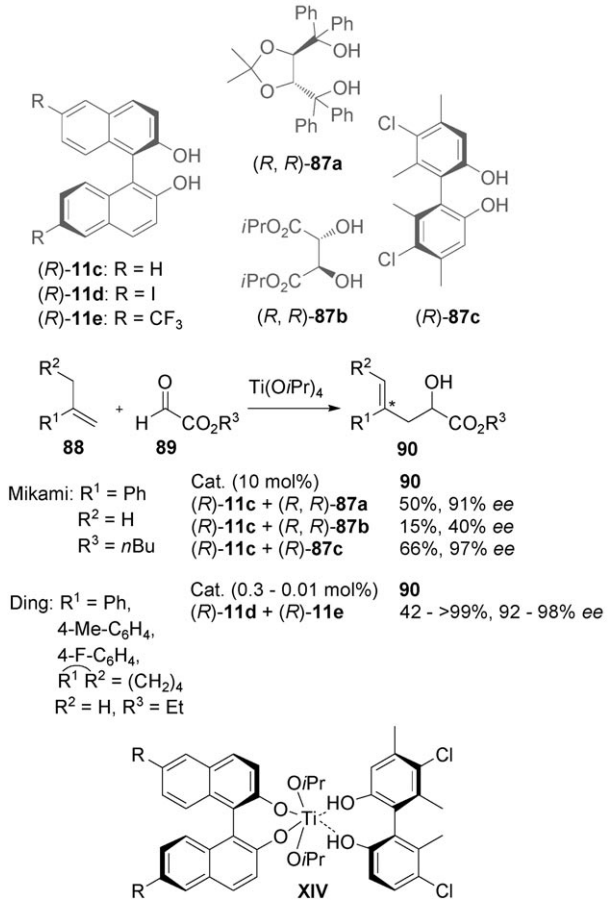
3.2. One Metal and Two Chiral Ligands

The examples in which two chiral ligands are assembled in a complex with a single transition metal are more abundant. The complexity of several organometallic catalytic systems renders the identification of the best-performing catalyst a process that is mostly driven by trial and error rather than rational design. Currently, the small energy differences between the two diastereotopic transition states leading to the two enantiomers of a product molecule are difficult to calculate, even with the most effective computational methods available. Among the new strategies emerging to tackle this problem, a very effective one relies on metal complexes of hetero-bidentate ligands as an alternative to those of simple bidentate ligands.[38] The advantage of such an approach is the possibility of applying combinatorial methods to catalyst discovery. Testing the various stereoisomers of the ligands adds a new dimension to the screening process, thus increasing the diversity of the system. The advantages and

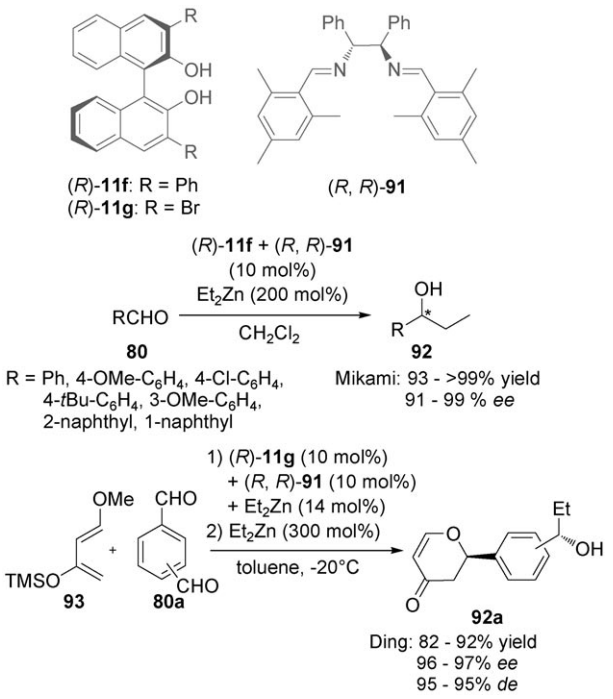
implications of using libraries built by the self-assembly of ligands and a single metal, as well as the theoretical foundation of this approach have already been reviewed by Ding et al.[39] We highlight herein some selected examples where two different chiral nonracemic ligands are employed and the consequences of using chiral ligands.

In 1997 Mikami and co-workers reported one of the early examples of this strategy by describing a highly stereoselective carbonyl–ene reaction mediated by two different chiral diols as ligands coordinated to a titanium catalyst (**XIV** in Scheme 19).[40]

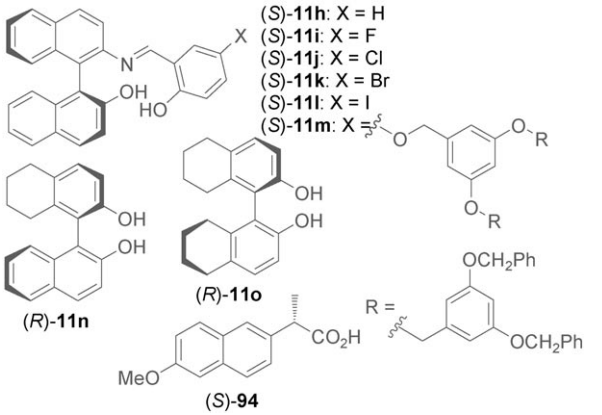
Since then, other reports have appeared and, though describing different reactions, a common motif can be identified: the binaphthols **11** are used as a chiral ligand for the metal center. For instance, Ding et al. have developed a new quasi-solvent-free version of the carbonyl–ene reaction wherein the second chiral ligand is another binaphthol (Scheme 19).[41] Binaphthol derivatives have also been employed in combination with diimine (*R*,*R*)-**91** for diethylzinc additions [binaphthyl (*R*)-**11 f**, Scheme 20];[42] or for the hetero Diels–Alder reaction/diethyl zinc addition [(*R*)-**11 g** Scheme 20].[43] Several other binaphthyl derivatives (**11**; Scheme 21) can be exploited in combination with chiral acids [(*S*)-**94**] to mediate a related transformation between diene **93** and aromatic aldehydes **80** (Scheme 22 and Table 7).[44,45]



