VIP Asymmetric Catalysis

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Chiral Magnesium(II) Binaphtholates as Cooperative Brønsted/Lewis Acid–Base Catalysts for the Highly Enantioselective Addition of Phosphorus Nucleophiles to α,β-Unsaturated Esters and Ketones**

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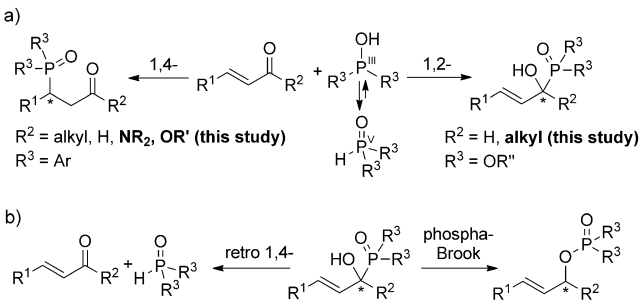
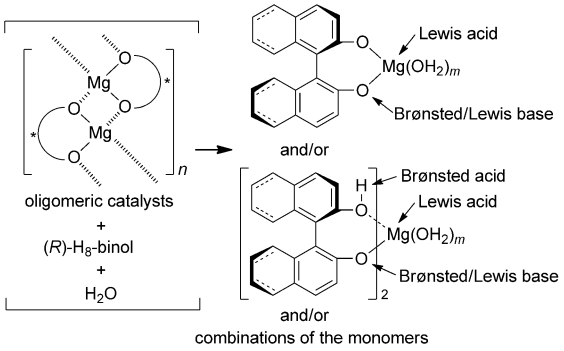
Chiral organophosphorus compounds show various forms of biological activity as a result of their chemical properties, and thus are used in many pharmaceuticals as biophosphate mimics, antibiotics, antiviral agents, and antitumor agents;[1] they are also used as chiral P and P,N ligands for metal catalysts.[2] In particular, the catalytic enantioselective addition of phosphorus nucleophiles is one of the most powerful synthetic methodologies for the construction of functionalized organophosphorus compounds through phosphorus–carbon bond formation (Scheme 1 a).[3–6] In general, reactivity



Scheme 1. a) Addition of phosphorus nucleophiles to α,β-unsaturated carbonyl compounds and b) side reactions observed for these transformations.

and regioselectivity in hydrophosphonylation and hydrophosphinylation reactions strongly depend on the substrates and the reaction conditions, such as the solvent and the temperature (see Table S1 in the Supporting Information).[3–6] In this regard, catalytic enantioselective 1,4-addition has been limited to α,β-unsaturated ketones, aldehydes, and amides,[4] and has not been described for α,β-unsaturated esters, despite their importance in synthesis. Moreover, catalytic enantioselective 1,2-addition has been developed with aldehydes and aldimines,[5] and there have been few examples of the use of much less reactive ketones.[6] In particular, with ketone substrates, which have inherent low reactivity owing to steric and electronic constraints, the resulting tertiary alcohols sometimes undergo a phospha-Brook rearrangement[7] or a retroreaction[8] under basic conditions (Scheme 1 b).

To overcome these difficulties in hydrophosphonylation and hydrophosphinylation, catalysts must exhibit not only suitable Brønsted basicity to activate the non-nucleophilic species $R_2P^V(=O)H$ (major) and provide nucleophilic $R_2P^{III}OH$ (minor; Scheme 1 a),[9] but also strong Brønsted or Lewis acidity to activate less-reactive substrates, such as esters and ketones. In this context, by taking advantage of asymmetric catalytic systems developed by our and other research groups with inexpensive and harmless Group I and II metal binaphtholates,[10–12] we envisioned that chiral magnesium(II) binaphtholate aqua complexes[11,12c] would be highly attractive as simple and practical acid–base combination catalysts[13] (Scheme 2). In such catalysts, naphthoxide moieties would exhibit strong Brønsted/Lewis basicity, whereas the Mg^{II} cation centers would show inherent strong Lewis acidity. Also, chelation of the Mg^{II} center by a hydroxy group in the 1,1′-bi-2-naphthol (binol) ligand would increase the Brønsted acidity of this hydroxy group and activate the complex effectively. Moreover, the aggregation of magnesium(II) binaphtholates[11c] could be controlled not only by the molar ratio of the metal ion and the binol ligand, but also by the use of highly coordinative water and alcohols as cocatalysts.[12] Overall, suitable disaggregated active species would be provided in situ as monomers and/or combi-



