Asymmetric Catalysis

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Self-Assembled Bifunctional Catalysis Induced by Metal Coordination Interactions: An Exceptionally Efficient Approach to Enantioselective Hydrophosphonylation**

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Dedicated to Professor Rugang Xie on the occasion of his 70th birthday

Enantiomerically enriched α-hydroxy-functionalized phosphonates and phosphonic acids have been widely employed to synthesize pharmaceutically and biologically active compounds.[1,2] Catalytic asymmetric hydrophosphonylation by addition of an appropriate phosphorus nucleophile to the carbonyl bond can provide a very convenient route to the corresponding optically active α-hydroxy phosphonates, which is probably the most general and widely applied approach.[1b] Much effort has been directed towards the development of this important type of asymmetric reaction. Shibasaki and co-workers described the first highly enantioselective addition of aldehydes with dimethyl phosphite using a heterobimetallic multifunctional catalyst based on 1,1′-bi-2-naphthol (binol). However, the catalytic system only gave rise to moderate enantioselectivities for aliphatic aldehydes.[3] A breakthrough was achieved with the C_1-symmetric [Al(salalen)] complex by Katsuki and co-workers (salalen = salen/salan hybrid; salen = *N*,*N*'-bis(salicylidene)ethylene diamine; salan = *N*,*N*'-bis(*O*-hydroxybenzyl)-1,2-diaminoethane).[4] Quite recently, Feng and co-workers presented another highly enantioselective example promoted by the tridentate Schiff base/Al^{III} complexes.[5] However, among these most outstanding examples, relatively high catalyst loadings and/or extended reaction times were generally required to induce acceptable conversions.[3–6] Clearly, the development of more efficient and practical catalytic systems for a broad range of phosphites and aldehydes (both aromatic and aliphatic) is a highly challenging topic.

The strategy of synergistic activation by two or more reactive centers constitutes a versatile approach for the development of high-performance asymmetric catalysis.[7,8] Recently, the concept of self-assembly by metal–organic coordination has been successfully employed to construct combinatorial chiral catalysts.[9,10] We wish to report the combination of the two concepts mentioned above to obtain a new type of bifunctional catalyst generated by the metal-organic self-assembly of substituted binols[3,11] and cinchona alkaloids[12] in combination with $Ti(OiPr)_4$[13] for the asymmetric hydrophosphonylation of aldehydes. The chiral Lewis base moiety (cinchona alkaloid) in these self-assembled bifunctional catalysts spontaneously coordinates to the central metal of the chiral Lewis acidic moiety (binol–Ti complex) to form the metal–organic assemblies (Figure 1).

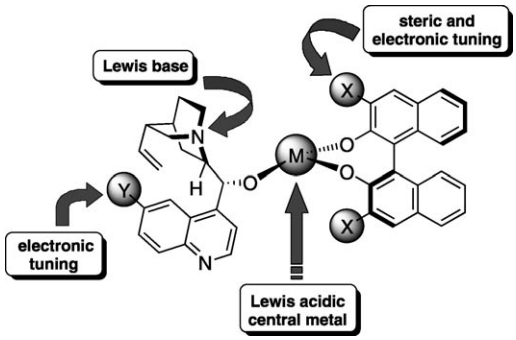

Figure 1. Strategy for designing self-assembled bifunctional catalysts.

In comparison with the conventional bifunctional catalysts in which Lewis acid/Lewis base (LALB) moieties are integrated into one molecule through covalent bonds,[6b,8a–g] the highly modular nature of the catalyst systems would easily allow better matching of the chiral ligand, metal ion, and substrate, and thus facilitate the achievement of excellent catalytic performance (activity and enantioselectivity; Scheme 1).

