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COMMUNICATION

Catalytic asymmetric construction of tetrasubstituted carbon stereocenters by conjugate addition of dialkyl phosphine oxides to β,β-disubstituted α,β-unsaturated carbonyl compounds†

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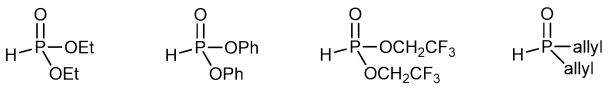
The catalytic asymmetric phospha-Michael reaction of dialkyl phosphine oxides with β,β-disubstituted α,β-unsaturated carbonyl compounds was achieved. The products bearing tetrasubstituted carbon stereocenters were obtained in high yields with excellent enantioselectivities (up to >99% ee).

Catalytic asymmetric construction of tetrasubstituted carbon stereocenters is a challenging objective in chemical synthesis.[1] The asymmetric conjugate addition of nucleophiles to acceptors such as β,β-disubstituted α,β-unsaturated carbonyl compounds is one of the most reliable approaches toward this challenge. To date, most studies have been focused on quaternary all-carbon stereocenters, which have been realized by using alkyl and aryl organometallic reagents with Cu- and Rh catalysts[2,3] or by using activated carbon nucleophiles such as cyanide.[4] Recently, several studies on asymmetric conjugate boration[5] and asymmetric epoxidation[6] of β,β-disubstituted α,β-unsaturated carbonyl compounds have been reported. By contrast, reports on building tetrasubstituted carbon stereocenters with nucleophiles of other elements including phosphorus nucleophiles have been much less developed yet.[7,8] This is due to the remarkably lower reactivity of β,β-disubstituted substrates and more difficult chiral discrimination derived from the smaller steric difference between the β-substituents. Recently, Ye, Liang and coworkers[8] reported an organocatalytic phospha-Michael reaction of cyclic β,β-disubstituted α,β-unsaturated enones. Still, the catalysis is ineffective to more challenging linear substrates.[9] Herein, we report the first conjugate addition of dialkyl phosphine oxides to β,β-disubstituted α,β-unsaturated enones and *N*-acylpyrroles.



Due to our continuous interest in phosphorus-containing nucleophiles and previous reports on the phospha-Michael reaction of dialkyl phosphites and dialkyl phosphine oxides with α,β-unsaturated compounds,[10] we began to investigate the reaction of (*E*)-1,3-diphenylbut-2-en-1-one **2a** with various phosphorus donors catalyzed by 20 mol% zinc–bis-ProPhenol **L1** complex.[11] The preliminary results indicated that the reactions with phosphites **1a**, **1b** and **1c** did not proceed at all in the presence of the catalyst. Surprisingly, when diallyl phosphine oxide **1d** was used as the nucleophile, the reaction proceeded slowly with <10% yield at room temperature for 12 h. This is probably because that the dialkyl phosphine oxides are more electron-rich and relatively softer nucleophiles than dialkyl phosphites.[10a,10c,12]

With this result in hand, we then tried to improve the yield of the reaction. When the reaction was performed at 60 °C, the conversion improved a little, the product was obtained in 32% yield with 82% ee (Table 1, entry 1). Inspired by the obtained enantioselectivity, we then focused on the structure of the ligand. When our previously reported thienyl-bis-ProPhenol **L2** was introduced to the present phospha-Michael reaction, the yield and enantioselectivity were both greatly improved (Table 1, entry 2, 74%, 99% ee). This phenomenon can be explained by the following two points: (1) the thienyl group will coordinate with the metal center and thereby prevent the unfavourable binding of the Lewis basic product to the Zn atom, which would poison the catalyst; (2) the thienyl coordination will increase the stability of the zinc catalyst, which might be decomposed gradually in the presence of dialkyl phosphine oxides at high temperature. The yield seemed not to improve upon further increase of the temperature to 60 °C. To our delight, when pyridine was added and the solvent was switched to toluene, the yield increased remarkably to 94% and the reaction temperature could be reduced to 40 °C (Table 1, entry 6). The reaction could also be performed with 10 mol% catalyst under modified conditions despite that both the yield and enantioselectivity were reduced (Table 1, entry 7).