Scheme 2. Chiral magnesium(II) binaphtholate aqua complexes as cooperative Brønsted/Lewis acid–base catalysts.

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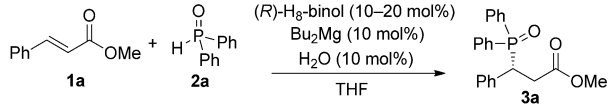
nations of monomers. Owing to the diversity of the supramolecular structures of chiral magnesium(II) binaphtholates as cooperative Brønsted/Lewis acid–base catalysts, conventional substituents at the 3,3′-positions in the binol skeleton would not be necessary. We describe herein the first catalytic enantioselective 1,4-hydrophosphinylation of α,β-unsaturated esters with diaryl phosphine oxides and the still problematic catalytic enantioselective 1,2-hydrophosphonylation of α,β-unsaturated ketones with dialkyl phosphites by the use of 3:2 catalysts of (*R*)-(H_8)binolate/Mg^{II} in situ.

We initially investigated the enantioselective hydrophosphinylation of methyl cinnamate (**1a**) with diphenylphosphine oxide (**2a**) in the presence of (*R*)-binol (10–20 mol%), Bu_2Mg (10 mol%), and H_2O (10 mol%) in THF at 0°C for 22 h (Table 1, entries 1–3; see also Tables S1–S5). Interestingly, the use of 15 mol% of (*R*)-binol (Table 1, entry 2) gave

Table 1: Optimization of the catalyst in the 1,4-hydrophosphinylation.[a]



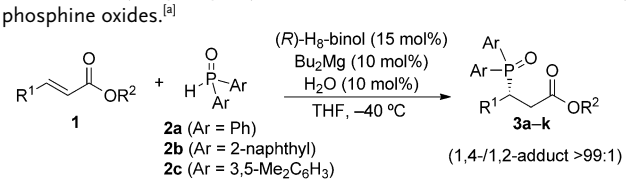
Entry	Ligand (mol%)	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	(*R*)-binol (10)	0	22	81	80
2	(*R*)-binol (15)	0	22	76	85
3	(*R*)-binol (20)	0	22	52	82
4	(*R*)-H_8-binol (15)	0	2	88	86
5	(*R*)-H_8-binol (15)	−40	16	91	95
6[b]	(*R*)-binol (15)	0	22	38	60

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), (*R*)-H_8-binol (10–20 mol%), Bu_2Mg (10 mol%), H_2O (10 mol%), THF. [b] The reaction was carried out without water.

3a in good yield with better enantioselectivity than the use of 10 or 20 mol% of (*R*)-binol (Table 1, entries 1 and 3). This result suggests that a 3:2 molar ratio of (*R*)-binol and Mg^{II} might be more effective than a 1:1 or 2:1 molar ratio [i.e., ((*R*)-binolate)Mg^{II} or ((*R*)-binolate)$_2Mg^{II}$]. The catalytic activity was increased and the reaction time was decreased to 2 h when we used (*R*)-H_8-binol in place of (*R*)-binol (Table 1, entry 4). Ultimately, the reaction proceeded smoothly at −40°C, and **3a** was obtained with high enantioselectivity (95% *ee*; Table 1, entry 5). Water was essential to induce the catalytic activity: a low yield and low enantioselectivity were observed under dry conditions without water (Table 1, entry 6).[14]

