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Highly Enantioselective 1,4-Addition of Diethyl Phosphite to Enones Using a Dinuclear Zn Catalyst

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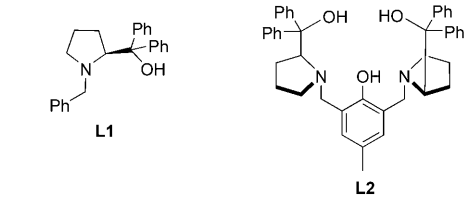
Chiral phosphonates and their phosphonic acid derivatives have attracted intense interest[1] in recent years due to their potential biological activity.[2] The asymmetric conjugate addition of phosphites to electron-deficient olefins provides a convenient and direct route toward functionalized chiral phosphonates.[3] In contrast, only a few catalytic asymmetric strategies for this transformation have been developed.[4,5] Very recently, Wang and co-workers[4a] described the first enantioselective 1,4-addition reactions of diphenyl phosphite to nitroalkenes with cinchona alkaloid[6] catalysts. Subsequently, Terada and co-workers[4b] also provided a straightforward organocatalytic approach for the phospha-Michael addition of nitroalkenes by employing a highly efficient chiral guanidine[7] catalyst. In addition, Jørgensen and co-workers[4c] reported an organocatalytic enantioselective phosphonylation of enals, and successfully applied the Michael adducts to the synthesis of biologically important compounds. However, to the best of our knowledge, the catalytic asymmetric phospha-Michael addition of enones has never been reported to date, despite the powerful synthetic potential of the phosphorus adducts. Herein, we report the first catalytic asymmetric 1,4-addition of diethyl phosphite to enones by using a dinuclear zinc catalyst.

Initially, it was found that diethylzinc was able to promote the addition of diethyl phosphite to enone **1a** (Table 1, entry 1). This process might be achieved by deprotonation of the phosphite to generate a highly nucleophilic zinc phosphonate intermediate.[8] Inspired by this finding, we hypothesized that diethylzinc in combination with chiral ligands such as amino alcohols[9] might lead to chiral induction for the current transformation. Thus **L1** was selected to examine the postulation. However, even in the best case, the enantioselectivity was poor (40% *ee*) owing to a side reaction (Table 1, entry 4).[10] Frustrated by these results, we

Table 1. Optimization of the catalytic asymmetric hydrophosphonylation of enones.



Entry[a]	**L** ([mol%])	Et_2Zn [mol%]	**2**	Solvent	Yield [%][b]	*ee* [%][c]
1	–	150	**2a**	toluene	75	–
2	**L1** (20)	20	**2a**	toluene	41	0
3	**L1** (20)	150	**2a**	toluene	60	−25
4[d]	**L1** (20)	150	**2a**	toluene	78	−40
5	**L2** (20)	150	**2a**	toluene	80	−5
6	**L2** (20)	40	**2a**	toluene	54	75
7	**L2** (20)	40	**2a**	THF	trace	n.d.[e]
8	**L2** (20)	40	**2a**	CH_2Cl_2	trace	n.d.[e]
9	**L2** (20)	40	**2a**	Et_2O	65	55
10	**L2** (20)	40	**2a**	hexane	91	35
11[f]	**L2** (20)	40	**2a**	toluene	98	99
12[f]	**L2** (10)	20	**2a**	toluene	90	95
13[f]	**L2** (20)	40	**2b**	toluene	55	99
14[f]	**L2** (20)	40	**2c**	toluene	60	79

[a] Reactions were carried out with **1a** (0.25 mmol) and **2** (1.5 equiv) in 2.5 mL solvent at room temperature for 12 h unless otherwise noted. [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC on a chiralcel OD-H column. [d] The reaction was carried out at 0 °C. [e] Not determined. [f] 4 A molecular sieves were used as an additive.

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set out to screen for an efficient system that would avoid the competitive background reaction.