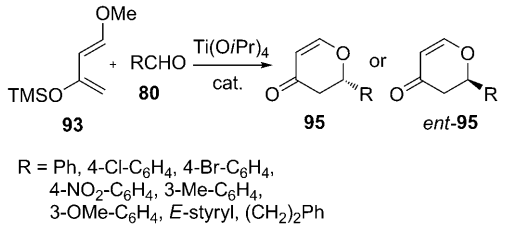
Scheme 19. Carbonyl–ene reactions reported by the groups of Mikami[40] and Ding.[41]



Scheme 20. Diethylzinc addition to aldehydes **80** (Mikami)[42a] and the tandem hetero-Diels–Alder/diethylzinc addition reaction to **80 a** (Ding).[42b,c]



Scheme 21. Chiral catalysts for the hetero Diels–Alder reaction of diene **93** with aldehydes **80** (see Scheme 22).



Scheme 22. Hetero Diels–Alder reaction of diene **93** with aldehydes **80**.

Asymmetric hydrogenation is one of the oldest and most important industrial asymmetric reactions. There has been an enormous effort in academia to identify the best and most

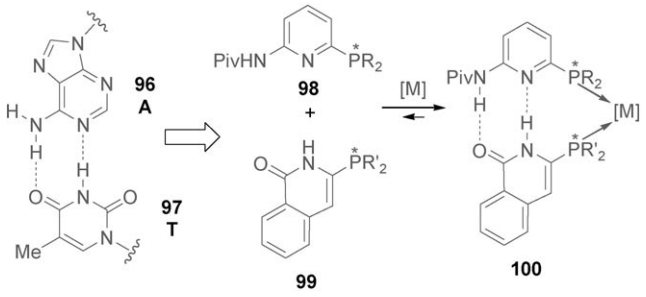
Table 7: Hetero Diels–Alder reaction of diene **93** and aldehydes **80** (for R see Scheme 22)

Entry	Catalyst	Product	Yield [%]	*ee* [%]	Ref.
1[a]	(*S*)-**11h**[b] + (*S*)-**94**[c]	**95**	81–>99	75–97	[38]
2[a]	(*S*)-**11i**[b] + (*S*)-**94**[c]	**95**	81–>99	76–94	[38]
3[a]	(*S*)-**11j**[b] + (*S*)-**94**[c]	**95**	81–>99	62–96	[38]
4[a]	(*S*)-**11k**[b] + (*S*)-**94**[c]	**95**	57–>99	43–96	[38]
5[a]	(*S*)-**11l**[b] + (*S*)-**94**[b]	**95**	50–>99	61–96	[38]
6[d]	(*R*)-**11n** + (*R*)-**11o**	**95**	82–>99	97–98	[38]
7[e]	(*S*)-**11m**[b] + (*S*)-**94**[c]	**95**	>99	64–97	[39]
8[d]	(*R*)-**11n** + (*R*)-**11o**	*ent*-**95**	57–>99	97–>99	[40]

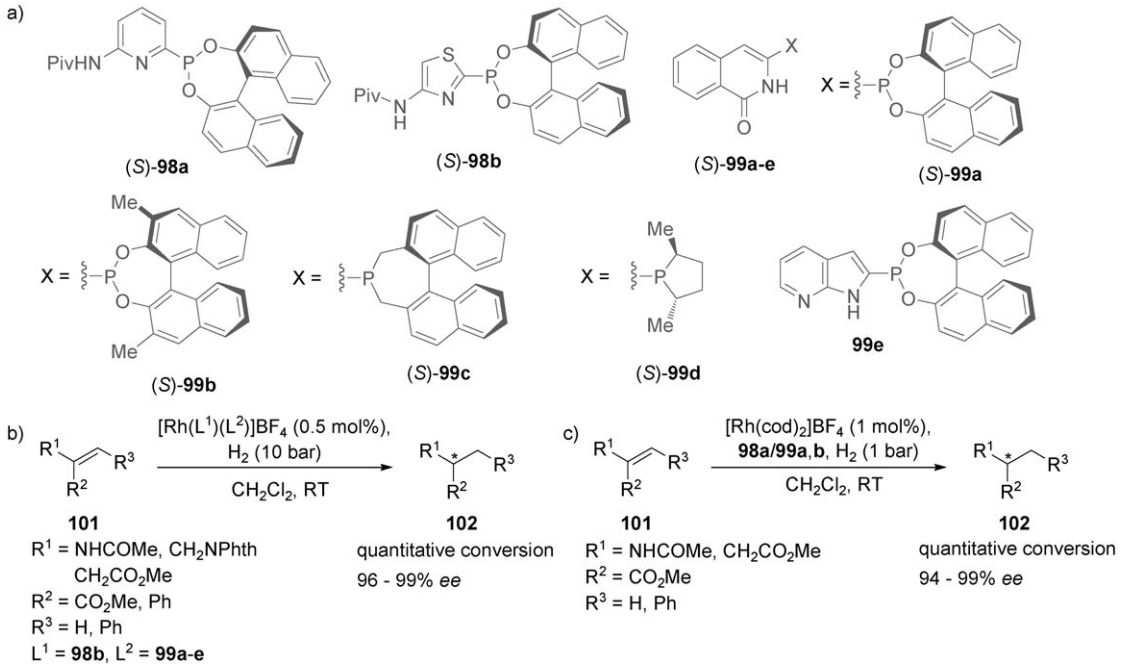
[a] $Ti(OiPr)_4$ (10 mol%), toluene, RT, 4 Å M.S. [b] 20 mol%. [c] 5 mol%. [d] $Ti(OiPr)_4$, catalyst loading 0.05 mol%, 24–96 h, RT. [e] $Ti(OiPr)_4$ (10 mol%), toluene, 48 h.