Preliminary experiments focused on varying the reaction parameters, such as solvent effect, catalyst loading, temperature, and concentration (see Table S1 in the Supporting Information for details). Encouraging results were obtained by using benzaldehyde and dimethyl phosphite as model reactants in the presence of 10 mol% of (*R*)-**1a**Ti^{IV}**3a** in *m*-xylene at −20 °C, as shown in Table 1. The catalytic system was prepared in situ by stirring binol ((*R*)-**1a**) and cinchoni-

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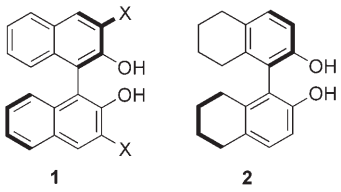
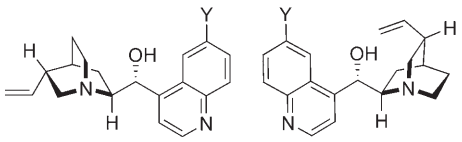


1 2

1a: X = H
1b: X = I
1c: X = 3,5-$(CF_3)_2C_6H_3$
1d: X = 2,4,6-$Me_3C_6H_2$
1e: X = 9-phenanthryl

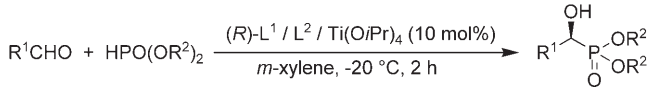


3 4

3a: Y = H (cinchonidine) **4a**: Y = H (cinchonine)
3b: Y = OMe (quinine) **4b**: Y = OMe (quinidine)

Scheme 1. Substituted binols and cinchona alkaloids.

Table 1: Some representative results from the screening of aldehyde and binol substituents.[a]



Entry	R^1	R^2	L^1	L^2	Yield [%][b]	*ee* [%][c]
1	Ph	Me	**1a**	**3a**	99	66
2	Ph	Me	**2**	**3a**	64	24
3	Ph	Me	**1b**	**3a**	99	99
4	Ph	Me	**1c**	**3a**	78	69
5	Ph	Me	**1d**	**3a**	23	49
6	Ph	Me	**1e**	**3a**	30	60
7	Ph	Me	**1b**	**3b**	98	94
8	Ph	Me	**1c**	**3b**	76	62
9	Ph	Me	**1b**	**4a**	34	78
10	Ph	Me	**1b**	**4b**	32	20
11	Ph	Bn	**1b**	**3a**	85	86
12[d]	Ph	*i*Pr	**1b**	**3a**	70	88
13	$PhCH_2CH_2$	Me	**1b**	**3a**	99	74
14	$PhCH_2CH_2$	Me	**1c**	**3a**	90	92

[a] General reaction conditions: (*R*)-L^1L^2/$Ti(OiPr)_4$/R^1CHO/phosphite = 0.1:0.1:0.1:1.0:1.1 (molar ratio) on a 0.5 mmol scale in *m*-xylene (1 mL) at −20 °C for 2 h. [b] Yield of isolated product based on 0.5 mmol aldehyde. [c] Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was carried out for 18 h.

dine (**3a**) in combination with $Ti(OiPr)_4$ in a molar ratio of 1:1:1 at room temperature for one hour. The assembled (*R*)-**1a**Ti^{IV}**3a** complex showed high catalytic activity with complete conversion of the starting material into product within two hours (Table 1, entry 1). However, the *ee* value obtained was only 66%. On the basis of these initial observations, we introduced further electronic and steric modifications to the ligands to optimize the catalytic performance (Table 1, entries 2–9). After screening the substituted binols (*R*)-**1b**–**e**, we found that the enantiocontrol and catalytic activity of the self-assembled catalysts were largely dependent on the electronic properties of the substituted binols (Table 1, entries 3, 4, and 14). In contrast, the steric hindrance at the 3,3′-positions has a negative influence on the activity of the catalyst (Table 1, entries 5 and 6). To our great delight, with iodine as the 3,3′ substituents, (*R*)-**1b**Ti^{IV}**3a** could smoothly promote the asymmetric hydrophosphonylation in high yields of up to 99% with excellent enantioselectivities of up to 99% *ee* (Table 1, entry 3). On the other hand, the stereochemistry of the cinchona alkaloid backbone could also influence both the stereoselectivity and yield of the model reaction (Table 1, entries 3, 7–10). The configurations of both the basic quinuclidine nitrogen center and the hydroxy group on C9 were demonstrated to be crucial for the catalytic performance.[14]