On the basis of this preliminary investigation, we examined the unprecedented 1,4-hydrophosphinylation of various methyl cinnamates with diaryl phosphine oxides (Table 2). For a variety of α,β-unsaturated methyl esters with an aryl moiety (compounds **3a**–**d**), a heteroaryl moiety (compounds **3e**,**f**), a conjugated olefin (compound **3g**), or an alicyclic moiety (compound **3h**), the corresponding 1,4-adducts were obtained exclusively with 85–95% *ee* (Table 2, entries 1–9). When the catalyst loading was decreased to 5 mol%, the reaction between **1a** and **2a** proceeded smoothly, and **3a** was obtained with 96% *ee* (Table 2, entry 2). Ethyl cinnamate was also a suitable substrate (Table 2, entry 10). Moreover, the

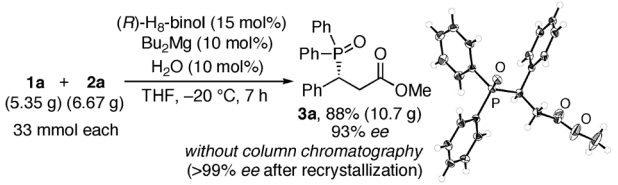
Table 2: 1,4-Hydrophosphinylation of α,β-unsaturated esters with diaryl phosphine oxides.[a]



Entry	R^1	R^2	**2**	**3**	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	Ph	Me	**2a**	**3a**	−40	16	91	95
2[b]	Ph	Me	**2a**	**3a**	−40	40	92	96
3	4-ClC_6H_4	Me	**2a**	**3b**	−40	5	93	92
4	4-$MeOC_6H_4$	Me	**2a**	**3c**	−20	4	80	95
5	4-MeC_6H_4	Me	**2a**	**3d**	−20	4	86	95
6	2-furyl	Me	**2a**	**3e**	−20	3	89	90
7	3-pyridyl	Me	**2a**	**3f**	−40	5	89	85
8	PhCH=CH	Me	**2a**	**3g**	−20	20	70	85
9	*c*-C_6H_{11}	Me	**2a**	**3h**	−20	18	86	95
10	Ph	Et	**2a**	**3i**	−40	10	78	91
11	Ph	Me	**2b**	**3j**	−20	4	91	92
12[c]	Ph	Me	**2c**	**3k**	−20	10	84	96

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), (*R*)-H_8-binol (15 mol%), Bu_2Mg (10 mol%), H_2O (10 mol%), THF, −40°C. [b] The reaction was carried out with (*R*)-H_8-binol (7.5 mol%), Bu_2Mg (5 mol%), and H_2O (5 mol%). [c] The reaction was carried out with 3.5 mmol each of **1a** and **2c**.

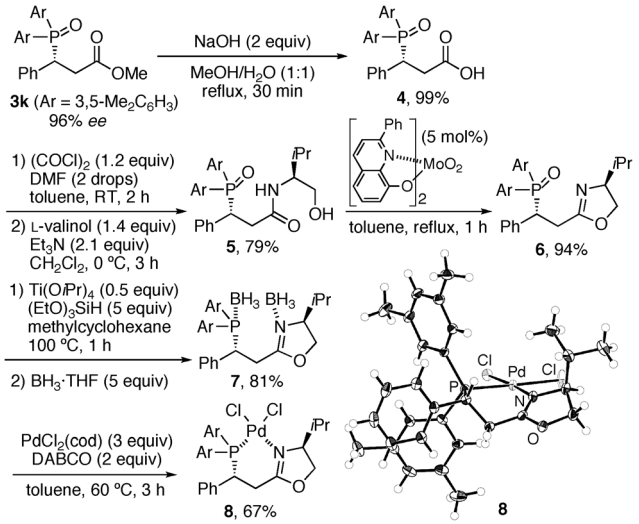
sterically demanding diaryl phosphine oxides **2b** and **2c** could be used, and the corresponding 1,4-adducts **3j** and **3k** were obtained with 92 and 96% *ee*, respectively, even on a gram scale (yield of **3k**: 1.24 g; entries 11 and 12). To test the synthetic potential of our approach, we carried out a large-scale synthesis with 33 mmol of each of the two substrates (Scheme 3). From the 1:1 mixture of **1a** and **2a**, the crude



Scheme 3. Catalytic 1,4-addition reaction on a 10 g scale.

product was obtained almost quantitatively. The product **3a** was highly crystalline, and when the crude mixture was washed with ether, we obtained 10.7 g of pure **3a** as a powder in 88% yield with 93% *ee* without silica-gel column chromatography. Furthermore, the recrystallization of **3a** from chloroform gave a single crystal (>99% *ee*), and we determined the absolute configuration of **3a** by X-ray crystal-structure analysis.

