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Asymmetric Organocatalytic Conjugate Addition of Diarylphosphane Oxides to Chalcones

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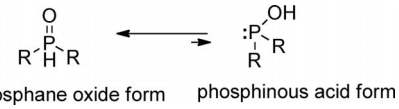
The first example of a convenient and enantioselective asymmetric conjugate addition of diarylphosphane oxides to chalcones is reported. By using commercially available dihydroquinine as the organocatalyst and diphenylphosphane oxide as the nucleophile, the adducts were isolated in high yield and up to 89 % *ee*. The final adducts can be easily recrystallized to enantiopure material.

Introduction

Enantiomerically enriched organophosphorus compounds play a dominant role in organic synthesis as attested by the importance of chiral phosphanes and phosphane oxides as ligands or preligands in metal-catalyzed transformations.[1] Moreover, the wide structural diversity and properties of phosphorus compounds make them not only a valuable class of building blocks, but also products of interesting biological activities witnessed by their naturally occurring representatives.[2] For example, α- and β-aminophosphonic acids are isosteric or bioisosteric analogues of the corresponding amino acids showing antibacterial and antifungal activities.[3] Moreover, they behave as enzyme inhibitors,[4] including HIV protease.[5] Consequently, increasing research efforts have been focused on the development of stereoselective approaches for the synthesis of organophosphorus compounds through metal-catalyzed protocols[1] and more recently by organocatalytic approaches.[6] The formation of a P–C bond can be straightforwardly achieved by a Michael addition reaction of trivalent and pentavalent phosphorus species to an electron-poor alkene.[7] In the area of organocatalytic phospha-Michael addition, a few successful achievements have been reported by using α,β-unsaturated aldehydes and nitroalkenes as the acceptors with different organic promoters mainly by using dialkyl phosphites.[8] Nevertheless, only very recently, enones have been investigated as acceptors by using trivalent and pentavalent phosphorus nucleophiles. Duan and co-workers developed a pincer-palladium-catalyzed Michael addition of diarylphosphanes to chalcones, whose adducts were in situ oxidized with hydrogen peroxide to the more stable phosphane oxides in good to high yield and excellent enantioselectivity.[9] A few studies have been focused on secondary aryl or alkylphosphane oxides as the donors to develop direct enantioselective approaches to phosphane oxide derivatives through conjugate addition to α,β-unsaturated carbonyl compounds. A metal-catalyzed highly enantioselective conjugate addition of dialkylphosphane oxides to α,β-unsaturated *N*-acylpyrroles has been reported by Wang and co-workers.[10] An organocatalytic Michael addition of diarylphosphane oxides to cyclic and aliphatic enones has been disclosed by Ye and co-workers employing diamino cinchona alkaloid derived thioureas.[11] These multifunctional catalysts enabled the formation of the adducts in high yield and enantioselectivity. Iminium ion/Brønsted base bifunctional activation of the reagents by the catalyst has been postulated to explain the stereochemical outcome of the reaction.

With the aim of enlarging the scope of relatively underexplored enantioselective phospha-Michael addition reactions, we undertook an investigation on easily accessible *trans*-chalcones as the acceptors and diarylphosphane oxides as the donors. Secondary phosphane oxides are known to equilibrate with the tautomer phosphinous acid (R_2POH), which is the nucleophilic form, although the phosphane oxide is almost exclusively prevalent under neutral conditions (Scheme 1).[12]



Scheme 1. Phosphane oxide–phosphinous acid equilibrium under neutral conditions.

The equilibrium shift toward the active phosphinous acid form is likely to be effected by the presence of a base.[13] Moreover, taking into consideration that chalcones generally require harsher conditions to proceed via iminium

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ion catalysis,[14] we devised an organocatalytic approach based on the use of noncovalent promoters such as cinchona alkaloids and their derivatives (Figure 1). We speculated that the tertiary base and an acidic group would provide bifunctional activation of the phosphane oxide and chalcone, respectively.[15] Herein, we wish to describe the first enantioselective direct phospha-Michael addition of diarylphosphane oxides to chalcones catalyzed by cinchona alkaloids.

