Synergistic effect of binary component ligands in chiral catalyst library engineering for enantioselective reactions†

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This article highlights our recent efforts in the development of highly efficient and cost-effective chiral catalysts for asymmetric reactions through a combinatorial approach by assembling the component ligands (at least one of which is in non-racemic form, while the other might be optically pure, racemic or achiral) with metal ions to generate modular chiral catalyst libraries. The synergistic effect of the binary ligands in terms of both enantioselectivity and activity of the catalysis has been observed in a variety of catalyst systems, including catalysts containing Ti(IV), Zn(II), Rh(I) or Ru(II) ions, for asymmetric hetero-Diels–Alder, carbonyl–ene, alkylation, and hydrogenation reactions, respectively.

Introduction

The development of efficient methodologies for providing optically active products is of great interest to both academia and industry due to the ever-increasing demand for chiral chemicals.[1,2] Among the various approaches employed for this purpose, asymmetric catalysis using chiral metal complexes represents one of the most general and attractive strategies in terms of chirality economy and environmental considerations. To achieve highly efficient and enantioselective catalysis of a target reaction, the chiral catalyst has to be well-tuned to make a perfect match among metallic ion, chiral ligand, additive, substrate and so on. This is often an unpredictable and challenging endeavor. Accordingly, the successful development of an efficient chiral catalyst usually relies on the combination of rational design, intuition, persistence, and experience, as well as a great deal of trial and error. Hence, adoption of diversity-based strategies for generating and screening a large number of chiral metallic complexes (chiral catalyst library) is essential and important. Another important consideration in favor of the creation of a chiral catalyst library is in regard to the catalyst scope and adaptability because there is no single catalyst that is universal to all substrates. Therefore, generation and screening of a combinatorial library of chiral metallic complexes for the target reaction and taking advantage of its diversity and efficiency may provide a potentially powerful approach to the discovery of highly efficient and enantioselective catalysts.[3]

In the past few years, we have systematically practised this chemistry[3e] by focusing on the strategy for the engineering of a chiral catalyst library through the assembly of binary component ligands with metal ions (Fig. 1). The attractive feature of this strategy lies in the ease of generating considerable catalyst

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† Dedicated to Professor Yangjie Wu on the occasion of his 80th birthday.

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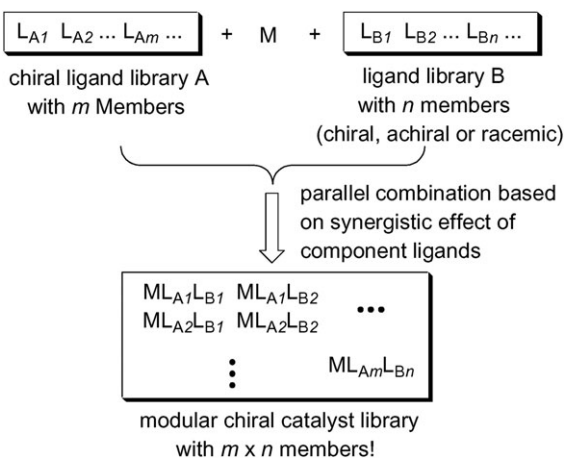


Fig. 1 Generation of a chiral catalyst library based on the synergetic effect of the component ligands.

diversity, which makes the fine-tuning of electronic and steric features of catalysts more convenient to achieve high activity and enantioselectivity of the catalysis. In a more general sense, any catalytic asymmetric transformation, where the enantioselectivity-determining transition state is capable of simultaneously accommodating two ligands, or requires the cooperation of two ligands, could potentially be optimized by tuning the ligand components. In terms of the practicality of the chiral catalysts, the use of achiral or racemic ligands is a more advisable choice of the component ligands in the creation of a chiral catalyst library because enantiopure ones are normally expensive. Accordingly, the cooperative or synergistic effect between the binary component ligands through a central metal ion is the key point for attaining a high level of enantioselective control in the catalysis. Herein we will provide an account of our efforts in the engineering of a chiral catalyst library based on the synergistic effect of binary component ligands.

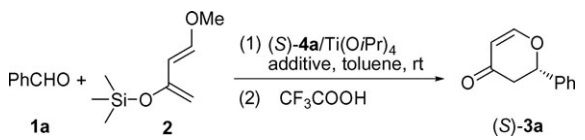
Engineering the chiral catalyst library with two enantiopure ligands

Synergistic effect of carboxylic acid additives on tridentate Ti(IV) catalyzed enantioselective hetero-Diels–Alder reaction

Enantioselective hetero-Diels–Alder (HDA) reaction of carbonyl compounds with 1,3-dienes constitutes one of the most important asymmetric C–C bond forming reactions in organic synthesis, and various chiral Lewis acidic metal complexes have been employed for this type of reaction.[4] The reaction between aldehydes **1** and Danishefsky's diene **2** provides a powerful access to 2-substituted 2,3-dihydro-4*H*-pyran-4-ones (**3**), a type of heterocycle with extensive synthetic applications in natural or unnatural products. In the development of NOBIN-derived (NOBIN = 2-amino-2′-hydroxy-1,1′-binaphthyl) chiral tridentate Schiff base ligands for Ti-catalyzed HDA reaction of Danishefsky's diene with aldehydes, we serendipitously discovered that benzoic acid exhibited a dramatically beneficial effect on the activity and enantioselectivity of the reaction promoted by Ti/(*S*)-**4a** complex (Table 1).[5]

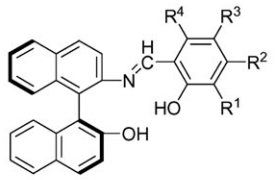
Inspired by this observation, a library of 22 tridentate ligands **4a–v** (Fig. 2) and a library of 36 carboxylic acid additives were set up to optimize the titanium catalyst through

Table 1 Effect of benzoic acid on chiral Schiff base–Ti(IV) catalyzed asymmetric HDA reaction[a]



Entry	MS 4A	Benzoic acid (%)	Yield (%)	Ee (%)
1	0	0	46	1
2	+	0	34	13
3[b]	0	0	75	68
4	+	5	80	85
5	+	10	69	78

[a] All of the reactions were carried out with ligand/$Ti(O^iPr)_4$/substrate = 0.2 : 0.1 : 1 at room temperature. [b] Aged benzaldehyde was used.



(*S*)-**4**

(*S*)-**4a**: R^1, R^2, R^3, R^4 = H
(*S*)-**4b**: R^1, R^3 = Cl, R^2, R^4 = H
(*S*)-**4c**: R^1, R^3= Br, R^2, R^4 = H
(*S*)-**4d**: R^1, R^3 = I, R^2, R^4 = H
(*S*)-**4e**: R^3 = F, R^1, R^2, R^4 = H
(*S*)-**4f**: R^3 = Cl, R^1, R^2, R^4 = H
(*S*)-**4g**: R^3 = Br, R^1, R^2, R^4 = H
(*S*)-**4h**: R^3 = I, R^1, R^2, R^4 = H
(*S*)-**4i**: R^1 = OCH_3, R^2, R^3, R^4 = H
(*S*)-**4j**: R^2 = OCH_3, R^1, R^3, R^4 = H
(*S*)-**4k**: R^3 = OCH_3, R^1, R^2, R^4 = H
(*S*)-**4l**: R^1 = CH_3, R^2, R^3, R^4 = H
(*S*)-**4m**: R^3 = CH_3, R^1, R^2, R^4 = H
(*S*)-**4n**: R^1 = *t*-Bu, R^2, R^3, R^4 = H
(*S*)-**4o**: R^3 = *t*-Bu, R^1, R^2, R^4 = H
(*S*)-**4p**: R^1, R^3 = *t*-Bu, R^2, R^4 = H
(*S*)-**4q**: R^1 = *t*-Bu, R^3 = CH_3, R^2, R^4 = H
(*S*)-**4r**: R^1 = Br, R^3 = CH_3, R^2, R^4 = H
(*S*)-**4s**: R^1 = Br, R^3= OCH_3, R^2, R^4 = H
(*S*)-**4t**: R^1 = Br, R^3 = *t*-Bu, R^2, R^4 = H
(*S*)-**4u**: R^1 = OCH_3, R^3= Br, R^2, R^4 = H
(*S*)-**4v**: R^3 - R^4 = -$(CH)_4$-, R^1, R^2 = H