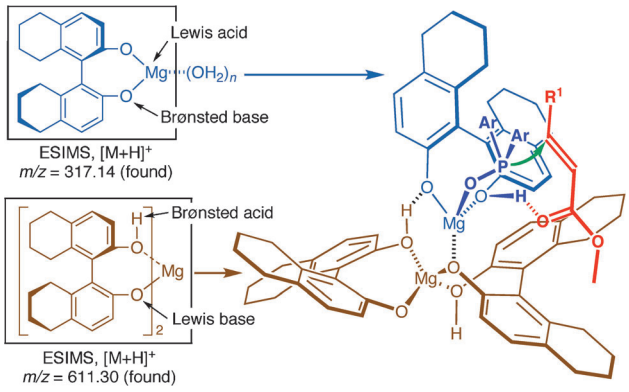
We took advantage of the synthetic utility of esters to synthesize a chiral palladium(II) complex with a phosphine–oxazoline ligand derived from the 1,4-adduct **3k**, since their use as chiral P,N ligands is one of the most important applications of organophosphorus compounds.[2,4g,15] The optically active 1,4-adduct **3k** (96% *ee*) was hydrolyzed,



Scheme 4. Synthesis of a chiral palladium(II) complex with a phosphine–oxazoline ligand from the 1,4-adduct **3k**. cod = 1,5-cyclooctadiene, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMF = *N*,*N*-dimethylformamide.

converted into an acid chloride, and subjected to amidation with L-valinol to give **5** (Scheme 4). To synthesize the oxazoline moiety, we used our bulky bis(7-phenylquinolinolate)dioxomolybdenum(IV) complex as a dehydrative cyclization catalyst,[16] and the reaction proceeded smoothly without epimerization to give **6** in 94% yield. This method is very important, since $[MoO_2(acac)_2]$[16] induced epimerization (product obtained with d.r. 87:13) with low reactivity (38% yield), and basic conditions with methanesulfonyl chloride/Et_3N were also much less effective (< 5% yield). The reduction of phosphine oxide **6** with $HSi(OEt)_3$ and $Ti(OiPr)_4$, followed by treatment with BH_3·THF,[17] resulted in the isolation of the diborane complex **7** in 81% yield as a stable ligand precursor. A straightforward and mild method involving the decomplexation of the BH_3 complex with DABCO[18] and recomplexation in situ with $[PdCl_2(cod)]$ gave the chiral P,N ligand–$Pd^{II}Cl_2$ complex **8** in 67% yield. Complex **8** was analyzed by X-ray crystallography. These procedures were performed without the purification of **3k**, **4**, and **5** by silica-gel column chromatography, and a short-column flash-chromatography technique was used to purify **6**, **7**, and **8**. The bulkiness of the P,N ligand with two sterically demanding 3,5-xylyl moieties, which were installed by hydrophosphinylation, could be useful for asymmetric transition-metal catalysis.[2]