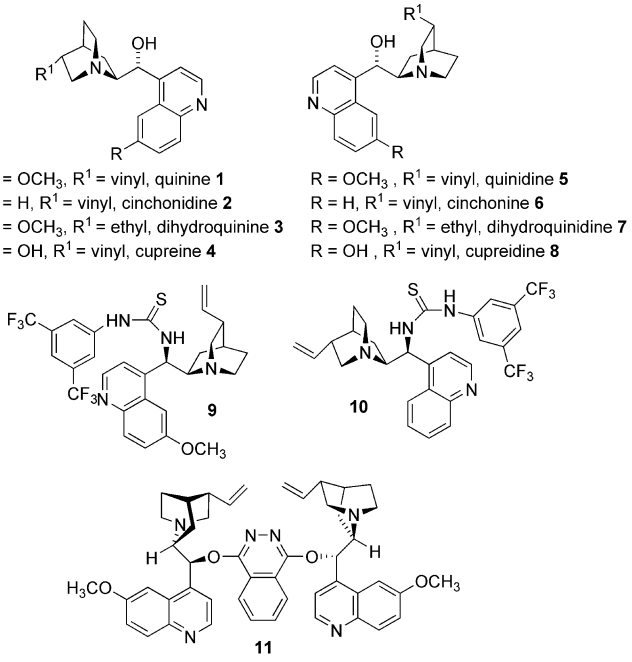


Figure 1. Cinchona alkaloids and their derivatives screened in the phospha-Michael addition.

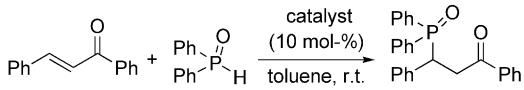
Results and Discussion

In a preliminary investigation, commercially available *trans*-chalcone **12a** and diphenylphosphane oxide **13a** were reacted at room temperature in toluene with a variety of catalysts **1**–**11** (Table 1).

As highlighted in Table 1, adduct **14a** was obtained in good to high yield but with a variable level of enantioselectivity, showing the relevant role played by structural features on catalytic efficiency. Dihydroquinine **3** and dihydroquinidine **7** afforded both enantiomerically enriched products with an acceptable *ee* value and in high yield (Table 1, Entries 3 and 7).

Cinchona alkaloids with additional or stronger Brønsted acidic moieties such as cupreine **4**, cupreidine **8**, and thiourea derivatives **9** and **10** proved to be among the worst promoters. Finally, dimeric ligand **11** led to racemic product. Having established dihydroquinine **3** as the most effective catalyst for the reaction, the influence of solvent and the nature of the phosphane oxides were next studied (Table 2). Polar or coordinating solvents were less suitable media for the phospha-Michael addition of compound **13a** to **12a**, whereas, as expected, the highest asymmetric induction and conversion were observed when using aromatic solvents (Table 2, Entries 4–7), with chlorobenzene as the best medium (Table 2, Entry 5).[16] Differently substituted

Table 1. Michael addition of diphenylphosphane oxide to *trans*-chalcone promoted by catalysts **1**–**11**.[a]

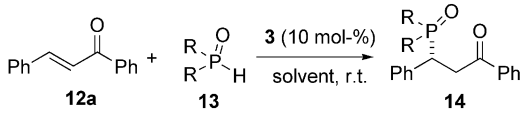


12a **13a** **14a**

Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1**	24	99	47 (*R*)
2	**2**	22	66	16 (*R*)
3	**3**	48	99	64 (*R*)
4	**4**	39	78	23 (*R*)
5	**5**	39	95	44 (*S*)
6	**6**	39	88	4 (*S*)
7	**7**	45	99	62 (*S*)
8	**8**	44	52	12 (*S*)
9	**9**	69	72	3 (*S*)
10	**10**	65	79	4 (*R*)
11	**11**	48	82	*rac*

[a] Reaction conditions: **12a** (0.2 mmol), **13a** (0.2 mmol), and catalyst (0.02 mmol) in toluene (1.0 mL). [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC. Absolute configuration determined by comparison with the optical rotation value given in the literature.[9]

Table 2. Screening of solvents and diarylphosphane oxides in the Michael addition to *trans*-chalcone promoted by compound **3**.[a]