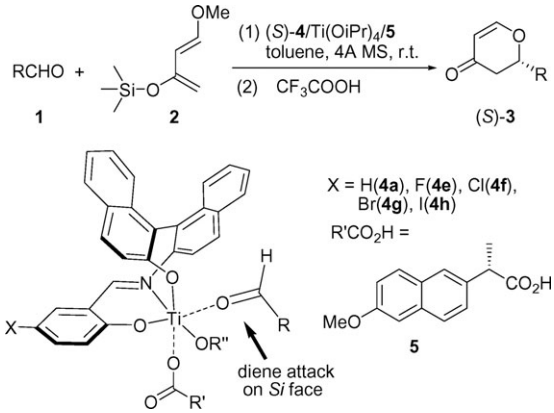
Fig. 2 A library of tridentate Schiff base ligands.

ligand and additive diversity. Considering that a thorough evaluation of all possible combinations ($22 \times 36 = 792$) would be a time-consuming process, we adopted a representational search strategy[3a] for upgrading the library. Thus, the catalysts prepared from the ligand library (*S*)-**4a–v** were first screened in the presence of benzoic acid and 4 Å molecular sieve (MS). The best results (ee = 85–91%) were achieved by using ligands (*S*)-**4a**, (*S*)-**4e–h** and (*S*)-**4m**. Subsequently, the screening of carboxylic acid additives disclosed that the optimal one was a chiral carboxylic acid, (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (Naproxen, **5**), giving (*S*)-**3a** in quantitative yield with 97% ee, although achiral carboxylic acid could improve the enantioselectivity in many cases. A catalyst prepared by combining (*R*)-**4a**, $Ti(O^iPr)_4$ and **5** showed much lower enantioselectivity (*R*, 76% ee) for the reaction, indicating the mismatched chirality of ligand and additive in this case.

Finally, the catalysts prepared by combination of the superior Schiff base ligands (*S*)-**4a**, (*S*)-**4e–h** and (*S*)-**4m** with $Ti(O^iPr)_4$ and the best additive **5** in the presence of 4 Å MS were evaluated for the HDA reaction. It was found that the catalysts derived from (*S*)-**4a** and (*S*)-**4e–h** showed excellent activity and enantioselectivity for the reaction, affording (*S*)-**3a** in quantitative yield and 93–97% ee. The substrate scope of the reaction was then extended to a variety of aldehydes using the above optimized catalysts, affording the corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones (**3**) in good to excellent yields and enantioselectivities (Table 2).[5]

The investigation of the quantitative effect of carboxylic acid additive on the reaction rate showed that the chiral acid additive **5** could enhance the reaction rate by one order of magnitude, which clearly indicated the remarkable synergetic effect of carboxylic acids. Another important feature of this type of catalyst system is the existence of a very strong positive nonlinear effect[6] in both HDA and aldol-type reactions.[7] On the basis of structural information of homochiral and heterochiral titanium complexes, as well as their reactivity difference with carboxylic acid **5**, the positive nonlinear effect

Table 2 The activated Schiff base–Ti(IV) catalysts for HDA reaction of aldehydes with Danishefsky's diene[a]



R in **1**	Yield % (Ee %)				
	4a/Ti/**5**	**4e**/Ti/**5**	**4f**/Ti/**5**	**4g**/Ti/**5**	**4h**/Ti/**5**
Ph (**a**)	>99 (97)	>99 (93)	>99 (97)	>99 (96)	>99 (96)
4-ClC_6H_4 (**b**)	>99 (96)	>99 (85)	94 (93)	>99 (93)	>99 (93)
4-BrC_6H_4 (**c**)	98 (95)	81 (77)	>99 (93)	>99 (95)	97 (95)
4-$O_2NC_6H_4$ (**d**)	91 (83)	85 (83)	91 (88)	93 (90)	91 (86)
3-BrC_6H_4 (**e**)	83 (85)	95 (92)	90 (91)	51 (69)	77 (92)
3-MeC_6H_4 (**f**)	81 (85)	94 (94)	91 (95)	87 (96)	78 (91)
3-$MeOC_6H_4$ (**g**)	96 (92)	94 (93)	>99 (91)	97 (91)	96 (91)
2-$MeOC_6H_4$ (**h**)	>99 (81)	>99 (80)	>99 (82)	>99 (55)	85 (57)
2-Furyl (**i**)	90 (75)	98 (71)	59 (63)	51 (45)	>99 (87)
PhCH=CH (**j**)	96 (83)	>99 (92)	94 (86)	93 (91)	>99 (93)
$PhCH_2CH_2$ (**k**)	83 (75)	81 (76)	81 (61)	57 (42)	50 (61)

[a] All of the reactions were carried out with (*S*)-**4**/Ti(O^{i}Pr)$_4$/**5**/substrate = 0.2 : 0.1 : 0.05 : 1 in toluene in the presence of 4A MS at room temperature.

has been rationalized using Fig. 3.[7] On the basis of the present catalyst system, we have also developed a type of recyclable dendritic chiral titanium catalyst for HDA reaction with excellent enantioselectivity.[8]

Discovery of exceptionally efficient catalysts for hetero-Diels–Alder and carbonyl–ene reactions

The search for truly efficient and practical chiral catalysts is often a challenging goal for synthetic chemists due to the facts that many currently available catalytic enantioselective reactions need a high loading (5–10 mol%) of expensive chiral catalysts. Using a combinatorial optimization of dynamic libraries[9] of chiral diol–titanium–diol complexes, we have recently developed some exceptionally efficient enantioselective catalysts for solvent-free hetero-Diels–Alder[10a] and carbonyl–ene[11] reactions. The chiral catalyst library was created by combining a diol ligand L_{Am} with another equivalent of diol ligand L_{Bn} (same as or different from L_{Am}) in the presence of Ti(O^{i}Pr)$_4$ in parallel style as shown in Fig. 1 (the ligand library is shown in Fig. 4). Each member of the library L_{Am}/Ti/L_{Bn} is actually a dynamic mixture of titanium complexes (a smaller library of titanium catalysts) owing to the ligand diversity and aggregation feature of titanium complexes,[12] and *in situ* selection of a highly reactive (and selective) metallic complex from a variety of thermodynamically dictated assemblies by a substrate can lead to highly active and enantioselective catalysis.

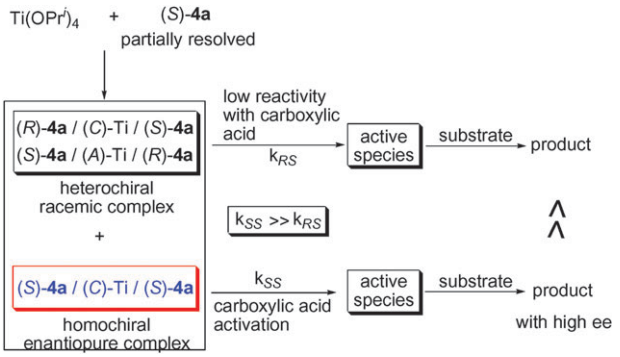


Fig. 3 The origin of the positive non-linear effect in the **4a**/Ti(IV)/**5** catalyst system.

Evaluation of the catalyst library (104 members) for the HDA reaction of benzaldehyde with Danishesky's diene revealed that the homocombination **6e**/Ti/**6e** and the heterocombination **6e**/Ti/**6f** were optimal catalysts, affording the HDA product in excellent yields (up to >99%) and enantiomeric excesses (up to >99% ee). The optimized catalysts,

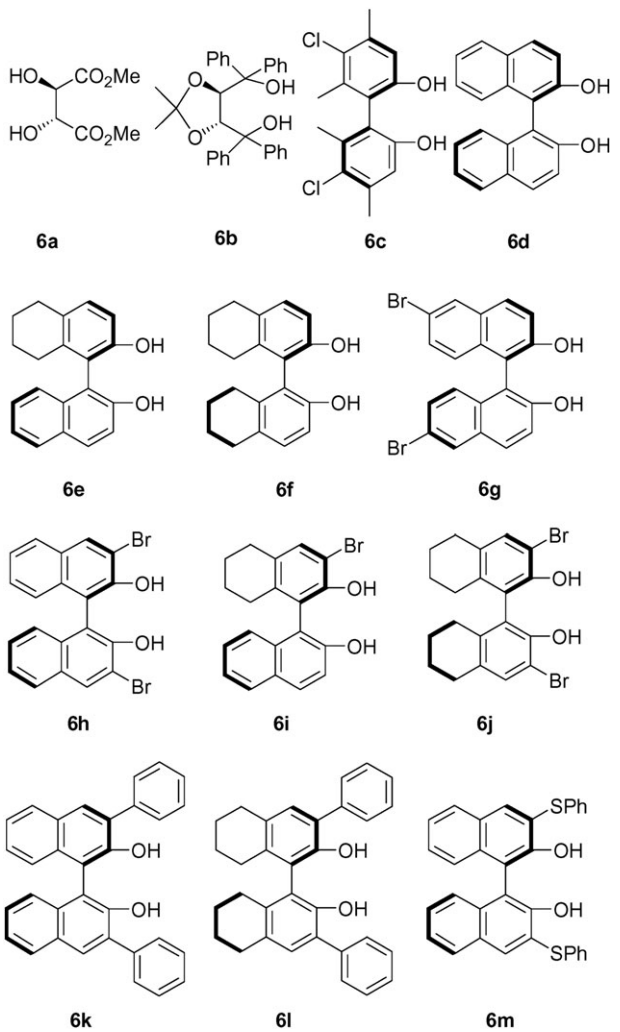
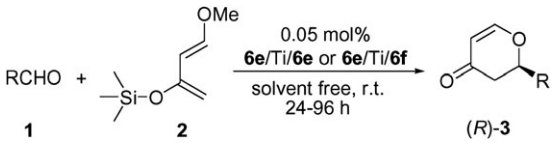


Fig. 4 A chiral diol ligand library.