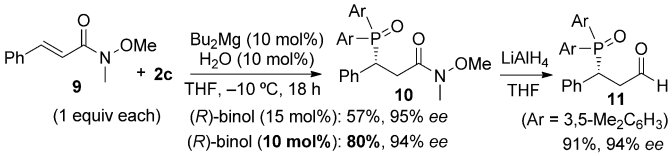
Next, we turned our attention to the characteristics of the active catalysts and mechanistic aspects of the reactions.[19] Unfortunately, the most likely 3:2 complex of (*R*)-H_8-binolate/Mg^{II} could not be identified by ESIMS analysis of a mixture of (*R*)-H_8-binol, Bu_2Mg, and H_2O (3:2:2 molar ratio) in THF, but 1:1 and 2:1 complexes of (*R*)-H_8-binolate/Mg^{II} were observed unambiguously (Scheme 5). We cannot deny the possibility that the transition state is based on independent 2:1 and 1:1 complexes, but we also propose a cooperative 3:2 complex of (*R*)-H_8-binolate/Mg^{II}, which might be constructed supramolecularly from the 2:1 and 1:1



Scheme 5. ESIMS analysis and possible transition state.

complexes. Nucleophile **2** would be activated by the highly Brønsted basic naphthoxide moiety, and then electrophile **1** would be activated by the associated Brønsted acid moiety of the naphthol. In this transition state, we can rationalize the absolute configuration of **3** as resulting from the significant steric hindrance of the congested naphthyl moieties even if 3,3′-nonsubstituted binols are used.

We next conducted a 1,4-addition reaction to an α,β-unsaturated amide:[4c,d,h] the particularly synthetically useful Weinreb amide **9** (Scheme 6). Interestingly, the use of

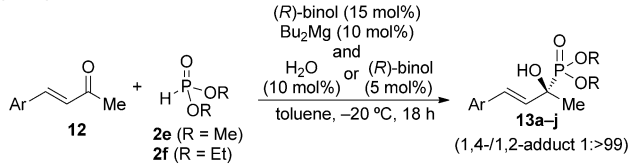


Scheme 6. 1,4-Hydrophosphinylation of the Weinreb amide **9**.

10 mol% of (*R*)-binol and 10 mol% of Bu_2Mg led to better reactivity than the conventional use of 15 mol% of (*R*)-binol and 10 mol% of Bu_2Mg; the corresponding 1,4-adduct **10** was obtained in 80% yield with 94% *ee*. Since compounds **9** and **10** can both readily chelate to Mg^{II}, a 3:3 (i.e., 1:1) molar ratio of (*R*)-binol and Bu_2Mg could be critical to enable the formation of the 3:2 complex of (*R*)-binolate/Mg^{II} in situ. Moreover, a transformation from the 1,4-adduct **10** to the aldehyde **11**, which is usually difficult to synthesize directly by hydrophosphinylation,[4a,f] occurred readily without epimerization upon treatment with $LiAlH_4$.

Finally, we explored the catalytic enantioselective 1,2-hydrophosphonylation of ketones, which has until now been limited to few examples.[6] The regioselectivity of such transformations depends strongly on the substrates and solvent. We were able to develop a 1,2-hydrophosphonylation of unreactive α,β-unsaturated ketones in the presence of a chiral magnesium(II) binaphtholate (Table 3; see also Tables S1–S5). For the reaction between various benzalacetones **12** and dimethyl phosphite (**2d**), the use of (*R*)-binol/Bu_2Mg/H_2O (3:2:2; 10 mol% in Mg^{II}) in toluene at −20 °C was effective (method A). Both aromatic and heteroaromatic moieties in **12** were acceptable, and the corresponding novel

Table 3: 1,2-Hydrophosphonylation of benzalacetones with dialkyl phosphites.