12a **13** **14**

R = Ph (**13a**)
R = 4-$CH_3OC_6H_4$ (**13b**)
R = 1-naphthyl (**13c**)
R = 2-naphthyl (**13d**)
R = 3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$ (**13e**)
R = 4-ClC_6H_4 (**13f**)

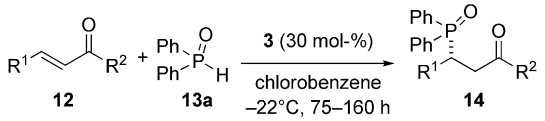
Entry	Solvent	**13**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	THF	**13a**	63	80	49
2	$CHCl_3$	**13a**	48	90	65
3	CH_3CN	**13a**	48	79	41
4	*m*-xylene	**13a**	39	99	65
5	ClC_6H_5	**13a**	48	99	69
6	1,3-$Cl_2C_6H_4$	**13a**	64	99	63
7	$CF_3C_6H_5$	**13a**	39	99	56
8[d]	ClC_6H_5	**13b**	71	83	73
9[d]	ClC_6H_5	**13c**	48	99	45
10[d]	ClC_6H_5	**13d**	46	88	75
11[d]	ClC_6H_5	**13e**	72	95	65
12[d]	ClC_6H_5	**13f**	48	52	54
13[d,e]	ClC_6H_5	**13d**	67	35	51
14[d,e,f]	ClC_6H_5	**13a**	67	77	78
15[d,f,g]	ClC_6H_5	**13a**	67	56	80

[a] Reaction conditions: **12a** (0.2 mmol), **13** (0.2 mmol), and **3** (0.02 mmol) in toluene (1.0 mL). [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC. Absolute configuration determined by comparison with the optical rotation value given in the literature.[9] [d] Using 30 mol-% of **3**. [e] Reaction performed at –20 °C. [f] Reaction performed at *c* = 0.1 M with respect to **12a**. [g] Reaction performed at –30 °C.

diarylphosphane oxides slightly affected the conversion and the enantioselectivity (Table 2, Entries 8–12). 2-Naphthyl derivative **13d** furnished the adduct in up to 75%*ee* (Table 2, Entry 10), but when performing the reaction at –20 °C the enantioselectivity decreased (Table 2, Entry 13). Nevertheless, the use of commercially available phosphane oxide **13a** at lower temperature afforded good results in terms of asymmetric induction and conversion (Table 2, Entries 14 and 15).

With optimized conditions in hands, the scope and limitations of the dihydroquinine-catalyzed Michael addition of diphenylphosphane oxide to a variety of chalcones was investigated (Table 3).

Table 3. Asymmetric phospha-Michael addition of diphenylphosphane oxide to *trans*-chalcones promoted by dihydroquinine **3**.[a]



12 **13a** **14**

Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	Ph	Ph (**a**)	91 (60)	80 (>99)
2	Ph	Ph (**a**)	85	81[d]
3	4-MeC_6H_4	Ph (**g**)	75	78
4	3-BrC_6H_4	Ph (**h**)	98 (58)	76 (>99)
5	4-$NO_2C_6H_4$	Ph (**i**)	99	65
6	2-$MeOC_6H_4$	Ph (**j**)	87 (64)	89 (>99)
7	2-ClC_6H_4	Ph (**k**)	99	86
8	2-ClC_6H_4	Ph (**k**)	80	79[d]
9	Ph	4-$MeOC_6H_4$ (**l**)	99	77
10	Ph	4-BrC_6H_4 (**m**)	95	82
11	Ph	4-ClC_6H_4 (**n**)	85	79
12	Ph	3-BrC_6H_4 (**o**)	99	76
13	cyclohexyl	Ph (**p**)	30	60

[a] Reaction conditions: **12** (0.2 mmol), **13a** (0.2 mmol), **3** (0.06 mmol) in solvent (2 mL). [b] Isolated yield after flash chromatography. Yield after crystallization is given in parentheses. [c] Determined by chiral HPLC. The *ee* value after crystallization is given in parentheses. [d] Dihydroquinidine **7** was used as the catalyst to give the opposite enantiomer.