Table 3 Solvent-free asymmetric HDA reaction of aldehydes with Danishefsky's diene

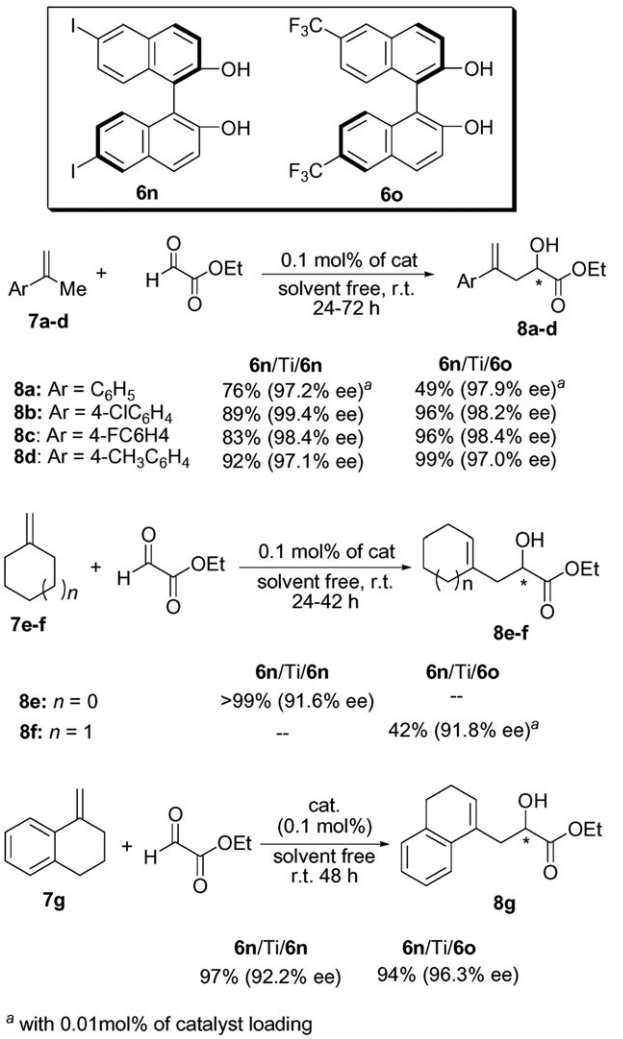


	Yield % (Ee %)	
R in **1**	**6e**/Ti/**6e**	**6e**/Ti/**6f**
Ph (**a**)	>99 (>99)	82 (>99)
4-ClC_6H_4 (**b**)	>99 (91)	>99 (>99)
4-BrC_6H_4 (**c**)	>99 (98)	>99 (98)
4-$O_2NC_6H_4$ (**d**)	>99 (97)	>99 (>99)
3-BrC_6H_4 (**e**)	>99 (97)[a]	98 (97)
3-MeC_6H_4 (**f**)	95 (98)[a]	92 (>99)
3-$MeOC_6H_4$ (**g**)	81 (96)	82 (>99)
2-$MeOC_6H_4$ (**h**)	95 (75)	99 (95)
2-Furyl (**i**)	>99 (>99)	>99 (>99)
2-Furyl (**i**)	37 (94)[a]	99 (97)[b]
PhCH=CH (**j**)	82 (98)[a]	57 (96)
$PhCH_2CH_2$ (**k**)	>99 (97)	>99 (98)
4-$MeOC_6H_4$ (**l**)	>99 (90)	>99 (98)
1-Naphthyl (**m**)	55 (85)	65 (98)
4-NCC_6H_4 (**n**)	>99 (92)[a]	98 (97)

[a] With 0.1 mol % of catalyst loading. [b] With 0.01 mol% of catalyst loading.

6e/Ti/**6e** and **6e**/Ti/**6f**, have been employed for the reactions of a variety of aldehydes, including aromatic, olefinic, and aliphatic derivatives (Table 3), at catalyst loadings of 0.1–0.05 mol% under solvent-free conditions.[10a] In general, the heterocombination catalyst **6e**/Ti/**6f** demonstrated superior catalytic performance to the homocombination **6e**/Ti/**6e**, indicating the synergetic effect of component ligands and the importance of fine-tuning of stereoelectronic modification on the ligands. Accordingly, the present catalytic systems have provided an attractive protocol for the synthesis of various optically active dihydropyrones because of their high efficiency, excellent enantioselectivity as well as the environmental benignity.[20]

By using a combinatorial diol–Ti–diol library strategy similar to that described above, we have also successfully discovered two highly efficient catalysts for carbonyl–ene reaction[13] of ethyl glyoxylate with a variety of olefins (**7**); good to excellent yields of α-hydroxy esters (**8**) with up to 99% ee could be obtained at catalyst loadings of 0.1–0.01 mol%.[11] A quick screening of the primary titanium catalyst library indicated that ligand **6g** is quite effective for enhancement of both the reactivity and the enantioselectivity of the reaction, suggesting that the increase of Lewis acidity of titanium complexes may be a key point for optimization. In the chiral titanium complexes catalyzed Friedel–Crafts reaction of aromatic amines with ethyl glyoxylate, we observed a similar trend of the impact of Lewis acidity of the titanium complexes on their catalytic behaviors.[14] Further optimization of the titanium complexes of chiral ligands with various electron-withdrawing groups (such as Br, I, CF_3) at the 6,6′-positions of BINOL revealed that the catalysts formed by homocombination of **6n** or heterocombination of **6n**/**6o** with titanium

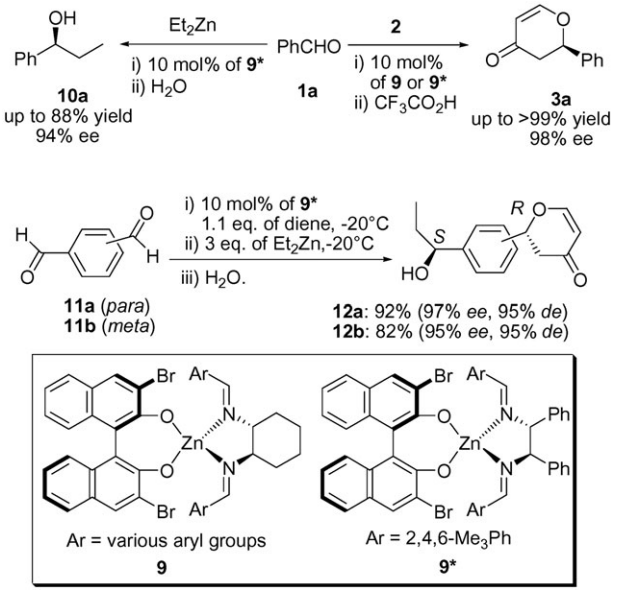


Scheme 1 Enantioselective carbonyl–ene reactions of ethyl glyoxylate with olefins.

isopropoxide were superior to other combinations, affording α-hydroxy ester **8a** with 97.2% and 97.9% ee, respectively. Extension of the **6n**/Ti/**6n** and **6n**/Ti/**6o** systems to a variety of olefinic substrates with diverse stereoelectronic features turned out to be very successful; excellent ees (91–99%) were achieved with catalyst loadings ranging from 0.01 to 0.1% (Scheme 1). Chan and coworkers also reported the self-assembly of BINOL and other chiral ligands such as a diol or sulfonamide into a highly effective titanium catalyst for the addition of alkynylzinc to aldehydes; 88–99% ees were obtained for a variety of aromatic aldehyde substrates.[15]

BINOL/Zn/diimine complex: a single catalyst for two distinct reactions

It was discovered by Mikami and coworkers,[16] and confirmed later by Walsh,[17] that the less active diol–Zn complexes could be activated for the catalysis of diethylzinc addition to aldehydes by the cleavage of zinc aggregates with diimine activators to shift the equilibrium to the monomeric side. Very recently, our group demonstrated that the BINOL/diimine/Zn



Scheme 2 Sequential asymmetric catalysis of HDA reaction and diethylzinc addition.

system was also an efficient chiral catalyst for asymmetric HDA reaction of benzaldehyde (**1a**) with Danishefsky's diene (**2**) (63% ee).[18] Following this preliminary finding, a parallel combinatorial approach was adopted to further improve the enantioselectivity of the reaction. A library of activated chiral zinc catalysts with diverse stereoelectronic features was set up, by combining the members of a chiral diol library (12 members) with those of a diimine library (20 members) in the presence of Et_2Zn. High throughput screening of the resulting chiral Zn catalyst library (240 members) indicated that the diimine-activated catalysts **9** were particularly effective, affording the adduct **3a** in up to quantitative yield and 98% ee (Scheme 2).