Recently, a dinuclear zinc catalyst developed by Trost and co-workers has emerged as a powerful asymmetric catalyst for many enantioselective reactions.[11] The dinuclear zinc catalyst formed from **L2** and diethylzinc is thought to function in a dual Lewis acid/Lewis base manner. In light of these results, we further speculated that this bifunctional catalyst might lead to the formation of a zinc phosphonate intermediate and catalyze the asymmetric phospha-Michael addition reaction. Fortunately, when the dinuclear zinc catalyst was introduced to the reaction, the enantiomeric excess increased remarkably to 75% *ee* (Table 1, entry 6). Solvent screening indicated that toluene was the best solvent for this reaction among those examined with respect to enantioselectivity. To our great delight, when 4 Å molecular sieves were added to the reaction, the conversion and enantioselectivity were significantly enhanced; the desired phospha-Michael adduct **3a** was obtained in 98% yield and 99% *ee* (Table 1, entry 11). A slight decrease of enantioselectivity and reactivity was observed when the loading of **L2** was reduced from 20 mol% to 10 mol% (Table 1, entry 12). Other dialkyl phosphites were also investigated. When dimethyl phosphite was employed as a nucleophile, a low yield was observed (Table 1, entry 13). Switching diethyl phosphite to diisopropyl phosphite bearing bulkier alkyl groups led to a deterioration in both yield and enantioselectivity (Table 1, entry 14).

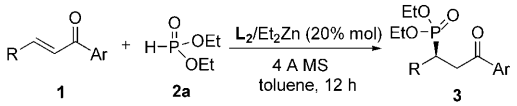
Under these optimized reaction conditions (20 mol% of **L2**/Et_2Zn and 4 Å MS in toluene at room temperature), a series of enones were investigated in the asymmetric phospha-Michael addition reaction. As illustrated in Table 2, consistently excellent enantioselectivities were observed for a broad range of enones. β-Aryl substituted enones with various substituents all afforded 1,4-adducts with excellent enantioselectivities (Table 2, entries 1–15). β-Heteroaromatic and β-aliphatic enones[12] were also excellent substrates for the present transformation (Table 2, entries 16–18). All enones underwent the phospha-Michael addition reaction smoothly to give the corresponding products in high yields. By comparison, enones with an *ortho*-substituted phenyl (Table 2, entry 4) or a naphthyl (Table 2, entries 12, 13) at the β-position showed a slightly reduced reactivity due to the steric hindrance.

The absolute configuration of compound **3n** was determined by chemical correlation with a known compound as follows. The Baeyer–Villiger oxidation of **3n** with CF_3CO_3H afforded the corresponding triester **4** without a loss in enantioselectivity (99% *ee*). Then compound **4** was hydrolyzed to give (*S*)-3-phenyl-3-phosphonopropanoic acid **5** of known absolute configuration (Scheme 1).[13] By comparison of the optical rotation, the absolute configuration of compound **3n** was determined to be *S*. The rest of the products were tentatively assigned by analogy.

Although the detailed reaction mechanism remains unclear, a plausible mechanism is postulated based on the observed results (Scheme 2). The initial step of this cycle involves deprotonation of diethyl phosphite by the catalyst to form the zinc phosphonate intermediate. Then the enone coordinates with another zinc of this catalyst and undergoes the phospho-transfer. The product is released by a proton exchange with the next diethyl phosphite and the catalyst is regenerated.

In conclusion, we have demonstrated the first asymmetric 1,4-addition reaction of diethyl phosphite with simple enones catalyzed by a dinuclear zinc complex. The γ-oxophosphonates were obtained in a straightforward manner in high yields with excellent enantioselectivities (up to 99% *ee*). Furthermore, this new catalytic phospha-Michael addition reaction was screened for a broad range of enones bearing both aryl and alkyl β-substituents. The strategy makes the asymmetric synthesis of biologically active phosphonates

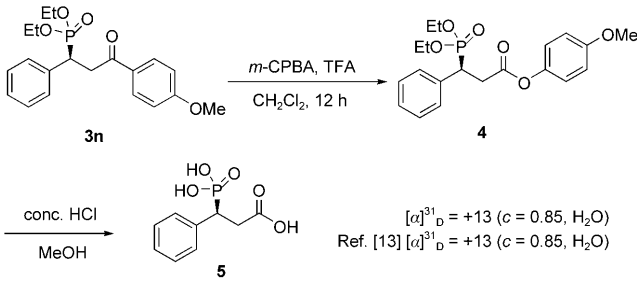
Table 2. Substrate scope for the catalytic asymmetric hydrophosphonylation of enones.