trans-Chalcones bearing electron-donating or electron-withdrawing groups at both the aromatic rings were smoothly converted into the final adducts in high yield. *R*-Configured adducts **14** were obtained with fairly good level of asymmetric induction. Strong electron-withdrawing groups slightly decreased the enantioselectivity, as observed with the nitrophenyl-substituted enone (Table 3, Entry 5). The *ortho*-substitution on the β-phenyl ring was found to be beneficial for stereocontrol, as the adducts were isolated with up to 89%*ee* (Table 3, Entries 6 and 7). Dihydroquinidine **7** afforded the *S*-configured adducts with almost comparable efficiency (Table 3, Entries 2 and 8). Although we have not fully explored the dihydroquinine-catalyzed phospha-Michael addition to β-alkyl-substituted enones, a preliminary study with a cyclohexyl derivative showed a decreased conversion to the product obtained with somewhat lower *ee* (Table 3, Entry 13).[17] Compounds **14** are solids and they can be recrystallized in enantiopure form (Table 3, Entries 1, 4, and 6).

On the basis of the absolute configuration of adducts **14**, a transition-state proposal for the dihydroquinine-catalyzed phospha-Michael addition is shown in Figure 2. The nature of the acidic moiety in the catalyst was found to be crucial for the activation, as attested by findings reported in Table 1. Indeed, thiourea derivatives **9** and **10** gave racemic adduct, whereas the hydroxy group of dihydroquinine proved to be superior in establishing a hydrogen-bonding interaction with the oxygen of the carbonyl moiety of *trans*-chalcone.

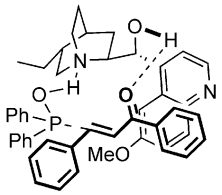


Figure 2. Postulated transition state for dihydroquinine-catalyzed phospha-Michael addition.

The diarylphosphane oxide is expected to be activated by the quinuclidine nitrogen atom by shifting the equilibrium toward the reactive phosphinous acid form (Scheme 1). The preferential attack of the activated nucleophile toward the *Re* face of chalcone would lead to the *R*-configured product.

Conclusions

In conclusion, we have developed the first enantioselective direct phospha-Michael addition of diarylphosphane oxides to *trans*-chalcones. The adducts are generally obtained in high yield and good to high enantioselectivity when using commercially available diphenylphosphane oxide and dihydroquinine as the catalyst. The final adducts can be easily recrystallized to enantiopure material. Chiral phosphane oxides and phosphanes are typically prepared using enantiopure starting materials, chiral auxiliaries, or by recrystallization of racemic compounds.[1,18] The present methodology provides simple and convenient access to both enantiomerically enriched phosphane oxides **14**, potentially useful ligands and building blocks for asymmetric synthesis.

Experimental Section

General Procedure for the Phospha-Michael Addition of Diphenylphosphane Oxide to *trans*-Chalcones: *trans*-Chalcone (**12**; 0.2 mmol) and dihydroquinine (0.06 mmol) were dissolved in anhydrous chlorobenzene (2 mL). Diphenylphosphane oxide (**13a**; 0.2 mmol) was added, and the reaction was stirred at –22 °C until completion as monitored by TLC. A white precipitate was formed. The mixture was directly purified by flash chromatography (pure chloroform) to give adducts **14** contaminated by residual **13a** (**13a** has the same TLC mobility of products **14**).[19] Compound **13a** could be removed by washing the mixture with warm hexane and collecting solid **14** as a pure compound. For recrystallization of adducts **14**, mixtures of $CHCl_3$/EtOH were used.

Supporting Information (see footnote on the first page of this article): General experimental methods, experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for new compounds, and HPLC traces.

Acknowledgments

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[16] Basic additives such as K_2CO_3, Na_2CO_3, and NaOAc were added in the model reaction using **13a** and catalyst **3** at room temperature in chlorobenzene. Conversion and enantioselectivity were not improved. Basic additives were previously reported to have beneficial effects in the asymmetric Pudovik reaction mediated by cinchona alkaloids, see: S. Nakamura, M. Hayashi, Y. Hiramatsu, N. Shibata, Y. Funahashi, T. Toru, *J. Am. Chem. Soc.* **2009**, *131*, 18240.

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[19] Characterisation data of all new compounds **14** are reported in the Supporting Information.

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