ORGANIC LETTERS

2011
Vol. 13, No. 16
4176–4179

Organocatalytic Asymmetric Michael-Type/Wittig Reaction of Phosphorus Ylides: Synthesis of Chiral α-Methylene-δ-Ketoesters

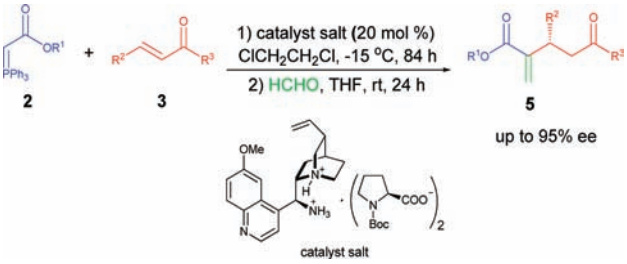
Aijun Lin,[†] Junying Wang,[†] Haibin Mao,[†] Huiming Ge,[‡] Renxiang Tan,[‡] Chengjian Zhu,*[,†] and Yixiang Cheng*[,†]

School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing, 210093, China, and State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing, 210093, China

cjzhu@nju.edu.cn; yxcheng@nju.edu.cn

Received June 1, 2011

ABSTRACT



An asymmetric Michael-type reaction of phosphorus ylides and α,β-unsaturated ketones under the catalysis of a chiral ion pair catalyst has been described. The ion pair catalyst containing a chiral counteranion was prepared by simply mixing 9-amino-(9-deoxy)-*epi*-quinine with L-*N*-Boc-proline. The optically active α-methylene-δ-ketoesters could be obtained with good to excellent enantioselectivities (up to 95% ee) under mild reaction conditions.

Since the pioneering work of MacMillan,[1] the asymmetric Michael-type reaction of α,β-unsaturated carbonyl compounds under the catalysis of chiral amine through the iminium-ion mediated pathway has been established as one of the most typical and versatile methods of C−C bond-forming reaction, which is widely applied in organic and medicinal chemistry.[2] Chiral δ-ketoesters, a type of useful synthetic intermediate, has been reported by Jørgensen[3] and Ley[4] through the decarboxylation of the Michael adducts of malonates and α,β-unsaturated ketones. Although the reaction could be performed in a one-pot decarboxylation−transesterification procedure, the decarboxylation strategy is still tedious. In this communication we would like to report the development of a novel

[†] School of Chemistry and Chemical Engineering.
[‡] School of Life Sciences.

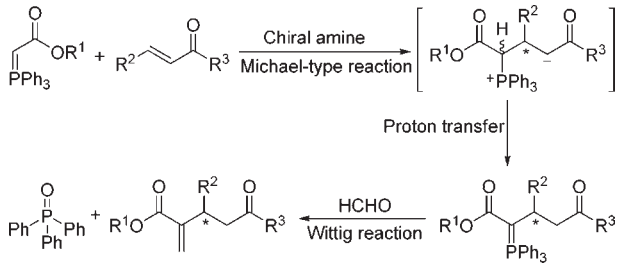
(1) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(2) (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (d) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.
(3) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661.
(4) Wascholowski, V.; Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem.—Eur. J.* **2008**, *14*, 6155.
(5) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.
(6) (a) Bestmann, H. J.; Schultz, H. *Tetrahedron Lett.* **1960**, *4*, 5. (b) Bestmann, H. J.; Seng, F. *Angew. Chem.* **1962**, *74*, 154. (c) Asunskis, J.; Shechter, H. *J. Org. Chem.* **1968**, *33*, 1164. (d) Von Strandtmann, M.; Cohen, M. P.; Puchalski, C.; Shavel, J., Jr. *J. Org. Chem.* **1968**, *33*, 4306. (e) Connor, D. T.; Von Strandtmann, M. *J. Org. Chem.* **1973**, *38*, 1047. (f) Nesmeyanov, N. A.; Kharitonov, V. G.; Zhuzhlikova, S. T.; Petrovskii, P. V.; Antipin, M. Yu.; Struchkov, Yu. T.; Reutov, O. A. *Zh. Org. Khim.* **1987**, *23*, 1577. (g) Aitken, R. A.; Al-Awadi, N. A.; Balkovich, M. E.; Bestmann, H. J.; Clem, O.; Gibson, S.; Gross, A.; Kumar, A.; Röder, T. *Eur. J. Org. Chem.* **2003**, 840. (h) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (i) Ye, L.-W.; Han, X.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2008**, *64*, 8149. (j) Ye, L.-W.; Wang, S.-B.; Wang, Q.-G.; Sun, X.-L.; Tang, Y.; Zhou, Y.-G. *Chem. Commun.* **2009**, 3092. (k) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Chem.—Eur. J.* **2010**, *16*, 7376.

10.1021/ol201483s
Published on Web 07/14/2011

and facile strategy to the enantioselective synthesis of α-methylene-δ-ketoesters.

