Enantioselective organocatalytic phospha-Michael reaction of α,β-unsaturated ketones†

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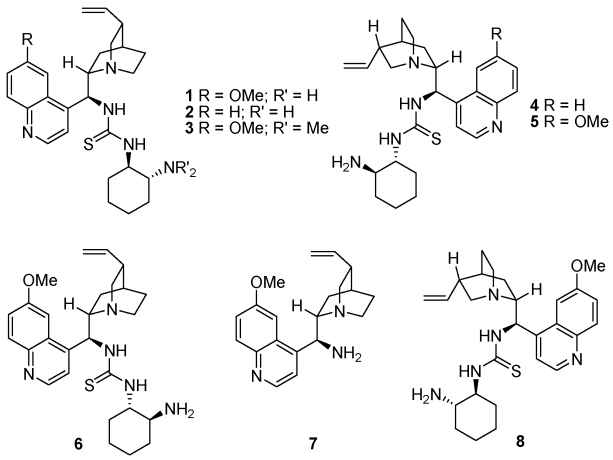
Enantioselective organocatalytic phospha-Michael reaction of α,β-unsaturated ketones and diaryl phosphine oxides has been developed for the first time employing multifunctional organocatalysts. Optically active products bearing quaternary chiral carbon stereocenters were obtained in high yields with good to excellent enantioselectivities (up to 98% ee).

Over the past decade, chiral phosphines have been used as powerful ligands for metal catalyzed enantioselective transformations, and have achieved enormous progress in the history of asymmetric catalysis.[1] Also, they are recognized as organocatalysts in organic reactions.[2] Chiral phosphines are traditionally obtained by standard resolution of racemic materials.[3] Recently, the catalytic asymmetric 1,4-addition of trivalent phosphine compounds (R_2PH) to electron-deficient olefins, has provided straightforward access to useful chiral phosphine compounds with different functional groups.[4–6] Further development of catalytic asymmetric methods to access diverse chemical functionalities, therefore, is still highly desirable. The direct addition of P(O)–H bonds of dialkyl or diaryl substituted phosphine oxides ($R_2P(O)H$) to activated alkenes is one of the most convenient routes to the stable precursors of phosphine compounds. However, there are only a few catalytic enantioselective methods available to access this transformation. Among these methods, the most direct approach is the asymmetric addition of phosphine oxides to nitroolefins catalyzed by chiral guanidine for synthesis of β-aminophosphine derivatives.[7] To the best of our knowledge, the asymmetric Michael reaction of phosphine oxides and enones has not been investigated in the literature,[8] in which more challenging molecular complexity with chiral quaternary carbon centers can be created.[9]

In this context, we have recently reported that a well-designed multifunctional organocatalyst was a valuable platform for the development of enantioselective Michael addition of α,β-unsaturated ketones.[10] Based on these results, we further expand this chemistry to achieve the first enantioselective organocatalytic Michael addition of pentavalent diaryl phosphine oxides to α,β-unsaturated ketones. This new approach of asymmetric conjugate addition also allows the construction of phosphino compounds with chiral quaternary carbon center using simple β,β-disubstituted α,β-unsaturated ketones and dirayl phosphine oxides.