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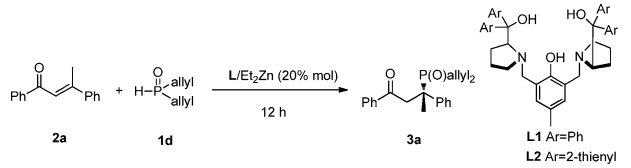
† Electronic supplementary information (ESI) available: Experimental procedures, analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. CCDC 842933. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc16079f

Table 1 Optimization of the reaction conditions



Entry[a]	L (mol%)	Solvent	Additive	T/°C	Yield[b] (%)	ee[c] (%)
1	**L1** (20%)	THF	—	60	32	82
2	**L2** (20%)	THF	—	40	74	99
3	**L2** (20%)	THF	—	60	75	99
4	**L2** (20%)	THF	Pyridine	60	89	99[d]
5	**L2** (20%)	Toluene	Pyridine	60	94	99[d]
6	**L2** (20%)	Toluene	Pyridine	40	94	99[d]
7	**L2** (10%)	Toluene	Pyridine	40	85	94[e]

[a] Reactions were carried out with **1d** (0.375 mmol, 1.5 eq), and **2a** (0.25 mmol). [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC analysis of the isolated product. [d] Reactions were carried out with 1 eq of pyridine. [e] Reaction was carried out with **1d** (0.75 mmol, 1.5 eq), **2a** (0.5 mmol) and 10 eq of pyridine in 2.5 mL toluene.

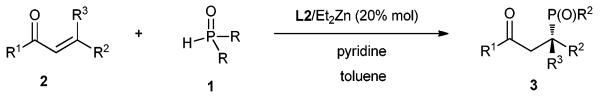
With the optimized reaction conditions established, the substrate scope was then evaluated. As shown in Table 2, consistently excellent enantioselectivities were achieved from a wide range of β,β-disubstituted enones including aromatic- and aliphatic-substituted substrates. The electronic nature of the substituent on the phenyl ring did not have obvious impact on the reaction. Interestingly, *Z*-**2h** gave the same enantiomer as *E*-**2h** and produced higher enantioselectivity than *E*-**2h** (Table 2, entries 8, 9). Other dialkyl phosphine oxides such as **1e** and **1f** were also found to be good substrates for the present catalysis (Table 2, entries 18, 19).

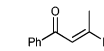
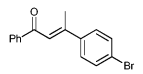
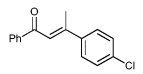
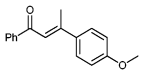
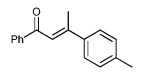
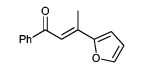
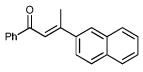
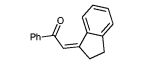
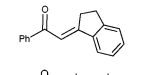
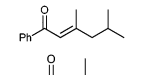
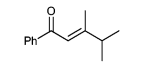
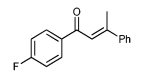
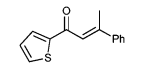
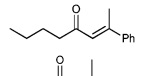
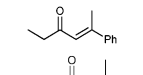
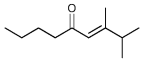
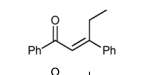
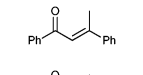
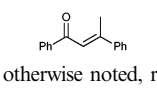
The present method was also applicable to Shibasaki's *N*-acylpyrroles[4a] which could serve as equivalents of β,β-disubstituted α,β-unsaturated esters. As shown in Table 3, good yields and excellent enantioselectivities were achieved for all aromatic and aliphatic substrates tested. To our surprise, alkyl substrates *E*-**5e** and *Z*-**5e** both gave high yields and enantioselectivities and produced opposite enantiomers (Table 3, entries 5, 6).

The X-ray crystallographic result suggests that the absolute configuration of **3q** is *S* (Fig. 1).[13] So we believe the *E*-enones may adopt s-*cis* conformation to react with the dialkyl phosphine oxides. In this case, the dialkyl phosphine oxide will attack the *Si*-face of the enones and the stereochemistry of the final product is *S*. However, for *Z*-enone **2h**, the s-*cis* conformation is extremely disfavored for the steric hindrance between the two substrates. So *Z*-enone **2h** has to select the s-*trans* conformation and thereby providing the same enantiomer with *E*-enone **2h**. In the case of alkyl substrates *Z*-**4e**, the flexible linear alkyl group does not provide enough steric hindrance, so the s-*cis* conformation is still favored in this situation and the resulting product has opposite configuration with that provided by *E*-**4e** (Fig. 2).

In conclusion, dialkyl phosphine oxides were found as a class of highly reactive nucleophiles in the catalytic asymmetric phospha-Michael reaction with β,β-disubstituted α,β-unsaturated carbonyl compounds. The products bearing tetrasubstituted carbon stereocenters were obtained in high yields with excellent enantioselectivities (up to >99% ee). A relatively wide range of substrates scope was achieved in this process. Further investigations