This finding in combination with that reported by Mikami[16] prompted us to explore the feasibility of using a single chiral diol/diimine/Zn catalyst for two distinct asymmetric tranformations in a one-pot fashion. To this end, activated Zn catalysts of type **9** were further optimized by a combinatorial approach for the diethylzinc addition to benzaldehyde. Variation of the stereoelectronic features of the diimine activator revealed that complex **9*** was the best catalyst for this reaction, affording (*S*)-1-phenylpropanol (**10a**) with 94% ee at a lower reaction temperature (−20 °C) (Scheme 2). Then, the optimized catalyst **9*** was reexamined for HDA reaction of benzaldehyde with Danishefsky's diene, affording (*R*)-**3a** with 97% ee in quantitative yield at −20 °C. Based on these results, complex **9*** was finally used for one-pot sequential asymmetric HDA reaction of dialdehydes **11a–b** (terephthalaldehyde (**11a**) and isophthalaldehyde (**11b**)) with Danishefsky's diene and diethylzinc addition to generate the corresponding optically active products **12a–b** bearing both chiral dihydropyranone and chiral alcohol moieties in one molecule (Scheme 2). As expected, the two asymmetric reactions proceeded efficiently in one pot to give products **12a–b** in 82–89% overall yields with 95–97% ee and 95% diastereoselectivity.[18b,c] Based on the synergistic effect of diimine activator on the BINOLate/Zn

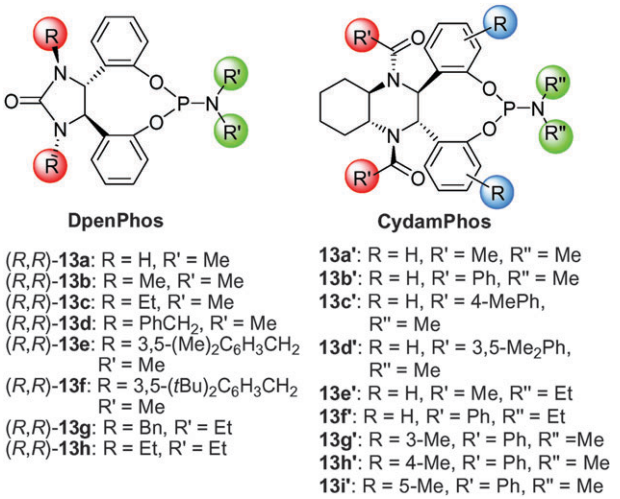


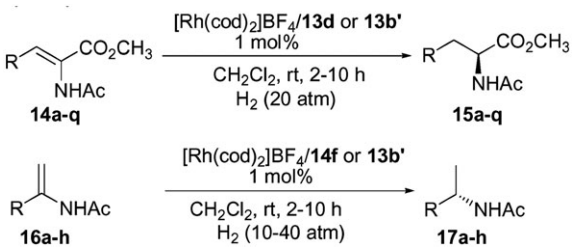
Fig. 5 Modular monodentate phosphoramidite ligands.

complex, Gong and coworkers recently demonstrated the feasibility of a similar library strategy for the discovery of BINOLate/diimine/Zn catalysts for enantioselective diethylzinc addition to imines, affording the corresponding secondary chiral amine derivatives with up to 94% ee.[19]

DpenPhos/Rh(I) catalysts for asymmetric hydrogenations: hydrogen-bonding between the component ligands makes a difference

The notion that the chelating structure of bisphosphine ligands is a prerequisite for efficient chiral induction in asymmetric hydrogenation[20] has recently been challenged by the

Table 4 Hydrogenation of dehydro-α-amino acid methyl esters and α-aryl acetyl enamides[a]



R in **14**	Ee (%)[b]	R in **14** or **16**	Ee (%)[b]
H (**14a**)	>99 (98)	2-$O_2NC_6H_4$ (**14n**)	>99 (96)
Me (**14b**)	98 (98)	3,4-$(MeO)_2C_6H_3$ (**14o**)	>99 (98)
C_6H_5 (**14c**)	>99 (>99)	3-AcO-4-$MeOC_6H_3$ (**16h**)	>99 (>99)
4-BrC_6H_4 (**14d**)	>99 (>99)	2-Naphthyl (**16h**)	97 (98)
3-BrC_6H_4 (**14e**)	>99 (>99)	C_6H_5 (**14c**)	98 (98)[c]
2-BrC_6H_4 (**14f**)	98 (>99)	C_6H_5 (**16a**)	97 (98)
4-ClC_6H_4 (**14g**)	99 (>99)	4-ClC_6H_4 (**16b**)	>99 (95)
3-ClC_6H_4 (**14h**)	98 (98)	4-$MeOC_6H_4$ (**16c**)	97 (95)
2-ClC_6H_4 (**14i**)	98	4-MeC_6H_4 (**16d**)	>99 (98)
4-$MeOC_6H_4$ (**14j**)	97 (97)	4-FC_6H_4 (**16e**)	98 (92)
3-$MeOC_6H_4$ (**14k**)	98 (>99)	4-BrC_6H_4 (**16f**)	>99 (95)
3-FC_6H_4 (**14l**)	>99 (98)	3-BrC_6H_4 (**16g**)	96 (92)
4-$O_2NC_6H_4$ (**14m**)	>99 (>99)	2-Naphthyl (**16h**)	98 (97)

[a] Rh/ligand = 1/2.1. [b] The data in parentheses are the ee values of the products with *R* configuration attained using ligand **13b'**. [c] With 0.1 mol% of catalyst.

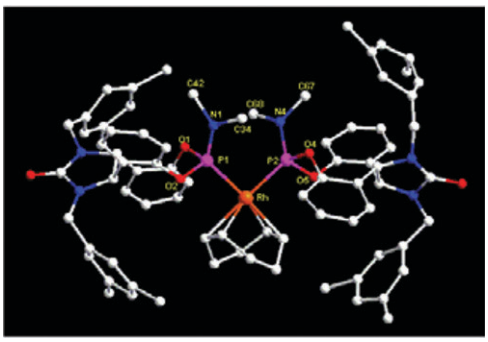
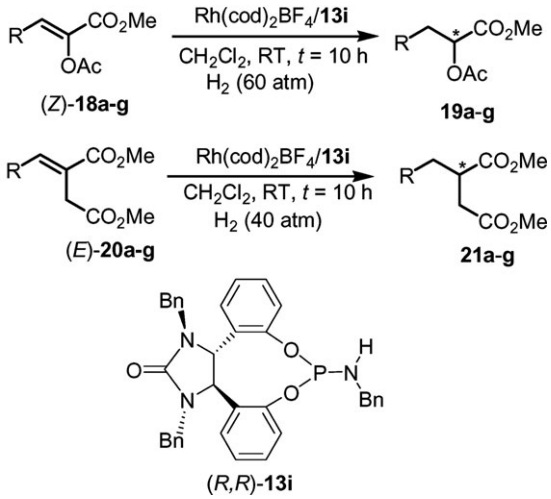


Fig. 6 The structure for the cation of $[Rh\{\mathbf{13e}\}_2(cod)]^+OH^-$ (reproduced with permission from ref. 22*a*).

development of monophosphites, monophosphonites, and monophosphoramidites.[21] Inspired by the pioneering work of Reetz, Feringa, de Vries, Pringle and others on the successful use of monodentate phosphorus ligands in asymmetric hydrogenations, we have developed a new class of monodentate phosphoramidite ligands (**13**, DpenPhos) (Fig. 5) on the basis of a modular concept.[22*a*] It was found that dual steric tuning of both R and R′ groups in the monodentate DpenPhos ligands was critically important for achieving excellent asymmetric induction in Rh(I) catalyzed hydrogenations of functionalized olefin derivatives. Under the optimized conditions, various dehydro-α-amino acid derivatives **14a–q** could be hydrogenated with the catalysis of Rh/(*R*,*R*)-**13d**, affording the corresponding α-amino acid derivatives with extremely high ee values (97–>99%) (Table 4). In the hydrogenation of enamide substrates (**16a–h**), the catalyst composed of (*R*,*R*)-**13f** was particularly effective, giving the corresponding α-arylamine derivatives quantitatively with excellent enantioselectivity (96–>99%) (Table 4). The drastic impacts of substituents R and R′ in the ligands on the enantioselectivities of the reactions can be addressed on the basis of molecular structure of catalyst precursor [Rh(*R*,*R*)-**13e**$_2$(cod)]OH as shown in Fig. 6. It is obvious that two monodentate phosphorus ligands adopt *cis* coordination around the Rh(I) center and the inner orientation of benzyl groups of (*R*,*R*)-**13e** in its Rh(I) complex will inevitably exert some impact on the enantiodiscrimination of the catalytic center.