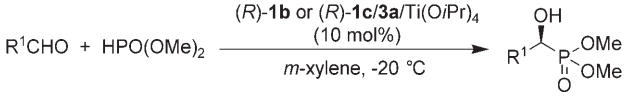
An extension of this strategy to include aliphatic aldehydes and other phosphites would significantly expand its versatility. In this study, we were pleased to find that the assembled (*R*)-**1b**Ti^{IV}**3a** was also capable of promoting the hydrophosphonylation of benzaldehyde with bulky diisopropyl phosphite and dibenzyl phosphite with high enantioselectivities of up to 88% *ee* (Table 1, entries 11 and 12). We examined the reactions of aliphatic aldehydes further and found that an excellent enantioselectivity was observed when (*R*)-**1c**Ti^{IV}**3a** was exposed to a mixture of phenylpropyl aldehyde and dimethyl phosphite (Table 1, entry 14).

Under optimal reaction conditions a series of aromatic aldehydes with sterically hindered, electron-poor, or electron-rich substituents afforded the corresponding α-hydroxy phosphonates in almost quantitative yields with *ee* values in the range 91–99% (Table 2, entries 1–12). The α,β-unsaturated aldehyde (cinnamaldehyde) also showed good enantioselectivity of 89% *ee* in 97% yield, which is the best result reported so far (Table 2, entry 13). Notably, (*R*)-**1c**Ti^{IV}**3a** could efficiently promote the addition of dimethyl phosphite to a variety of aliphatic (including linear, cyclic, and branched) aldehydes, in excellent yields (94–97%) and excellent *ee* values (92–94%) (Table 2, entries 14–17). To the best of our knowledge, the self-assembled (*R*)-**1c**Ti^{IV}**3a** is the most efficient catalyst system in the literature for the asymmetric hydrophosphonylation of aliphatic aldehydes.[3–6]

Low catalyst loading is clearly desirable for a catalytic reaction. Although the catalytic asymmetric hydrophosphonylation has proven successful in many respects, most of these processes require 10 mol% of the catalyst for sufficient product formation and maintenance of stereoselectivity.[3–6] The reactions reported herein could be performed without notable loss of selectivity and reactivity even with a catalyst loading of 2.5 mol%, albeit with somewhat extended reaction times (Table 3). It should be noted that this is the lowest catalyst loading for the asymmetric hydrophosphonylation of aldehydes reported to date.

Although more detailed investigations of the reaction mechanism are currently underway, the proposed transition-state model is consistent with experimental observations and accounts for the absolute configurations of some selected products (Scheme 2). The self-assembled systems of substituted binols and cinchona alkaloids with $Ti(OiPr)_4$ serve as the bifunctional catalysts, in which the Ti^{IV} metal center

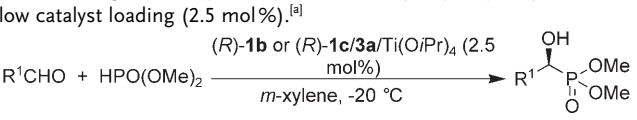
Table 2: Range of aldehydes explored in the catalytic hydrophosphonylation.[a]



Entry	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	2	99	99
2	3-MeC_6H_4	2	97	98
3	4-MeC_6H_4	2	96	97
4	2-$MeOC_6H_4$	2	98	98
5	2-ClC_6H_4	2	99	95
6	3-ClC_6H_4	2	99	94
7	4-ClC_6H_4	2	99	92
8	4-FC_6H_4	2	99	91
9	4-CNC_6H_4	2	99	91
10	4-$NO_2C_6H_4$	2	99	93
11	1-naphthyl	2	99	>99
12	2-naphthyl	2	99	>99
13	(*E*)-PhCH=CH	4	97	89
14[d]	$PhCH_2CH_2$	4	95	92
15[d]	cyclohexyl	6	95	92[e]
16[d]	*n*Oct	4	97	94[e]
17[d]	*i*Pr	6	94	94[e]

[a] General reaction conditions: (*R*)-**1b**/**3a**/Ti(O*i*Pr)$_4$/R^1CHO/dimethyl phosphite = 0.1:0.1:0.1:1.0:1.1 (molar ratio) on a 0.5 mmol scale in *m*-xylene (1 mL) at −20 °C. [b] Yield of isolated product based on 0.5 mmol aldehyde. [c] Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase. The absolute configuration of the adduct was assigned by comparison with literature data. [d] 10 mol% of (*R*)-**1c** was used. [e] After conversion of the product into the corresponding benzoate.