1 2a 3

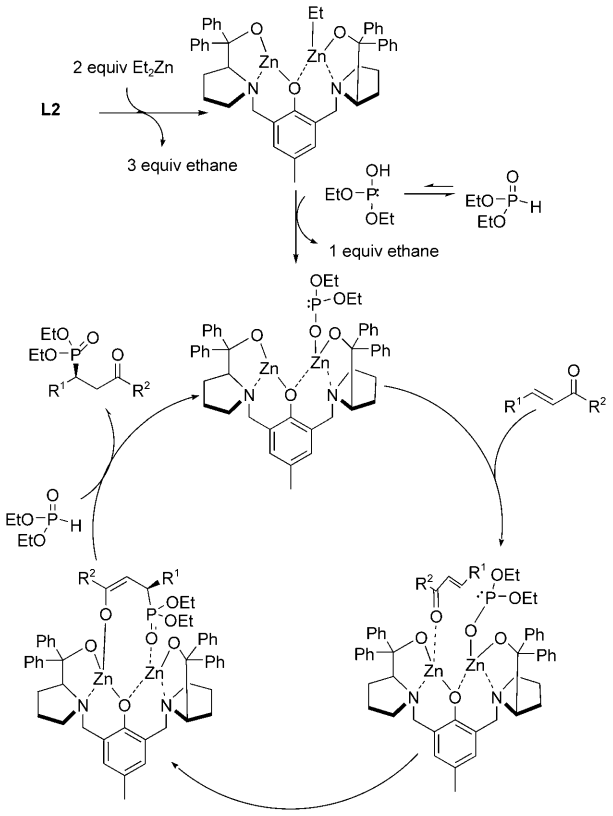
Entry[a]	1	R	Ar	Product [%][b]	*ee* [%][c]
1	**1a**	Ph	Ph	**3a** (98)	99
2	**1b**	3-MeC_6H_4	Ph	**3b** (94)	98
3	**1c**	4-MeC_6H_4	Ph	**3c** (92)	98
4	**1d**	2-$MeOC_6H_4$	Ph	**3d** (80)[d]	94
5	**1e**	3-$MeOC_6H_4$	Ph	**3e** (98)	97
6	**1f**	4-$MeOC_6H_4$	Ph	**3f** (90)	96
7	**1g**	4-FC_6H_4	Ph	**3g** (99)	93
8	**1h**	3-ClC_6H_4	Ph	**3h** (89)	97
9	**1i**	4-ClC_6H_4	Ph	**3i** (95)	96
10	**1j**	4-BrC_6H_4	Ph	**3j** (99)	95
11	**1k**	4-CNC_6H_4	Ph	**3k** (93)	96
12	**1l**	1-naphthyl	Ph	**3l** (86)[e]	93
13	**1m**	2-naphthyl	Ph	**3m** (85)[e]	95
14[f]	**1n**	Ph	4-$MeOC_6H_4$	**3n** (96)	99
15	**1o**	Ph	4-ClC_6H_4	**3o** (99)	96
16	**1p**	2-furyl	Ph	**3p** (93)	99
17	**1q**	*i*Pr	Ph	**3q** (99)	94
18	**1r**	*n*Bu	Ph	**3r** (94)	98

[a] Reactions were carried out with **1** (0.25 mmol) and **2a** (1.5 equiv) in 2.5 mL toluene at room temperature for 12 h unless otherwise noted. [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC analysis (see the Supporting Information). [d] Reaction stirred for 36 h. [e] Reaction stirred for 24 h. [f] The absolute configuration of **3n** was determined to be *S* by chemical correlation.



3n 4 5

Scheme 1. Determination of the absolute configuration of compound **3n**.



Scheme 2. Proposed catalytic cycle of the phospha-Michael addition.

and derivatives thereof more accessible. Further investigation of the detailed reaction mechanism and synthetic methodology are in progress.

Experimental Section

Typical experimental procedure: Diethylzinc (0.1 mL, 1 M in toluene, 0.1 mmol) was added to a stirred solution of **L2** (32 mg, 0.05 mmol) in toluene (0.5 mL) under an argon atmosphere. The mixture was stirred at room temperature for 0.5 h to generate the zinc catalyst. The resulting solution of catalyst was then added by syringe to a stirred and cooled (0 °C) mixture of 4 Å molecular sieves (100 mg, dried at 200 °C under vacuum for 12 h), (*E*)-chalcone (52 mg, 0.25 mmol), and diethyl phosphite (48 μL, 0.375 mmol) in toluene (2 mL) under an argon atmosphere. After the addition, the mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was cooled to 0 °C and quenched with aqueous HCl (1 M). The mixture was extracted with CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under vacuum. The pure product was afforded by column chromatography on silica gel (petroleum ether/ethyl acetate 7:1–1:2).

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Keywords: asymmetric catalysis · enones · hydrophosphonylation · Michael addition · phosphonates

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