Based on the scaffold of DpenPhos, we further developed a new class of monodentate phosphoramidite ligands, CydamPhos (**13a′–13i′**) (Fig. 5), with diverse modular structure.[22*b*] CydamPhos can be easily prepared from very cheap and readily accessible *trans*-1,2-diaminocyclohexane and salicylaldehyde derivatives through a three-step transformation, and retain the advantages of DpenPhos, such as structural diversity and remote stereocontrol capability of backbone substituents. The optimized ligand **13b′** exhibited excellent enantioselectivities in Rh(I)-catalyzed hydrogenations of dehydro-α-amino acid methyl esters (96–>99% ee) and *N*-acetyl α-arylenamides (92–98% ee) (Table 4). The impact of backbone substituents on the enantioselectivity of the catalysis can be rationalized by the orientation of *N*-benzoyl groups of the ligands in its Rh(I) complex.[22*b*] One of the *N*-benzoyl phenyl rings of each ligand points towards the labile cod moiety, constituting an integral part of the chiral environment around the Rh(I) center and thus can exert a profound influence on the process of the catalysis.

Table 5 Hydrogenation of (*Z*)-methyl α-(acetoxy)acrylates (**18**) and (*E*)-β-aryl itaconate derivatives (**20**)[a]



R in **18** or **20**	Substrate/Catalyst[b]	Ee (%)
C_6H_5 (**18a**)	100	>99
$CH_3(CH_2)_2$ (**18b**)	100	99
$(CH_3)_2CH$ (**18c**)	100	99
4-FC_6H_4 (**18d**)	100	>99
3-ClC_6H_4 (**18e**)	100	96
2-BrC_6H_4 (**18f**)	100	96
2-Naphthyl (**18g**)	100	98
C_6H_5 (**20a**)	4000	97
4-FC_6H_4 (**20b**)	1000	99
3-ClC_6H_4 (**20c**)	1000	97
2-Naphthyl (**20d**)	1000	96
2-BrC_6H_4 (**20e**)	100	97
3-$MeOC_6H_4$ (**20f**)	100	99
H (**20g**)[b]	10^5	94

[a] Rh/**13i** = 1/2. [b] Under 30 atm of H_2.

Although the Rh(I) catalysts composed of DpenPhos ligands (*R*,*R*)-**13d** and (*R*,*R*)-**13f** showed excellent activity and enantioselectivity in the hydrogenation of various dehydro-α-amino acid α-aryl-enamide derivatives,[22] no reaction was observed at all in the hydrogenations of more difficult substrates, such as (*Z*)-methyl α-acetoxyacrylate or (*E*)-β-aryl-itaconate derivatives, with these catalysts.[23] Very recently, we

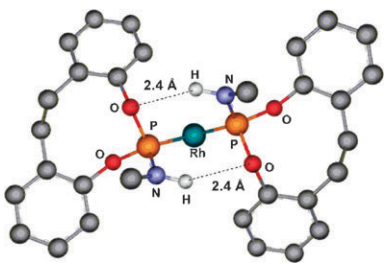


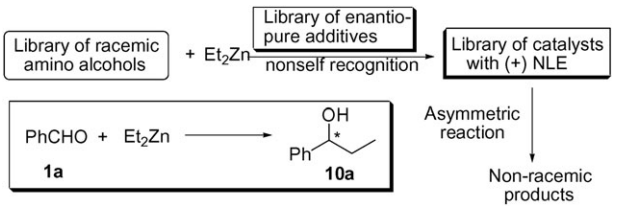
Fig. 7 B3LYP/6-31G optimized structural model of Rh/**13i** (reproduced with permission from ref. 23).

found that the Rh(I) complex of a further generation of monodentate phosphoramidite ligand (**13i**) bearing a secondary amine moiety is remarkably efficient for the asymmetric hydrogenation of these challenging substrates. Under optimized reaction conditions, hydrogenations of (*Z*)-methyl α-(acetoxy)acrylates and β-aryl itaconate derivatives catalyzed by Rh/**13i** afforded the corresponding products in excellent ee (96–>99%) (Table 5).[23]

Although the steric arguments suggest that smaller R-groups on the amine of phosphoramidite ligands result in better catalyst performance,[24] we further considered the possibility of the NH-group participating in hydrogen-bonding (HB) interactions. Both the ^{1}H NMR studies and theoretical calculations show the existence of hydrogen bonds between the two constituent monophosphoramidite ligands situated adjacently about the Rh-metal center in the precatalyst (Fig. 7). Here, the attractive nature of the hydrogen bonding and the proximity of the participating ligands are expected to subtly influence catalyst structure, particularly to reduce the inter-ligand bite angle.[22,23] The exceptional reactivity may be related to the change of this bite angle. Further studies of HB effects on reaction parameters and catalysis are currently being pursued. This finding might provide a new basis for bridging the gap between the use of mono- and bidentate phosphoramidite ligands in the design of new chiral catalyst systems.[25]

Engineering the catalyst library with racemic or achiral ligands

The appropriate combination of two enantiopure ligands for chiral catalyst optimization can lead to favorable results in many cases. However, one has to undertake the resolution of both chiral ligands from their racemic forms beforehand. A better approach for assembly of a chiral catalyst would be the use of only one enantiopure ligand in combination with a racemic or even achiral ligand by cooperative stereocontrol.[26,27] The racemic or achiral ligand is usually substantially less expensive and much more easily accessible than the enantiopure one, which accordingly makes the strategy more attractive in terms of chirality economy. The following text will describe our efforts in the engineering of chiral catalysts using racemic or achiral ligands.



Scheme 3 Generation of a chiral catalyst library on the basis of nonself recognition with enantiopure additives.

Zinc catalysts for asymmetric diethylzinc addition: addition of a racemic ligand makes a difference

In the enantioselective addition of diethylzinc to aldehyde catalyzed by nonracemic amino alcohols, the asymmetric amplification is well recognized as a consequence of an *in situ* increase in the ee value of the active catalyst, since racemic ligand is trapped in the more stable, unreactive meso species.[27] Although the reaction will definitely give racemic product if only racemic ligands are used, the addition of an alternative nonracemic additive (which should be cheap or easily accessible) to the racemic catalyst may produce an enantiomerically enriched product by selectively binding with only one of the enantiomers of the racemic catalyst through 'nonself recognition'[28] and releasing the opposite enantiomer to catalyze the reaction (Scheme 3).