general catalytic system. An approach for the search of effective catalytic systems, based on hetero-bidentate ligands for rhodium, has been pioneered by the groups of Breit and Reek. In a recent report Breit and Wieland describe, how two ligands are assembled through complementary hydrogen bonding(**98**+**99**→**100**; Scheme 23), thereby mimicking the self assembly of DNA bases (e.g., **96** and **97**).[46a] According to their hydrogen-bond properties, two classes of ligands can be identified, that is, acceptor–donor (AD, **98**) or donor–acceptor (DA, **99**), and they were used to build a 10×12 library (Scheme 24a). This approach is even more attractive considering that, although the 120 combinations of ligands could actually be tested individually in a parallel screening, a combinatorial approach, where more sets of ligands are mixed together, would allow a faster screening and the identification of the most catalytically active species (Scheme 24b). In this specific work, the issue of ligand configuration was addressed by Breit and Wieland in an early stage of the screening process by identifying the homochiral *S,S* combination as the one giving the highest enantioselectivity. However, in an early publication by the same group[46b] (Scheme 24c), it was highlighted that it cannot be assumed whether the homochiral or heterochiral combination will perform better, because the matching pair can be different for each specific couple of ligands and for each substrate.

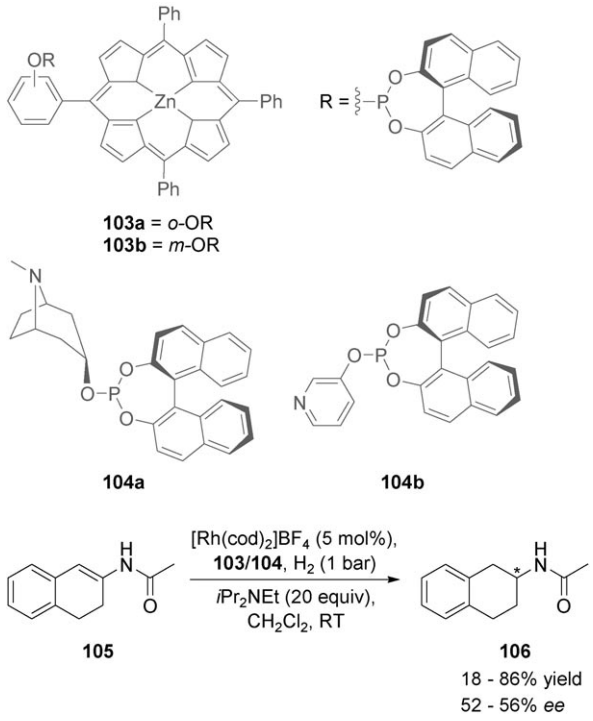
In a paper published at about the same time, Reek and coworkers described the identification of the more-effective catalysts for the asymmetric hydrogenation of a difficult enamide substrate (Scheme 25).[46c] The authors examined only marginally the stereochemical matched/mismatched effects; nevertheless, they identified a very effective ligand combination. However, it can be foreseen that an extended screening, which includes the ligand configuration, can be very helpful if the best-performing combination is not found, or when an especially difficult substrate is examined.



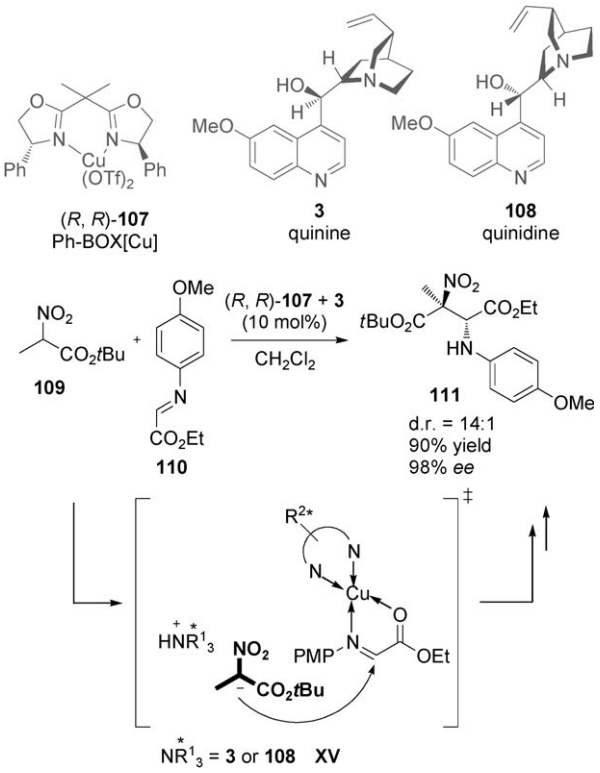
Scheme 23. Self-assembly of an A–T pair of DNA and chiral metal ligands through hydrogen bonds. Piv = pivaloyl.