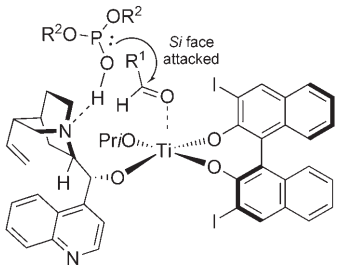
Table 3: Range of aldehydes explored in the hydrophosphonylation with low catalyst loading (2.5 mol%).[a]



Entry	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	6	92	94
2	3-MeC_6H_4	8	90	95
3	4-MeC_6H_4	8	92	94
4	2-$MeOC_6H_4$	8	95 (82)[d]	96 (>99)[d]
5	2-ClC_6H_4	4	99	90
6	4-ClC_6H_4	8	87	90
7	4-$NO_2C_6H_4$	4	99	90
8	1-naphthyl	6	97	>99
9	2-naphthyl	6	97	>99
10[e]	$PhCH_2CH_2$	12	96	92
11[e]	cyclohexyl	18	93	92[f]
12[e]	*n*Oct	12	98	94[f]
13[e]	*i*Pr	24	90	94[f]

[a] General reaction conditions: (*R*)-**1b**/**3a**/Ti(O*i*Pr)$_4$/R^1CHO/dimethyl phosphite = 0.025:0.025:0.023:1.0:1.1 (molar ratio) on a 1.0 mmol scale in *m*-xylene (1 mL) at −20 °C. [b] Yield of isolated product based on 1.0 mmol aldehyde. [c] Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase. [d] After recrystallization from *n*-hexane/*i*PrOH 4:1. [e] 2.5 mol% of (*R*)-**1c** was used. [f] After conversion of the product into the corresponding benzoate.

captures the aldehyde, while the basic quinuclidine nitrogen atom of the cinchona alkaloids simultaneously reacts with the phosphite.[12c] The aldehyde favors the approach of the phosphite from the less hindered *Si* face. Thus, cooperative interaction between each component of the catalyst could lead to excellent chemical yields and enantioselectivities of the products.



Scheme 2. Proposed transition-state model.

In summary, we have developed a new type of bifunctional catalyst generated from the metal–organic self-assembly of substituted binols and cinchona alkaloids in combination with Ti(O*i*Pr)$_4$ for the highly efficient asymmetric hydrophosphonylation of aldehydes. The protocols are capable of tolerating a relatively wide range of substrates, even in the presence of 2.5 mol% of catalyst. In particular, their modular nature enables easy tuning of the steric and electronic properties of each moiety. Furthermore, the components of these self-assembled catalysts are commercially available, thus making this process even more accessible. This strategy could provide a powerful approach for discovering new types of bifunctional catalysts.

Experimental Section

Under an N_2 atmosphere, Ti(O*i*Pr)$_4$ (15 μL, 0.05 mmol) was added to a dry tube containing a suspension of **3a** (14.8 mg, 0.05 mmol), (*R*)-**1b** (27 mg, 0.05 mmol), and *m*-xylene (1 mL). The mixture was stirred at room temperature for 1 h to give a clear solution. Aldehyde (0.5 mmol) was then added at −20 °C, followed by addition of dimethyl phosphite (0.55 mmol, 52 μL). After the reaction mixture had stirred at −20 °C for 2 h, aqueous solutions of hydrochloric acid (1M, 2 mL) and diethyl ether (3 mL) were added. The resulting mixture was stirred for 0.5 h at room temperature, and the mixture was then extracted with diethyl ether (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel with elution with petroleum ether/acetone (2:1–1:2) to give the corresponding α-hydroxy phosphonate. The *ee* values were determined by HPLC on a chiral stationary phase(Chiralcel OD-H or AD-H).

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