First, the Michael addition of cyclohex-2-enone and diphenylphosphine oxide was examined using **1** (prepared from (1*R*,2*R*)-1,2-diaminocyclohexane and 9-amino (9-deoxy) epiquinine) as a catalyst, and the representative results are presented in Table 1. The Michael addition proceeded with low enantioselectivity of 33% in THF solvent. Studies of the effect of the solvent showed that CH_2Cl_2 was suitable for both conversion (76%, entry 8) and enantioselectivity (90% ee). Other primary amine-thiourea catalysts (**2**, **4**, **5**) with different chiral elemental assembly also afforded moderate to good ee values (60–71%, entries 9, 11-12). If the primary amine in **1** was substituted with two methyl groups (catalyst **3**), the conversion and enantioselectivity of the reaction dramatically decreased to 22% and 15%, respectively. It indicates that the primary amine group plays a key role in the catalytic process (entry 10). The stereochemical outcome of the Michael product remained when the cinchona alkaloid scaffold of organocatalysts was changed to its pseudo enantiomer. As (1*R*,2*R*)-1,2-diaminocyclohexane was switched to its enantiomer (**1** *vs.* **6**), the stereochemical outcome of the Michael product was reversed (entry 13). Therefore, it could be concluded that the stereochemistry was dictated by the chiral 1,2-diaminocyclohexane scaffold. And this also could explain the fact that low enantioselectivity was obtained when the primary amine was blocked. When 9-amino (9-deoxy) epiquinine (**7**) was used as the catalyst, only 30% of conversion and 36% ee value were afforded (entry 14). Therefore, the existence of a thiourea group is also necessary for the catalytic process and stereochemical control. The Michael addition proceeded well in the presence of **8**, a pseudo enantiomer of **1**, and produced an opposite stereochemical outcome (entry 16).

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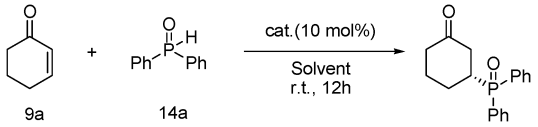
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of the Michael addition products. CCDC 767563 & 767564. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00094a

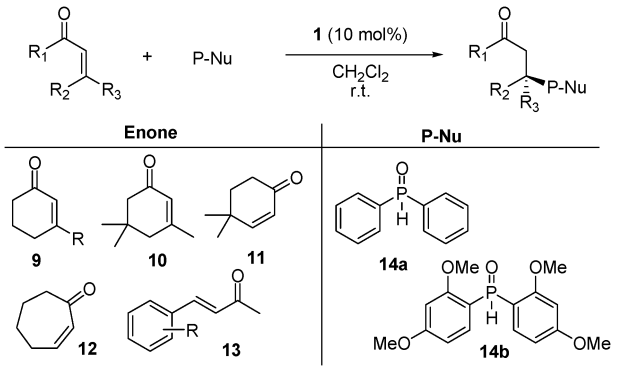
Table 1 Enantioselective organocatalytic phospha-Michael reaction of cyclohexanone with diphenylphosphine oxide[a]



Entry	Cat.	Solvent	Conv.(%)[b]	ee(%)[c]
1	**1**	THF	80	33
2	**1**	EtOAc	79	23
3	**1**	Toluene	76	70
4	**1**	Et_2O	82	37
5	**1**	Dioxane	81	26
6	**1**	MeCN	76	56
7	**1**	$CHCl_3$	72	80
8	**1**	CH_2Cl_2	76	90
9	**2**	CH_2Cl_2	65	71
10	**3**	CH_2Cl_2	22	15
11	**4**	CH_2Cl_2	23	64
12	**5**	CH_2Cl_2	49	60
13	**6**	CH_2Cl_2	46	−10
14	**7**	CH_2Cl_2	30	−36
15[d]	**1**	CH_2Cl_2	98	90
16[d]	**8**	CH_2Cl_2	90[e]	−90

[a] Unless otherwise noted, all reactions were carried out using 0.1 mmol of **1** (10 mol %), 1.0 mmol of **14a**, and 3.0 mmol of **9a** (3.0 equiv) in 2.0 mL of indicated solvent at room temperature. [b] Conversion was determined by GC. [c] Enantiomeric excess was determined by chiral HPLC analysis (see ESI† for details). [d] For 48 h. [e] Isolated yield.