To exemplify this strategy, Oguni's racemic amino alcohols[29] were chosen to carry out asymmetric catalysis through interaction with another chiral additive, such as an amino acid, tartaric acid, diol, diamine, or amino alcohol. From the preliminary random screening, amino alcohols were found to be one of the most effective types of chiral additives for this purpose. Thus, a library of five racemic amino alcohols (**21a–e**) and a library of 13 enantiopure amino alcohols (**22a–m**) (Fig. 8) were prepared. The combined use of 10 mol% of racemic amino alcohols (**21a–e**) and 5 mol% of optically pure additives (**22a–m**) in the presence of diethylzinc afforded a chiral catalyst library with 65 members, which were then evaluated for the reaction of benzaldehyde. It was found

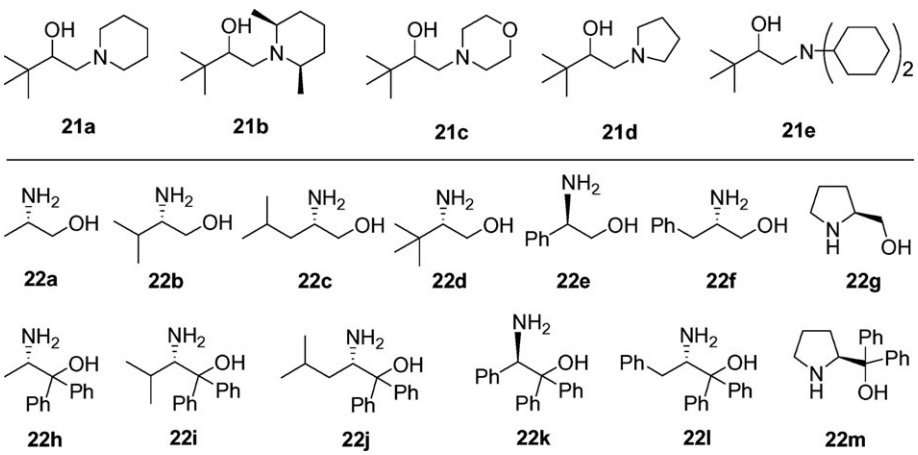
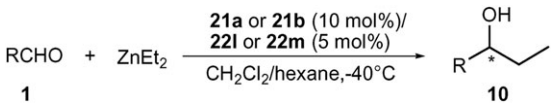


Fig. 8 Racemic (**21**) and enantiopure (**22**) ligand libraries employed for generating a chiral catalyst library.

Table 6 Enantioselective diethylzinc addition to aldehydes in the presence of racemic ligands[a]



1 10

R in **1**	Ee (%)			
	21a/**22l**	**21b**/**22l**	**21a**/**22m**	**21b**/**22m**
Ph (**a**)	86	86	92	90
4-ClC_6H_4 (**b**)	69	82	84	92
4-BrC_6H_4 (**c**)	76	73	82	79
3-MeC_6H_4 (**f**)	85	81	90	87
3-$MeOC_6H_4$ (**g**)	79	80	76	76
2-$MeOC_6H_4$ (**h**)	69	76	74	86
PhCH=CH (**j**)	67	82	69	69
4-$MeOC_6H_4$ (**l**)	87	90	90	91
1-Naphthyl (**m**)	69	72	69	86
Ferrocenyl (**o**)	81	90	91	72
4-$Me_2NC_6H_4$ (**p**)	23	55	36	81[a]
4-MeC_6H_4 (**q**)	74	80	82	80
MeCH=CH (**r**)[b]	78	84	80	84

[a] The reaction was carried out at 0 °C. [b] The reactions were carried out at −20 °C.

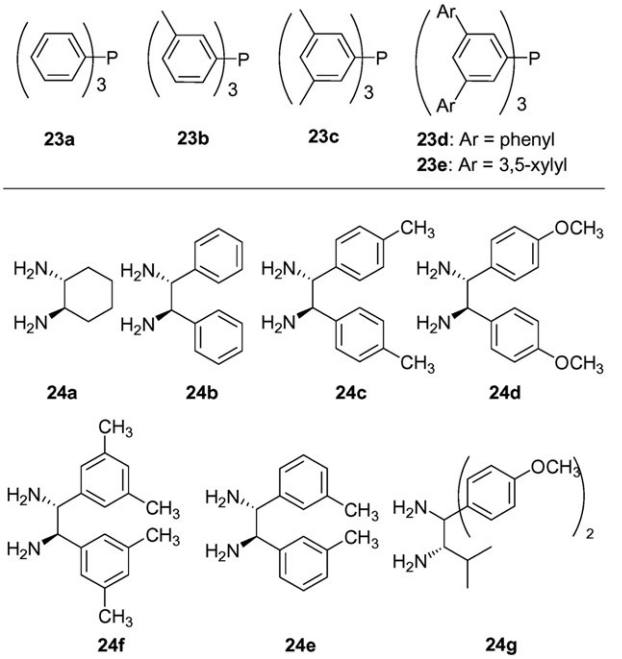


Fig. 9 The libraries of achiral monophosphine (**23**) and chiral diamine ligands (**24**).

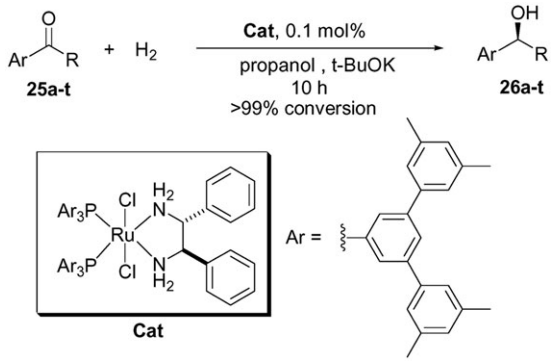
that **22l** and **22m** showed a significant synergistic effect in terms of the enantioselectivity of the reaction. For example, with only **22m** as chiral inducer, (*R*)-1-phenylpropanol (**10a**) was obtained in 15% ee. However, the addition of racemic **21a** or **21b** to the **22m**-catalyzed reaction system resulted in the formation of *S* product in 65% and 70% ee, respectively.[30]

The reactions catalyzed by the better combinations, **21a**/**22l**, **21b**/**22l**, **21a**/**22m**, and **21b**/**22m**, were further optimized by decreasing the reaction temperature to −40 °C. (*S*)-1-Phenylpropanol could be obtained with up to 92% ee and in >95% yield under the catalysis of **21a**/**22m**. Under the optimized conditions, catalyst combinations **21a**/**22l**, **21b**/**22l**, **21a**/**22m**, and **21b**/**22m** were also found be efficient for the ethylation of a variety of aldehydes (up to 81–92% ee) (Table 6). The investigation of the nonlinear effect in the catalytic system and kinetic behaviors of catalyst combinations (*S*)-**22m**/(*R*)-**21a** and (*S*)-**22m**/(*S*)-**21a** further supported the presence of nonself recognition between **21** and **22**, providing a rationale for the feasibility of the approach.

Ru(II) complexes of achiral mono-phosphine ligands and enantiopure 1,2-diamines: chirality relay between the component ligands

The use of achiral ligands in combination with enantiopure ligands in asymmetric catalysis is an alternative cost-effective approach to optically active products. Very recently, we have also been successful in the development of highly efficient and enantioselective Ru(II) catalysts for hydrogenation of ketones (up to 96% ee) by combination of achiral monodentate phosphine ligand (**23**) with enantiopure 1,2-diamine (**24**) (Fig. 9)[31] based on Noyori's early discovery on the use of a Ru(II) catalyst for asymmetric hydrogenation.[32] The combinatorial chemistry approach was employed for the screening of efficient achiral ligands through random screening of a variety of simple triarylphosphanes (**23**) and enantiopure diamines (**24**). [$RuCl_2${**23e**}$_2${**24b**}] turns out to be the best combination in the hydrogenation of a wide variety of aromatic and heteroaromatic ketones; 87–96% ee values of the secondary alcohols could be obtained with quantitative conversion of the ketones under the optimized conditions (Table 7). It is obvious that the steric hindrance of achiral monophosphine ligands in Ru(II) complexes was a critical impact factor for the high enantioselectivity of the catalysis. This simple catalyst system is particularly effective for the asymmetric hydrogenation of β-amino ketone **25t**, affording the corresponding β-amino alcohol **26t**, an important chiral drug intermediate, with 96% ee. This result is comparable to that obtained by using Noyori's [$RuCl_2${xylBINAP}$_2${**18g**}] catalyst (97% ee).[32] When the catalyst loading was reduced to 0.01 mol%, the hydrogenation of **25a** proceeded smoothly without obvious loss of enantioselectivity (95% ee), demonstrating the high activity of the present catalyst system. Although the use of Ru(II) complexes composed of racemic BINAP or chirally flexible diphosphine ligands in the presence of enantiopure diamine,[33] or Ru(II) complexes of enantiopure diphosphine in combination with cheap achiral amine[34] has been successful in the asymmetric hydrogenation of ketones, the results obtained with [$RuCl_2${**23e**}$_2${**24b**}] were unprecedented in terms of using achiral monophosphine ligands. On the basis of structural information and the CD spectra of the catalyst precursors, it was found that achiral triarylphosphine ligands adopt a chiral helical structure through steric communication around the Ru(II) center because of sufficiently close proximity of the *P*-aryl group and phenyl group of (*R*,*R*)-Dpen (Fig. 10a). This type of chirality relay between the

Table 7 Hydrogenation of ketones under the catalysis of a Ru(II) complex containing an achiral monophosphine ligand and an enantiopure 1,2-diamine