Scheme 24. a) Ligands used in the reactions of (b) and (c). b) Asymmetric hydrogenation by self-assembled ligand/rhodium complexes. c) Asymmetric hydrogenation by a rhodium complex; cod = 1,5-cyclooctadiene.



Scheme 25. Asymmetric hydrogenation of enamide **105** using a library of catalysts derived from the self-assembly of compounds **103a**,**b** and **104a**,**b**.



Scheme 26. Addition of nitroalkane **109** to imine **110**. PMP = *para*-methoxyphenyl, Tf = trifluoromethanesulfonyl.

4. Reactions Mediated by the Combination of a Metal Catalyst, an Organocatalyst, and an Enzyme

Hybrid systems comprising organocatalysts and metal catalysts can effectively work if true orthogonality is achieved, especially when the organic molecule does not act as ligand for the transition-metal ion. The development of such mixed systems has not been straightforward, because the majority of the organocatalysts initially employed were amines, which in most cases are also strong ligands.

Several groups have extensively studied the asymmetric aza-Henry (nitro-Mannich) reaction catalyzed by metal complexes.[47] When organocatalysts were used, achieving a high diastereoselection was quite challenging.[48] In 2005 Knudsen and Jørgensen developed a highly stereoselective addition of the nitroalkane **109** to imine **110** by employing a mixed catalytic system formed by the metal complex (*R*,*R*)-**107** and the cinchona alkaloid quinine **3** (Scheme 26).[49] This reaction is an example of how chiral amines and chiral metal complexes can effectively cooperate without interfering with one another. Although product **111** bears two adjacent chiral carbon centers, a quaternary one and a tertiary one, it is formed in high yield (90%), diastereo- (d.r. = 14:1) and enantioselectivity (98% *ee*, Table 8, entry 1).

The inversion of the absolute configuration of the product is observed when using the enantiomer of the metal chiral ligand [(*S*,*S*)-**107**, thus the principal catalyst; entry 2], and when the quinidine **108** is used as a secondary catalyst a decrease in the diastereoselection is observed (entry 3). The proposed intermediate **XV** is depicted in Scheme 26.

Table 8: Addition of nitroalkane **109** to imine **110** (see Scheme 26).

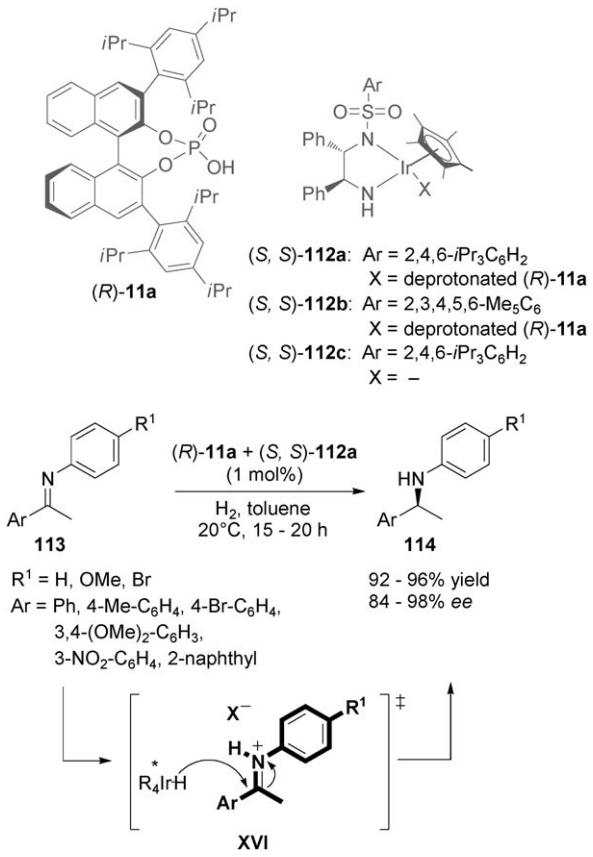
Entry	Catalyst	Yield [%]	d.r.	*ee* [%]
1	(*R*,*R*)-**107** + **3**	90	14:1	98
2[a]	(*S*,*S*)-**107** + **3**	76	8.5:1	−93
3	(*R*,*R*)-**107** + **108**	80	8.5:1	96

[a] *ent*-**111** was formed.

The development of weaker ligands, in particular of chiral Brønsted acids, offers new opportunities for the application of mixed systems.

The reduction of acyclic imines and imines generated in situ has been performed by means of organocatalytic[50] and metal-complex-based methods.[51] In this context the use of mixed catalytic systems represents a new approach. For example, Xiao et al. exploited the contemporary usage of a chiral iridium complex and a binaphthol-derived phosphoric acid in two important papers.[52,53] In the first article, they describe the hydrogenation of acyclic imines **113** employing the catalytic system (*R*)-**11a**/(*S*,*S*)-**112a** and suggesting the transition-state **XVI** (see Scheme 27).[52]

It should be noted that iridium complex (*S*,*S*)-**112c** does not catalyze the reaction when used alone (Table 9, entry 1), but with the addition of the chiral phosphoric acid (*R*)-**11a** compound **114** is obtained with good conversion and high enantioselectivity (entry 2). There is also a strong matched/mismatched effect as both the conversion and stereoselection of this reaction decrease when (*R*,*R*)-**112c** is used (entry 3). When the catalyst (*S*,*S*)-**112a** was used along with the



Scheme 27. Asymmetric reduction of imines **113**.

Table 9: Asymmetric hydrogenation of imine **113** (R^1 = OMe, Ar = Ph; see Scheme 27).