Table 2 Enantioselective organocatalytic phospha-Michael reaction of various α, β-unsaturated ketones catalyzed by **1**



Entry	Enone	*P*-Nu	Adduct	Yield[a] (%)	ee[b] (%)
1	**9a**, R = H	**14a**	**15aa**	94	90
2	**9b**, R = Me	**14a**	**15ba**	96	98
3	**9c**, R = Et	**14a**	**15ca**	95	94
4[c]	**9d**, R = Pr	**14a**	**15da**	87	94
5[c]	**9e**, R = Bu	**14a**	**15ea**	85	97
6[c]	**9f**, R = *i*-Bu	**14a**	**15fa**	88	94
7[c]	**9g**, R = Pentyl	**14a**	**15ga**	94	92
8	**9h**, R = C_2H_4Ph	**14a**	**15ha**	82	92
9[c]	**9i**, R = cyclohexyl	**14a**	**15ia**	85	90
10	**10**	**14a**	**16**	90	96
11	**11**	**14a**	**17a**	95	98
12	**12**	**14a**	**18**	87	90
13	**9a**	**14b**	**19ab**	86	91
14	**9b**	**14b**	**19bb**	84	94
15[c]	**9i**	**14b**	**19ib**	92	94
16	**11**	**14b**	**17b**	90	98
17	**13a**, *R* = 4-NO_2	**14a**	**20aa**	90	92
18	**13b**, *R* = 4-MeO	**14a**	**20ba**	97	85
19	**13c**, *R* = 4-Br	**14a**	**20ca**	94	94
20	**13d**, *R* = 3-Me	**14a**	**20da**	92	84

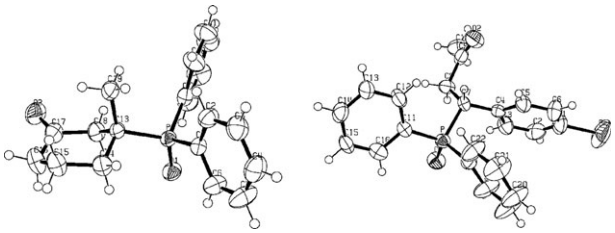
[a] Isolated yield of pure adducts. [b] Enantiomeric excess was determined by chiral HPLC. [c] Reaction performed at 30 °C temperature with 20 mol% catalyst loading for the given time (see ESI† for details).

The generality of the methodology is shown in Table 2 under optimized conditions. The reactions between cyclic enones and phosphine oxide nucleophiles are very successful and the substituents on cyclohex-2-enone hardly affect the yields and enantioselectivities of the Michael addition. Cyclohex-2-enone reacted with **14a** quite smoothly to form the product in 94% isolated yield with 90% ee (entry 1). It should be noted that 85–96% isolated yields with excellent enantioselectivities (90–98%) were obtained in the reaction of diphenylphosphine oxide and a variety of 3-substituted cyclohex-2-enones (**9b–i**, **10**). The reaction constructs phosphine substituted quaternary stereocenters (entries 2–10), which is an important yet challenging task in asymmetric synthesis.[8] Especially, the reaction of 3-methylcyclohex-2-enone afforded the desired adduct in up to 96% isolated yield with 98% ee (entry 2). For sterically hindered **10**, 90% isolated yield and up to 96% ee were obtained (entry 10). The phospha-Michael addition of 4-disubstituted cyclohex-2-enone (**11**) also proceeded in excellent isolated yield and asymmetric induction (entry 11). The addition of cyclohept-2-enone was further investigated and 87% isolated yield and 90% ee were obtained (entry 12). It is noteworthy that the sterically hindered nucleophile **14b** is also successfully used in this type of Michael addition and 1,4-adducts were formed in 84–92% isolated yields with 91–98% ee values (entries 13–16).