Table 2 Scope of the phospha-Michael reaction



Entry[a]	Substrate	R	Product	Yield (%)	ee[b] (%)
1		Allyl	**3a**	94	99
2		Allyl	**3b**	98	96
3		Allyl	**3c**	94	98
4		Allyl	**3d**	97	98
5		Allyl	**3e**	94	96
6		Allyl	**3f**	93	98
7		Allyl	**3g**	94	96
8		Allyl	**3h**	72	96
9		Allyl	**3h**	90	80
10		Allyl	**3i**	90	93
11		Allyl	**3j**	92	90
12		Allyl	**3k**	91	98
13		Allyl	**3l**	97	98
14		Allyl	**3m**	98	>99
15		Allyl	**3n**	84	>99
16		Allyl	**3o**	87	96
17		Allyl	**3p**	84	94
18		Et **1e**	**3q**	82	>99[c,d]
19		Bu **1f**	**3r**	90	99[d]

[a] Unless otherwise noted, reactions were carried out with **1** (0.375 mmol, 1.5 eq) and **2** (0.25 mmol) in 2.5 mL toluene at 40 °C for 12 h. [b] The enantiomeric excess was determined by HPLC analysis. [c] Absolute configuration of **3q** was determined to be *S* by X-ray crystallography and the rest were assigned by analogy. [d] The reaction was performed at 60 °C.

of the reaction mechanism and applications of the phospha-Michael adducts are ongoing.

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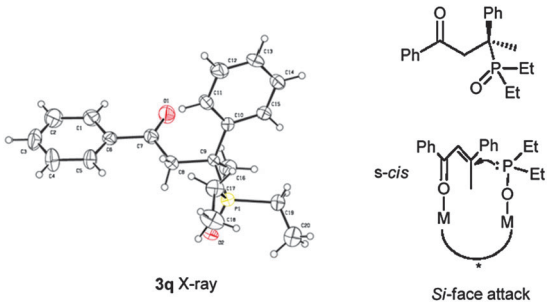
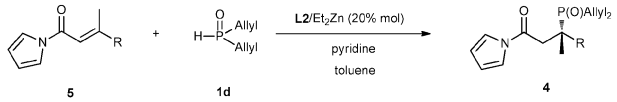
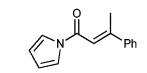
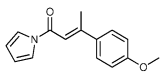
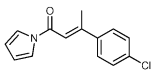
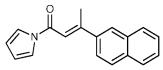
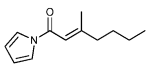
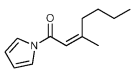


Fig. 1 X-Ray of **3q** and proposed transition-state model.

Table 3 Scope of the β,β-disubstituted *N*-acylpyrroles



5 1d 4

Entry[a]	Substrate	Product	Yield (%)	ee[b] (%)
1		**4a**	88	>99
2		**4b**	91	96
3		**4c**	96	94
4		**4d**	93	94
5		**4e**	90	98
6		**4e**	95	−97

[a] Unless otherwise noted, reactions were carried out with **1d** (0.375 mmol, 1.5 equiv.) and **5** (0.25 mmol) in 2.5 mL toluene at 40 °C for 12 h. [b] The enantiomeric excess was determined by HPLC analysis.

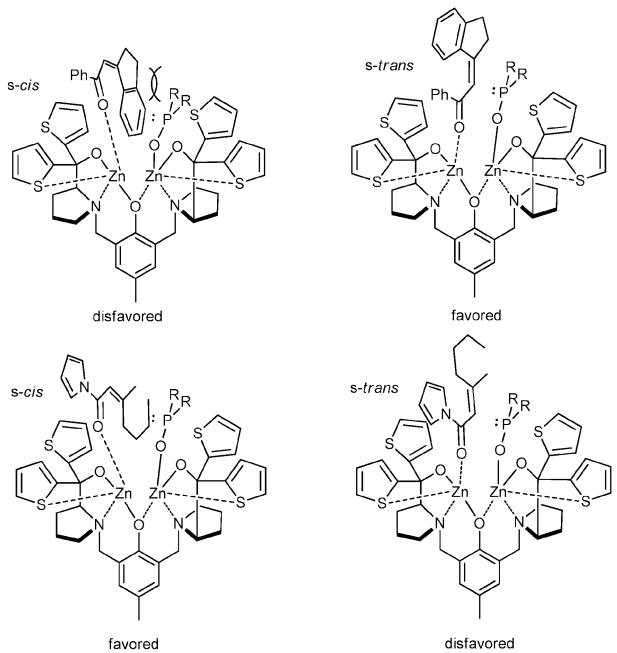


Fig. 2 Different pathways of *Z*-substrates.

Notes and references

1 For reviews on the synthesis of quaternary stereocenters, see: (*a*) I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105; (*b*) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363; (*c*) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (*d*) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (*e*) J. T. Mohr and B. M. Stoltz, *Chem.–Asian J.*, 2007, **2**, 1476; (*f*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969; (*g*) B. Wang and Y.-Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207.

2 For an excellent comprehensive review, see: C. Hawner and A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295.

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