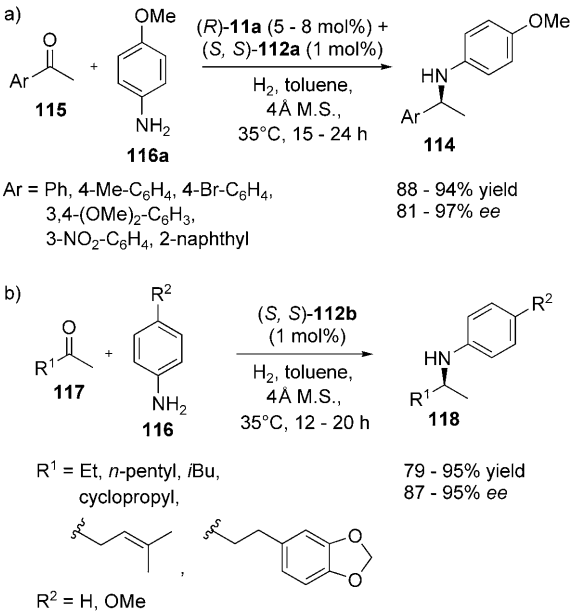
Entry	Catalyst	Conv. [%]	*ee* [%]
1	(*S*,*S*)-**112c**[a]	0	–
2	(*S*,*S*)-**112c**[a] + (*R*)-**11a**[b]	60	97
3	(*R*,*R*)-**112c**[a] + (*R*)-**11a**[b]	47	−38[c]
4	(*S*,*S*)-**112a**[a] + (*R*)-**11a**[d]	92	97

[a] 1 mol%. [b] 6 mol%. [c] A negative *ee* value indicates formation of the enantiomer. [d] 1 mol%.

conjugate base of (*R*)-**11a** the product **114** was obtained with almost complete conversion and high enantioselectivity (entry 4).

In the second publication, which appeared one year later, the direct asymmetric reductive amination (DARA) of prochiral ketones in a one-pot strategy was described (Scheme 28a).[53] Notably, for the DARA of alkyl methyl ketones the catalyst (*S*,*S*)-**112b** gave better results in terms of yield and stereoselection when used without (*R*)-**11a** (Scheme 28b).

The discovery of new synthetic methodologies to introduce fluorine atoms into organic skeletons has become an important target in organic chemistry. Substances with high enantiopurity are usually obtained by means of an enantioselective epoxidation with a subsequent epoxide opening by either fluoride derivatives[54] or HF-containing reagents and a salen/metal complex as the catalyst;[55] however, the epoxide



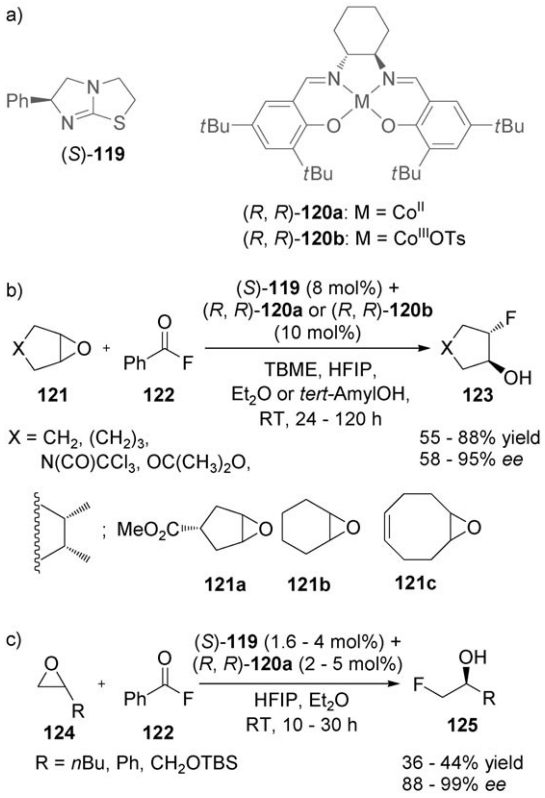
Scheme 28. DARA of asymmetric ketones.

opening in the presence of a fluoride source is still quite challenging. Recently Doyle and Kalow described an elegant asymmetric ring opening of epoxides **121** by combining two different activation strategies, namely N-heterocyclic carbene and Lewis acid catalysis. For this reaction the authors employed either (*R*,*R*)-**120a** or (*R*,*R*)-**120b** and the amine (*S*)-**119** (Scheme 29a) as the catalysts in presence of benzoyl fluoride **122**, which serves as a the latent fluoride source.[56]

The opening of achiral epoxides **121**(Scheme 29b) proceeded in good yield (up to 88%, Table 10, entry 1) and enantioselectivity (up to 95% *ee*, entry 2), but when the enantiomer of the metal complex [(*S*,*S*)-**120a**; the principal catalyst) was used, there was a notable mismatched effect (7% yield, 22% *ee* compared to 64% yield, 77% *ee*, entries 3 and 4). The kinetic resolution of the terminal epoxide **124** also showed very high yield and good enantioselectivity (Scheme 29c).

Enzymes are "perfect machines" that nature uses to obtain products with excellent enantiopurity. In organic chemistry they can be useful alternatives to newly synthesized catalysts and several researchers have studied their applicability in different reactions.[57] The combination of an enzyme with organic or organometallic molecules is still a relatively unexplored field. In this area, Córdova et al. have worked out a one-pot procedure involving L-proline (L-**7**) in the first step of the reaction and the enzyme Amano I (**126**; lipase extracted from *Pseudomonas cepacia*) in the second step (Scheme 30).[58] The aldol reaction between aldehydes **80** and acetone **63a**[3a] proceeds via **XVII**, and then the subsequent kinetic resolution of **XVIII** affords the desired products with good yield and excellent enantioselectivity.