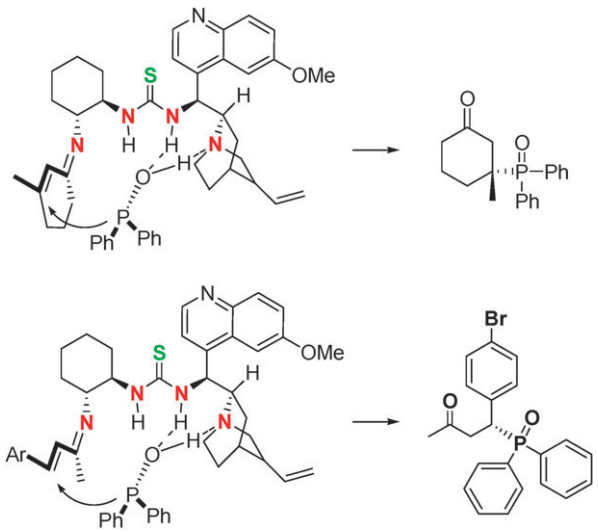
Further exploration found that the catalytic Michael additions of a series of aromatic enones took place quite successfully to form the products in 90–97% isolated yields (entries 17–20). Although the asymmetric induction of aromatic enones was slightly lower than that of cyclic enones, good to excellent enantioselectivities (84–94%) were obtained. It should be noted that electron-withdrawing (entries 17, 19 and 20) and electron-donating substituents (entries 18, 21) can be introduced into the aromatic ring without dramatic effect on the yield or enantioselectivity. In contrast, the enantioselectivities of less sterically hindered acyclic alkyl enones decreased.[11] Unfortunately, no product was observed in the reaction of cyclohex-2-enone and 4,4′-dibromodiphenylphosphine oxide.

On the basis of the absolute configuration of the chiral Michael products **15ba** and **20ca** from X-ray crystal structure analysis (Scheme 1), a plausible catalytic mechanism by concerted activation was proposed (Scheme 2).‡ The sense of the enantioselectivity is dictated by the chiral *trans*-1,2-diamino-cyclohexane unit, but the level of the stereoselection is determined by the presence of a match rather than a mismatch chiral 9-amino (9-deoxy) cinchona alkaloid unit.

In summary, we have developed a highly efficient and enantioselective Michael addition of α,β-unsaturated ketones with diaryl phosphine oxides using a multifunctional catalyst. Optically active products bearing a quaternary chiral carbon stereocenter were obtained in high yields with good to excellent enantioselectivities (up to 98% ee). Current studies in our laboratories aim at further expanding the scope and application of this chemistry.



Scheme 1 X-ray crystal structures of **15ba** and **20ca**.



Scheme 2 Plausible catalytic mechanism by concerted activation.

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Notes and references

‡ General procedure for asymmetric Michael addition: To a solution of α,β-unsaturated ketone (3.0 mmol) in DCM (2.0 mL) was added diphenylphosphine oxide (1.0 mmol), catalyst (0.10 mmol). The reaction mixture was stirred at given temperature. After completion monitored by TLC, the product was purified by silica gel chromatography to yield the desired addition product. The enantiomeric excess of the product was determined by HPLC analysis on chiral column.

Crystal structure determination of compound **15ba**: $C_{19}H_{21}O_2P$, M = 312.33; a block crystal (0.56 × 0.52 × 0.44 mm), T = 296(2), λ(Mo-Kα) = 0.71073 Å, Orthorhombic, space group: $P2_12_12_1$, a = 6.3328(2) Å, b = 9.3463(3) Å, c = 28.2033(10) Å, V = 1669.30(10) Å3, 19388 total reflections, 2953 unique, R_{int} = 0.0257, R_1 = 0.0302 ($I > 2\sigma$), wR_2 = 0.0775. Flack parameter: 0.03(8).

Crystal structure determination of compound **20ca**: $C_{22}H_{20}BrO_2P$, M = 427.26; a block crystal (0.10 × 0.05 × 0.05 mm), T = 273(2), λ(Mo-Kα) = 0.71073 Å, Monoclinic, space group: C2, a = 19.698(4) Å, b = 5.7772(13) Å, c = 17.469(4) Å, V = 1983.8(8) Å3, 3306 total reflections, 1965 unique, R_{int} = 0.0343, R_1 = 0.0427 ($I > 2\sigma$), wR_2 = 0.0860, Flack parameter: 0.05(2).

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11 Pent-3-en-2-one (92% yield, 70% ee), oct-3-en-2-one (70% yield, 67% ee).