Ar and R in ketone	Ee (%)	Ee (%) using Noyori's catalyst[a]
Ar = Ph, R = Me (**25a**)	95.5 (*S*)	87–99
Ar = 2′-MeC_6H_4, R = Me (**25b**)	95.1 (*S*)	95–99
Ar = 4′-MeC_6H_4, R = Me (**25c**)	93.7 (*S*)	84–98
Ar = 2′-$MeOC_6H_4$, R = Me (**25d**)	93.7 (*S*)	82–92
Ar = 4′-$MeOC_6H_4$, R = Me (**25e**)	87.9 (*S*)	86–100
Ar = 2′-BrC_6H_4, R = Me (**25f**)	96.1 (*S*)	96–98
Ar = 3′-BrC_6H_4, R = Me (**25g**)	93.3 (*S*)	77–99.5
Ar = 2′-ClC_6H_4, R = Me (**25h**)	96.3 (*S*)	94–98
Ar = 3′-ClC_6H_4, R = Me (**25i**)	95.3 (*S*)	—
Ar = 2′-FC_6H_4, R = Me (**25j**)	95.1 (*S*)	82–97
Ar = 4′-FC_6H_4, R = Me (**25k**)	91.5 (*S*)	73–97
Ar = 2′-$CF_3C_6H_4$, R = Me (**25l**)	96.5 (*S*)	99
Ar = 3′,5′-$(CF_3)_2C_6H_3$, R = Me (**25m**)	90.9 (*S*)	—
Ar = 1-naphthyl, R = Me (**25n**)	94.7 (*S*)	97–99
Ar = 2-naphthyl, R = Me (**25o**)	90.5 (*S*)	98
Ar = ferrocenyl, R = Me (**25p**)	87.3 (*S*)	87
Ar = 2-furyl, R = Me (**25q**)	89.5 (*S*)	99
Ar = 2-thienyl, R = Me (**25r**)	95.9 (*S*)	99
Ar = Ph, R = Et (**25s**)	96.3 (*S*)	92–99
Ar = Ph, R = $Me_2NCH_2CH_2$ (**25t**)	96.7 (*S*)	97.5
Ar = Ph, R = Me (**25a**)	95.1 (*S*)[b]	87–99

[a] The data are cited from ref. 32. [b] At 0.01 mol% of catalyst loading and 24 h of reaction time.

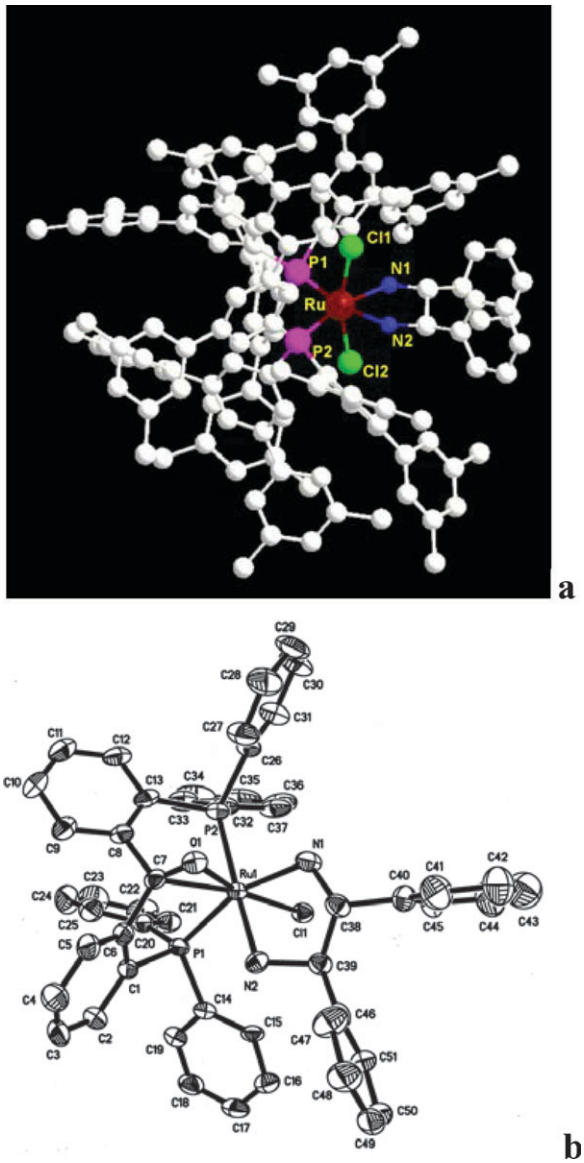


Fig. 10 (a) Ball and stick representation of the energy-minimized structure of complex [$RuCl_2${**23e**}$_2${**24b**}] (reproduced with permission from ref. 31). (b) Crystal structure of (*M*,*RR*)-**28** (reproduced with permission from ref. 36*a*).

component ligands might be a key point for its excellent enantiocontrol for the catalysis, which may lead to a favored transition state that mimics Noyori's [$RuCl_2${(BINAP)-{Dpen}}] catalyst.[32]

Ru(II) complexes of achiral benzophenone-based bisphosphine ligands and enantiopure 1,2-diamines: complete chiral induction between the component ligands

Benzophenone, although an achiral molecule, has been shown to exist in two different enantiomeric forms in the solid state.[35] Very recently, Mikami's and our groups independently reported the use of achiral benzophenone-based bisphosphine ligands to generate a Noyori-type Ru(II) catalyst for asymmetric hydrogenation of ketones.[36] A library of Ru(II) catalysts was set up by combining a series of achiral benzophenone-based bisphosphine ligands (**27a–d**) (Fig. 11) and enantiopure 1,2-diamines (**24a–g**). The optimized catalyst **28** showed excellent enantioselectivities and activities in the hydrogenation of a variety of aromatic ketones (Table 8).[36*a*]

This catalyst is particularly effective for the sterically hindered substrate. For example, up to 97% ee of the products has been obtained in the hydrogenation of 2′-methylacetophenone (**25b**) and 1′-acetonaphthone (**25n**). Complete chirality induction from enantiopure 1,2-diamine to achiral bisphosphine ligand in catalyst **28** was observed in both the solid state (see Fig. 10b) and solution.[36*a,c*] The coordination of C=O to the cationic Ru(II) center is considered the key feature in providing the thermodynamic and kinetic bias for single diastereomer formation. Coupled with the structure of the precatalyst **28** and the observed sense of asymmetric induction, a proposed mode of asymmetric induction for the present catalyst system is thus depicted in Fig. 12. Here, it is assumed that the (C=O) Ru(II) interaction itself persists during the hydrogenation step, keeping the flexible configuration of ligand 'locked' in the

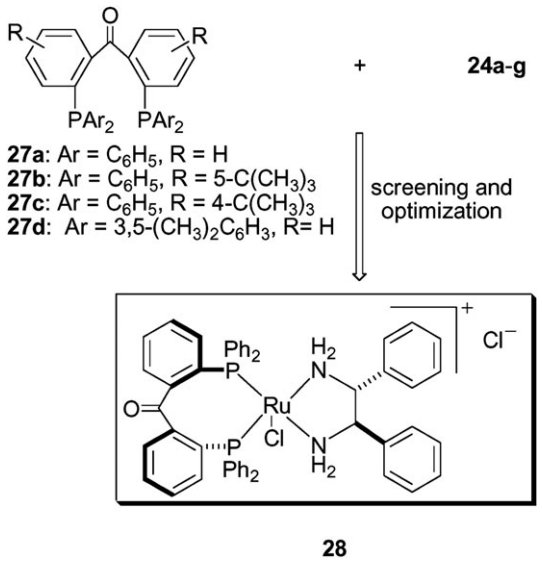


Fig. 11 Screening of Ru(II) complexes containing achiral benzophenone-based bisphosphine ligands and enantiopure 1,2-diamines for asymmetric hydrogenation of ketone.

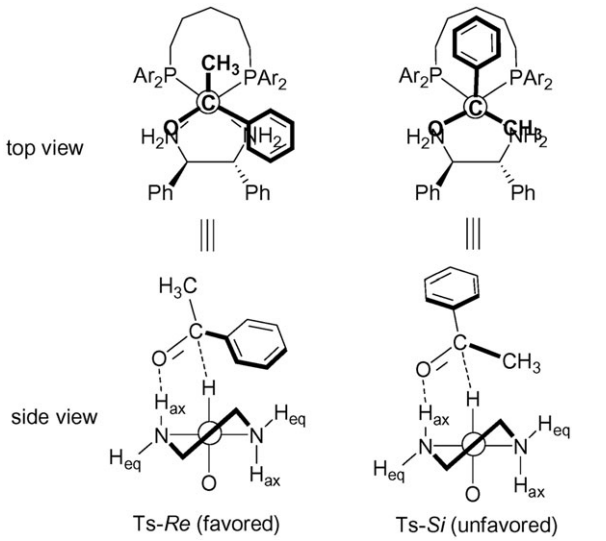


Fig. 12 Schematic representation of asymmetric induction mode in hydrogenation of **25a** with **28** (reproduced with permission from ref. 36*a*).