The addition of α-ketonitriles **131** to aldehydes **80**, mediated by the metal catalyst (*S*,*S*)-**129**, organocatalysts DBU or DMAP, and the enzyme **130**, is a similar example (Scheme 31).[59] The salen/metal complex promotes the addition of **131** to **80**, and the enzyme selectively hydrolyzes the



Scheme 29. a) Catalysts used in the reactions of (b) and (c). b) Asymmetric ring opening of epoxides **121** and c) kinetic resolution of terminal epoxides **124**. HFIP = hexafluoro-2-propanol, TBME = *tert*-butyl methyl ether, TBS = *tert*-butyldimethylsilyl.

Table 10: Asymmetric ring opening of epoxides **121** (see Scheme 29).

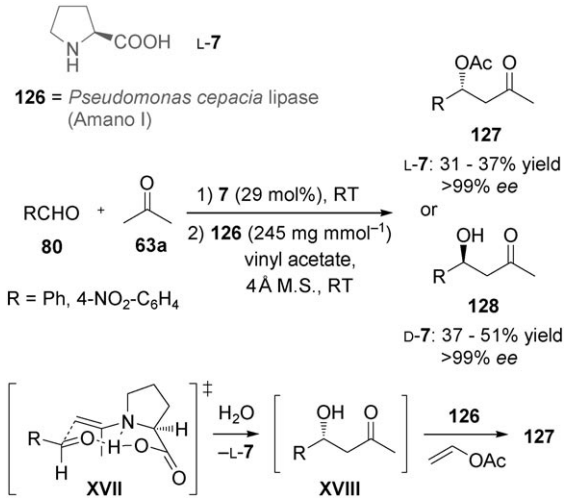
Entry	Product	Catalyst	Yield [%]	*ee* [%]
1	**123a**	(*R*,*R*)-**120b** + **119**	88	86
2	**123b**	(*R*,*R*)-**120b** + **119**	87	95
3	**123c**	(*S*,*S*)-**120a** + **119**	7	−22[a]
4	**123c**	(*R*,*R*)-**120a** + **119**	64	7

[a] A negative *ee* value indicates formation of the enantiomer.

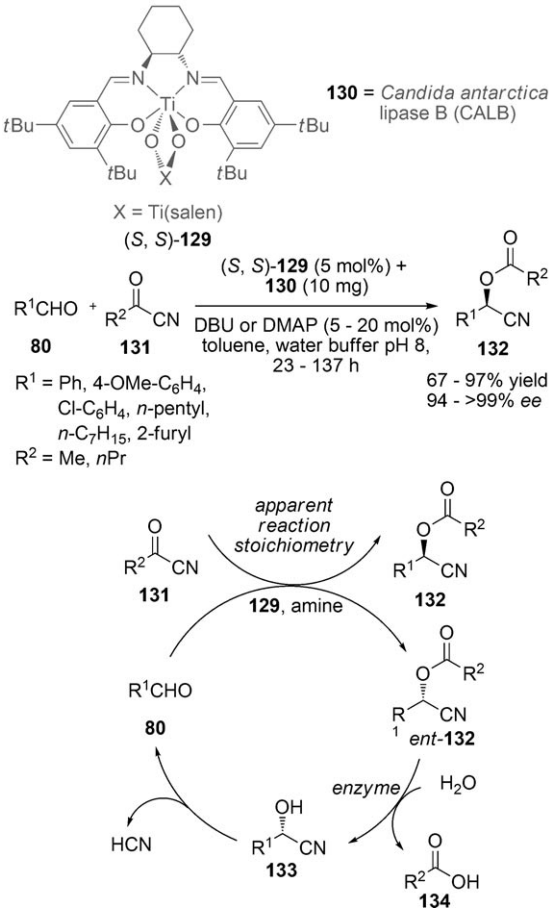
minor enantiomer of the product (*ent*-**132**) by removing the carboxylic acid **134**. In this way the undesired enantiomer is converted back into the aldehyde, which can enter the catalytic cycle again. This allows one to obtain products in high yield and with excellent enantioselection.

5. Conclusion and Outlook

The use of chiral multiple catalysts in asymmetric synthesis is a new emerging trend, as evidenced by the publication of an increasing number of papers belonging to this field, even during the preparation of this review. The search of a new efficient asymmetric catalyst can be the limiting factor in research performed either in academia or in industry. In this context, an empirical approach based on chiral multiple catalysis can be a viable choice, especially for a newly discovered asymmetric reaction. If the reaction mechanism is investigated in depth and the intermediates are known, then considerable investment of time required to prepare a multifunctional catalyst can be worth the effort. A



Scheme 30. Aldol reaction and kinetic resolution of **80** and **63a** catalyzed by **7** and the enzyme Amano I (**126**).



Scheme 31. Stereoselective addition of α-ketonitriles **131** to aldehydes **80**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = *N*,*N*-dimethylamino pyridine.

combinatorial approach based on chiral multiple catalysis could also be effective when dealing with very complex systems, such as hetero-bidentate transition-metal complexes (see Section 3.2) where the current level of computational analysis is not developed enough to predict the small difference of energy between the diastereotopic transition states. In conclusion, chiral multiple catalysis is an efficient strategy, at least for the transformations illustrated in this review, and could be considered a complementary approach to multifunctional catalysis.