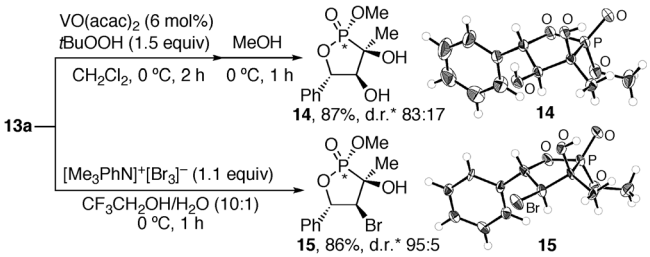


Entry	Ar	2	13	Method[a]	Yield [%]	*ee* [%]
1	Ph	**2d**	**13a**	A	89 (82)[b]	86 (>99)[b]
2	3-MeC_6H_4	**2d**	**13b**	A	77 (70)[b]	86 (99)[b]
3	3,5-$Cl_2C_6H_3$	**2d**	**13c**	A	96 (89)[b]	81 (94)[b]
4[c]	3,5-$(MeO)_2C_6H_3$	**2d**	**13d**	A	81	85
5[c]	2-naphthyl	**2d**	**13e**	A	74	84
6	2-furyl	**2d**	**13f**	A	79	83
7	3-thienyl	**2d**	**13g**	A	63 (59)[b]	82 (91)[b]
8	4-ClC_6H_4	**2d**	**13h**	B	82	81
9[d]	4-$MeOC_6H_4$	**2d**	**13i**	B	59	82
10	Ph	**2e**	**13j**	B	81	82

[a] Method A: (*R*)-binol (15 mol%), Bu_2Mg (10 mol%), H_2O (10 mol%), toluene, −20°C; method B: (*R*)-binol (20 mol%), Bu_2Mg (10 mol%), toluene, −20°C. [b] The yield and *ee* value of **13** after a single recrystallization are given in parentheses. [c] The reaction was carried out at −15°C. [d] The reaction was carried out at −10°C.

optically active tertiary allylic alcohols **13a–g** were obtained with good to high enantioselectivity (Table 3, entries 1–7). Although some substituents in the aryl moiety decreased the enantioselectivity in method A, the use of (*R*)-binol (20 mol%) and Bu_2Mg (10 mol%) without water was effective (method B), and the enantiomeric purity of **13h** and **13i** was improved to 81 and 82% *ee*, respectively (Table 3, entries 8 and 9). Some of the (*R*)-binol in method B probably plays the role of the water in method A. We also applied method B to a reaction with diethyl phosphite (**2e**), and the corresponding 1,2-adduct **13j** was obtained in 81% yield with 82% *ee* (Table 3, entry 10). Overall, despite the intrinsic low reactivity of ketones **12** and the possibility of a retroreaction and/or phospha-Brook rearrangement of products **13**, good conversion was observed without any side reactions.[7,8] The products were highly crystalline, and recrystallization from ethanol increased their optical purity to between 91 and >99% *ee* (Table 3) without any serious loss of yield. Moreover, according to the absolute configuration of products **13**, the same enantioface of α,β-unsaturated esters and ketones is discriminated, and thus a similar transition state to that shown in Scheme 5 might be involved.

Since the obtained 1,2-adducts are functionalized tertiary allylic alcohols, we carried out an oxidative transformation of **13a** in the form of a diastereoselective epoxidation with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate (Scheme 7).[20] In a one-pot process, the initial product was stirred in methanol, and the corresponding cyclized compound **14** was then obtained in 87% yield with d.r. 83:17. We also examined the bromocyclization of **13a**. The use of sterically demanding $[PhMe_3N]^+[Br_3]^-$ in H_2O–trifluoroethanol gave the desired cyclized compound **15** in 86% yield with d.r. 95:5. These novel five-membered oxaphospholanols **14** and **15** are analogues of bioactive materials with anticholinesterase properties.[21] The relative configurations of the four successive stereogenic centers (C–C–C–P) of **14** and **15** were determined by X-ray crystal-structure analysis.



Scheme 7. Synthesis of cyclic oxaphospholanols. acac = acetylacetonate.

In summary, we have developed a highly enantioselective 1,4-hydrophosphinylation of α,β-unsaturated esters with diaryl phosphine oxides and a highly enantioselective 1,2-hydrophosphonylation of α,β-unsaturated ketones with dialkyl phosphites by the use of simple and practical chiral magnesium(II) binaphtholate aqua complexes as cooperative Brønsted/Lewis acid–base catalysts. This practical methodology enabled by the diverse supramolecular structures of simple, inexpensive, and harmless Mg^{II} catalysts could find application in further efficient asymmetric catalytic transformations.

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Keywords: acid–base catalysts · hydrophosphinylation · hydrophosphonylation · magnesium · P ligands

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