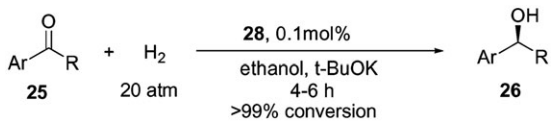
Ru(II) complex. This is reasonable considering the higher observed ee values compared to the BINAP analog.

A critical view on diversity-based approaches for chiral catalyst development

Owing to the hard-to-predict nature of enantioselective catalytic processes, it is impossible to select an ideal set of experimental parameters just by rational catalyst design and chemical intuition, and thus the adoption of diversity-based approaches is essential and important in catalyst development. Since the chiral ligand is often regarded as the most crucial single factor in fine-tuning the catalysis, the most classical way for achieving catalyst diversity is one-by-one chemical synthesis of a substantial collection of chiral ligands, which are subsequently tested in combination with the metals in the target catalytic reaction. Unfortunately, the ligand synthesis can often become a laborious and time-consuming endeavor, which might severely hamper a time-demanding catalyst development process.[37] From this point of view, approaches allowing for efficient generation of a large number of chiral metallic complexes with a high degree of structural diversity are particularly attractive. This is why combinatorial library methods have begun to gain an increasing importance in enantioselective catalysis during recent years.[3,38–42] In essence these approaches rely on the efficient generation of a library of potential asymmetric catalysts with diversified structural features, and high-throughput screening (HTS) of the library for the target reaction. Several approaches have been developed for preparation of the chiral catalyst libraries, either on a solid support or in the liquid phase, with the major efforts being focused on construction of modular chiral ligands using molecular building blocks.

The solid-phase synthesis of a chiral ligand library, as seen for instance in the elegant work of Ellman,[43] Jacobsen,[44] Gilbertson,[45] Snapper and Hoveyda,[46] Miller,[47] Liskamp,[48] Meldal,[49] Uozumi,[50] and Arai,[51] has achieved some eye-catching successes in the discovery or optimization of highly efficient chiral catalysts for a number of enantioselective catalytic reactions. The ligands are often constructed by sequential attachment of various linkers (usually peptide) and ligating groups to a polymeric resin support. Upon metal loading, the resultant catalysts are assayed on bead. The modular nature of the ligand preparation as well as the types of metal precursors allows for a high degree of structural diversity in the catalyst library, and thus provides a good probability of finding an excellent enantioselective catalyst for asymmetric catalysis. Moreover, ligand synthesis on a solid support can also bring about the advantages of solid-phase chemistry such as automation and ease of workup. However, a prerequisite for implementation of this strategy is the appropriate selection of a ligand system, which has to be amenable to solid-phase synthesis (high-yield reactions) and systematic

Table 8 Hydrogenation of ketones under the catalysis of Ru(II) complex containing achiral benzophenone-based bisphosphine ligand and enantiopure 1,2-diamine



Ar and R in **25**	Ee (%)	Ar and R in **25**	Ee (%)
Ph, CH_3 (**25a**)	91	2′-FC_6H_4, Me (**25j**)	85
2′-MeC_6H_4, Me (**25b**)	97	4′-FC_6H_4, Me (**25k**)	87
4′-MeC_6H_4, Me (**25c**)	92	2′-$CF_3C_6H_4$, Me (**25l**)	91
4′-$MeOC_6H_4$, Me (**25e**)	89	1-Naphthyl, Me (**25n**)	97[a]
2′-BrC_6H_4, Me (**25f**)	94	2-Naphthyl, Me (**25o**)	91
3′-BrC_6H_4, Me (**25g**)	87	Ph, Et (**25s**)	92
2′-ClC_6H_4, Me (**25h**)	90	4′-BrC_6H_4, Me (**25u**)	86
3′-ClC_6H_4, Me (**25i**)	84	3′-MeC_6H_4, Me (**25v**)	91

[a] ^{i}PrOH was used as solvent.

structural variation. In addition, it is conceivable that the extension of the catalytic results for support-bound ligands directly to those of free ligands in liquid-phase experiments may not always yield reliable conclusions, since the possible presence of an equilibrium between monomeric species and higher catalytic agglomerates, the interaction between active sites and the linker/polymer matrix, and the favored formation of mononuclear complexes on the solid support (site isolation effect) while a synergistic interaction is found in solution, may all contribute to the deviation. Although very promising and extremely powerful, until now the strategy for creation of chiral ligand libraries on a solid support is still in its infancy. Very recently, Arai and coworkers combined the advantages of solid-phase synthesis for creation of a chiral ligand library and a simple circular dichroism (CD) detection technique for HTS, providing a new direction of combinatorial asymmetric catalysis.[51]

Alternatively, the construction of a modular chiral ligand library may also be accomplished in the liquid phase. In favorable cases, the ligand libraries can be prepared by parallel synthesis, using readily available starting materials that can be combined in a modular manner in high yield and in just a few steps.[52] For example, with this type of modular approach a ligand library based on chiral β-amino sulfonic acids has been developed by Gennari and tested in the $Ti(O^iPr)_4$-mediated addition of Et_2Zn to aldehydes.[52h] Some other types of chiral ligands such as the monodentate phosphates and phosphoramidites can be synthesized very efficiently and thus also facilitate the ligand library formation.[53] Non-covalent interactions such as hydrogen bonding have also been effectively used to generate supramolecular libraries of chelating bidentate ligands for homogeneous catalysis.[54–56] Although considerable progress has been made in the parallel and combinatorial approaches for synthesis of ligands,[57] the development of more high yielding reactions for efficient coupling of various functionalized building blocks in a chiral ligand, in the author's opinion, would still be highly desirable to overcome the inherent limitation of the ligand library approaches.

The strategy of using binary component ligands in chiral catalyst library engineering for enantioselective reactions, featured in this article with our own results and which can also be seen for instance in the excellent work of Mikami,[58] Feringa and Minnaard,[59] de Vries,[60] Reetz,[61] Walsh,[17,62] Gennari,[63] Chan,[15,64] *etc*., constitutes yet another diversity-based method for chiral catalyst development as is clear from the previously discussed examples. The method is operationally simple, cost-effective and time saving. Simply mixing the members of two or more ligand libraries together with an appropriate catalytic metal ion precursor affords the catalyst libraries which can be screened for catalytic performance in the target reaction. Even racemic or achiral ligands/additives might be used synergistically with the other components in appropriate systems, which may cause considerable enhancement in reactivity and/or enantioselectivity. Apart from the economic benefits, a highly attractive feature of this strategy is that it can be easily modified to a combinatorial approach as outlined in Fig. 1.

In a general sense, any catalytic asymmetric transformation where the enantioselectivity-determining transition state is capable of simultaneously accommodating two ligands, or requires the cooperation of two ligands, could potentially be optimized by tuning the ligand/coligand (at least one of them should be in enantiopure form) diversity. Taken the other way, this can also be regarded as a limitation in the application scope of the strategy. Although in favorable cases concepts such as 'asymmetric activation'[65] or 'chiral poisoning'[26] can indeed be used as a theoretical guide for fine tuning of the catalysis using the binary component ligand approach, there is no unifying principle underlying all the possible interactions in a catalytic system and thus most reactions have to be examined on a case-by-case basis. In addition, the dynamic nature of the multiple species system and *in situ* selection of the most efficient catalytic species often render the spectroscopic characterization very difficult and thus complicate mechanistic understanding. Since none of the diversity-based approaches discussed above is likely to be universally applicable, adoption of various and complementary strategies would be desirable for chiral catalyst development.

Conclusions

In conclusion, the feasibility of generating combinatorial chiral catalyst libraries for asymmetric transformations has been demonstrated on the basis of the synergistic effect of component ligands. The catalyst libraries were created by the assembly of binary ligands (at least one of which is in non-racemic form, while the other might be optically pure, racemic or achiral) with a metal ion. Using this strategy, a variety of highly efficient and cost-effective chiral catalyst systems, including Ti(IV), Zn(II), Rh(I) and Ru(II) complexes, have been discovered for asymmetric hetero-Diels–Alder, carbonyl–ene, alkylation, and hydrogenation reactions, respectively. It can be expected that the strategy described in this article will be a promising approach for the discovery of highly efficient and enantioselective catalysts, as well as unexpected classes of catalysts or catalytic reactions in chiral chemistry.

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