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[1] a) *Asymmetric Synthesis Vol. 1–5* (Ed.: J. D. Morrison), Academic Press, New York, **1983–1985**; b) J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**; c) *Handbook of Chiral Chemicals, 2nd ed.* (Ed.: D. J. Ager), Marcel Dekker, New York, **2005**. For a general review see: d) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734.

[2] See the Nobel Lectures K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2126; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024; R. Noyori, *Angew. Chem.* **2002**, *114*, 2108; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008; W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998; and M. Beller, C. Bolm, *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, 2nd ed.*, *Vol. 1 and 2*, Wiley-VCH, Weinheim, **2004**. For reviews of recent advancements in transition-metal catalysis, see: D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; S. Das, G. W. Brudvig, R. H. Crabtree, *Chem. Commun.* **2008**, 413; S. Dez-Gonzlez, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.

[3] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; For general reviews on organocatalysis, see: c) P. L. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; d) special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*(8); e) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis:From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; f) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 5573; g) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; h) special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, 5413; i) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; j) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; k) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; l) M. Ueda, T. Kano, K. Maruoka, *Org. Biomol. Chem.* **2009**, *7*, 2005; m) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583; n) B. List, *Angew. Chem.* **2010**, *122*, 1774; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730.

[4] For organocatalytic syntheses of natural products and biologically active molecules, see: a) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575. Examples of metal catalyzed syntheses of natural products: b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; c) Y. Yamamoto, K. Yamashita, T. Hotta, T. Hashimoto, M. Kikuchi, H. Nishiyama, *Chem. Asian J.* **2007**, *2*, 1388; d) Z. Lu, S. M. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258; e) B. A. Arndtsen, *Chem. Eur. J.* **2009**, *15*, 302; f) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193.

[5] a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; b) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999.

[6] a) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; b) J.-H. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566; c) M. Shibasaki, M. Kanai, S. Matsunaga, *Aldrichimica Acta* **2006**, *39*, 31; d) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117.

[7] a) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496; b) S. J. Connon, *Chem. Commun.* **2008**, 2499; c) A. Lattanzi, *Chem. Commun.* **2009**, 1452; d) P. S. Bhadury, B. A. Song, S. Yang, D. Y. Hu, W. Xue, *Curr. Org. Synth.* **2009**, *6*, 380; e) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393; f) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; g) S. Matsunaga, M. Shibasaki, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60.

[8] a) M. L. Clarke, J. A. Fuentes, *Angew. Chem.* **2007**, *119*, 948; *Angew Chem. Int. Ed.* **2007**, *46*, 930; b) J. Zhou, *Chem. Asian J.* **2010**, *5*, 422.

[9] We are unaware of any example with three or more chiral catalysts.

[10] a) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; b) M. Bella, D. M. Scarpino Schietroma, P. P. Cusella, T. Gasperi, V. Visca, *Chem. Commun.* **2009**, 597.

[11] E. J. Corey, Z. Wang, *Tetrahedron Lett.* **1993**, *34*, 4001.

[12] For a comprehensive review, see: T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464; *Angew. Chem. Int. Ed.* **2009**, *48*, 456.

[13] For a classification of the activation mechanisms in organocatalysis and metal catalysis, see Ref. [3f].

[14] For leading references on the self assembly and the combinatorial screening on multiple catalysts, see: a) R. H. Crabtree, *Chem. Commun.* **1999**, 1611; b) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292; *Angew. Chem. Int. Ed.* **2001**, *40*, 284; c) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814; *Angew. Chem. Int. Ed.* **2003**, *42*, 790; d) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071; e) C. Jaekel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912; f) M. T. Reetz, *Angew. Chem.* **2008**, *120*, 2592; *Angew. Chem. Int. Ed.* **2008**, *47*, 2556; g) J. Meeuwissen, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 615..

[15] a) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; b) S. B. Tsogoeva, S. B. Jagtap, *Synlett* **2004**, *14*, 2624.

[16] S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193.

[17] N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368.

[18] X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070.

[19] a) J.-W. Xie, X. Huang, L.-P. Fan, D.-C. Xu, X.-S. Li, H. Su, Y.-H. Wen, *Adv. Synth. Catal.* **2009**, *351*, 3077; b) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685.

[20] G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.

[21] A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492.

[22] a) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703; b) F. De Vincentiis, G. Bencivenni, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Galzerano, P. Melchiorre, *Chem. Asian J.* **2010**, *5*, 1652.

[23] P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49.

[24] a) H. Sugihara, K. Daikai, X. L. Jin, H. Furuno, J. Inanaga, *Tetrahedron Lett.* **2002**, *43*, 2735; b) L. Ma, D.-M. Du, J. Xu, *J. Org. Chem.* **2005**, *70*, 10155; c) J. X. Xu, L. G. Ma, P. Jiao, *Chem. Commun.* **2004**, 1616.

[25] Catalytic versions of the sulfa-Michael reaction are less developed than the corresponding stoichiometric chiral auxiliary methodologies; for catalytic sulfa-Michael reactions, see: a) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417; b) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87; c) K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *J. Am. Chem. Soc.* **2007**, *119*, 12974.

[26] E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang, Y.-L. Song, *J. Am. Chem. Soc.* **2009**, *131*, 14626.

[27] S.-P. Luo, Z.-B. Li, L.-P. Wang, Y. Guo, A.-B. Xia, D.-Q. Xu, *Org. Biomol. Chem.* **2009**, *7*, 4539.

[28] a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; b) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; c) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2002**, *4*, 3611; d) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; e) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955; f) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147; g) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808; h) S. Mossé, A. Alexakis, *Org. Lett.* **2005**, *7*, 4361; i) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66; j) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Chem. Commun.* **2006**, 1563; k) C. Palomo, S. Vera, A. Mielgo, E. Gomez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984; l) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559; m) C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039; n) E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717; o) B. Ni, Q. Zhang, A. D. Headley, *Green Chem.* **2007**, *9*, 737; p) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555; *Angew. Chem. Int. Ed.* **2008**, *47*, 545.

[29] A.-B. Xia, D.-Q. Xu, S.-P. Luo, J.-R. Jiang, J. Tang, Y.-F. Wang, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 801.

[30] S. Bertelsen, N. Halland, S. Bachmann, M. Marigo, A. Braunton, K. A. Jørgensen, *Chem. Commun.* **2005**, 4821.

[31] B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su, J.-H. Liao, *J. Org. Chem.* **2007**, *72*, 8459.

[32] a) Y. Inokoishi, N. Sasakura, K. Nakano, Y. Ichikawa, H. Kotsuki, *Org. Lett.* **2010**, *12*, 1616. For the same transformation employing a proline-derived sulfonamide and an achiral benzylamine base, see: b) H. Yang, R. G. Carter, *Org. Lett.* **2010**, *12*, 3108.

[33] T. Mandal, C.-G. Zhao, *Angew. Chem.* **2008**, *120*, 7828; *Angew. Chem. Int. Ed.* **2008**, *47*, 7714.

[34] D.-Q. Xu, H.-D. Yue, S.-P. Luo, A.-B. Xia, S. Zhang, Z.-Y. Xu, *Org. Biomol. Chem.* **2008**, *6*, 2054.

[35] Z.-B. Li, S.-P. Luo, Y. Guo, A.-B. Xia, D.-Q. Xu, *Org. Biomol. Chem.* **2010**, *8*, 2505.

[36] H.-L. Cui, J. Peng, X. Feng, W. Du, K. Jiang, Y.-C. Chen, *Chem. Eur. J.* **2009**, *15*, 1574.

[37] G. M. Sammis, H. Danjo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 9928.

[38] a) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek, *Angew. Chem.* **2003**, *115*, 5777; *Angew. Chem. Int. Ed.* **2003**, *42*, 5619; b) J. N. H. Reek, M. Röder, P. E. Goudriaan, P. C. J. Kamer, P. W. N. M. van Leeuwen, V. F. Slagt, *J. Organomet. Chem.* **2005**, *690*, 4505; c) B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608; d) C. Waloch, J. Wieland, M. Keller, B. Breit, *Angew. Chem.* **2007**, *119*, 3097; *Angew. Chem. Int. Ed.* **2007**, *46*, 3037.

[39] K. L. Ding, H. F. Du, Y. Yuan, *Chem. Eur. J.* **2004**, *10*, 2872; K. L. Ding, *Chem. Commun.* **2008**, 909.

[40] K. Mikami, S. Matsukawa, T. Volk, M. Terada, *Angew. Chem.* **1997**, *109*, 2936; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2768.

[41] Y. Yuan, X. Zhang, K. Ding, *Angew. Chem.* **2003**, *115*, 5636; *Angew. Chem. Int. Ed.* **2003**, *42*, 5478.

[42] a) K. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, *111*, 519; *Angew. Chem. Int. Ed.* **1999**, *38*, 497; b) H. Du, K. Ding, *Org. Lett.* **2003**, *5*, 1091; c) H. Du, X. Zhang, Z. Wang, K. Ding, *Tetrahedron* **2005**, *61*, 9465.

[43] Y. Yuan, J. Long, J. Sun, K. Ding, *Chem. Eur. J.* **2002**, *8*, 5033.

[44] B. Ji, Y. Yuan, K. Ding, J. Meng, *Chem. Eur. J.* **2003**, *9*, 5989.

[45] J. Long, J. Hu, X. Shen, B. Ji, K. Ding, *J. Am. Chem. Soc.* **2002**, *124*, 10.

[46] a) J. Wieland, B. Breit, *Nat. Chem.* **2010**, *2*, 832; b) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188; c) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223.

[47] a) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843; b) K. Yamada, G. Moll, M. Shibasaki, *Synlett* **2001**, 980.

[48] a) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3080; *Angew. Chem. Int. Ed.* **2001**, *40*, 2992; b) M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418; c) T. Okino, S. Nakamura, T. Furukuwa, Y. Takamoto, *Org. Lett.* **2004**, *6*, 625; d) T. P. Yoon, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 470; *Angew. Chem. Int. Ed.* **2005**, *44*, 466.

[49] K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362.

[50] a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; b) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.

[51] a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) H.-U. Blaser, F. Spinder in *Handbook of Homogeneous Hydrogenation* (Eds.: G. J. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, p 1193.

[52] C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450.

[53] C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967.

[54] a) S. Hara, T. Hoshio, M. Kameoka, M. Sawaguchi, T. Fukuhara, N. Yoneda, *Tetrahedron* **1999**, *55*, 4947; b) K. Miokami, S. Ohba, H. Ohmura, *J. Organomet. Chem.* **2002**, *662*, 77; c) S. Ghilagaber, W. N. Hunter, R. Marquez, *Org. Biomol. Chem.* **2007**, *5*, 97.

[55] S. Bruns, G. Haufe, *J. Fluorine Chem.* **2000**, *104*, 247.

[56] J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 3268.

[57] C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Elsevier, Oxford, **1994**.

[58] M. Edin, J.-E. Bäckvall, A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 7697.

[59] E. Wingstrand, A. Laurell, L. Fransson, K. Hult, C. Moberg, *Chem. Eur. J.* **2009**, *15*, 12107.