Stabilized phosphorus ylides (P-ylides), which were extensively used in organic chemistry since the discovery of the Wittig reaction,[5] have previously been shown as good nucleophiles in organic synthesis.[6] However, the application of phosphorus ylides in asymmetric synthesis is currently limited. In 2008, Chen presented the first asymmetric Mannich-type reaction of phosphorus ylides and aldimines, followed by a Wittig reaction; the aza-Morita–Baylis–Hillman products could be obtained with excellent enantioselectivities.[7] Subsequently, Lee[8] and Singh[9] independently reported the asymmetric Michael-type reaction of phosphorus ylides and nitroolefin with good results. Inspired by these successful examples with phosphorus ylides as nucleophiles in the asymmetric addition reaction, we are recently surprised to find that the phosphorus ylides are also suitable nucleophilic species for the addition of α,β-unsaturated ketones under the catalysis of chiral amine salts. After proton transfer, a stabilized phosphorus ylide intermediate could be obtained, which undergoes a Wittig reaction with formaldehyde to give α-methylene-δ-ketoesters in a novel reaction pathway (Scheme 1).

Scheme 1. A Novel Pathway to the Synthesis of α-Methylene-δ-Ketoesters



Recently, the introduction of a chiral Brønsted acid to the amine catalytic system has been proven as an impactful catalytic system in asymmetric aminocatalysis.[10] In these catalytic systems, the yielded chiral anions could enhance the chiral communication between the iminum ions and the substrates by shielding one of the two enantiotopic faces. And the stereochemical control could be effectively induced by these chiral anions. This strategy has been defined as asymmetric counterion-directed catalysis (ACDC) by List.[10b] Additionally, 9-amino cinchona alkaloids, directly derived from natural cinchona alkaloids,[11] in combination with various acids, have been shown as excellent iminium activators of simple ketones in asymmetric conjugate addition reactions.[12] Herein we show that the combination of 9-amino-(9-deoxy)-*epi*-quinine and L-*N*-Boc-proline resulted in an effective catalytic amine salt for the enantioselective Michael-type reaction of phosphorus ylides and α,β-unsaturated ketones.

Initial examination was carried out by using the P-ylide **2a** and *trans*-4-phenyl-3-buten-2-one **3a** as the substrates in the presence of a series of chiral primary amine salt catalysts in CH_2Cl_2 at −15 °C. Preliminary studies confirmed that AcOH salts of catalyst **1a**–**1d** were able to promote the reaction, and the expected P-ylide intermediate **4a** could be isolated as a relatively stable compound. After reaction with formaldehyde, the product **5a** was obtained in moderate yield with low enantioselectivity (Table 1, entries 1–4). Notably, when 9-amino-(9-deoxy)-*epi*-quinine **1e** combined with AcOH was tested, **5a** was isolated with an obvious increased enantioselectivity (Table 1, entry 5). When **1e** together with TFA, *p*-nitrobenzoic acid, or *p*-toluenesulfonic acid was tested, moderate enantioselectivity was obtained (Table 1, entries 6–8). Considering the nature of the counteranion is an important factor in the asymmetric induction, we thus decided to introduce chiral acid to the catalytic system to improve the enantioselectivity. To our delight, when **1e** with L-*N*-Boc-phenylglycine (**A**) was tested in the reaction, an increased enantioselectivity was achieved (Table 1, entry 9). The best enantioselectivity (80% ee) was observed when L-*N*-Boc-proline (**B**) was used (Table 1, entry 10). A lower temperature (−30 °C) caused the loss of yields from 56% to 33% without an obvious increased ee value (Table 1, entry 14).

(7) Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008**, *130*, 2456.

(8) Hong, B.-C.; Jan, R.-H.; Tsai, C.-W.; Nimje, R. Y.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2009**, *11*, 5246.

(9) Allu, S.; Selvakumar, S.; Singh, V. K. *Tetrahedron Lett.* **2010**, *51*, 446.

(10) For recent reviews, see: (a) Piovesana, S.; Schietroma, D. M. S.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2. For selected examples, see: (b) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (c) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (d) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (e) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (f) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119. (g) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703. (h) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626. (i) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. (j) Liu, C.; Lu, Y. *Org. Lett.* **2010**, *12*, 2278. (k) Xia, A.-B.; Xu, D.-Q.; Luo, S.-P.; Jiang, J.-R.; Tang, J.; Wang, Y.-F.; Xu, Z.-Y. *Chem.—Eur. J.* **2010**, *16*, 801.

(11) Brunner, H.; Ngler, J. B.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699.

(12) For recent reviews on asymmetric primary amine catalysis, see: (a) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. (b) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (c) Chen, Y.-C. *Synlett*. **2008**, 1919. (d) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759. (e) Xu, L.-W.; Lu, Y. *Chem. Commun.* **2009**, 1807. For selected excellent examples about 9-amino cinchona alkaloids as iminium activators of simple ketones, see: (f) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (g) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (h) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656. (i) Lu, X.-J.; Deng, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 7710. (j) Reisinger, C. M.; Wang, X. -W.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112. (k) Singh, P. R.; Bartelso, K.; Wang, Y.; Su, H.; Lu, X.-J.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. (l) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (m) Lu, X.-J.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. (n) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196. (o) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (p) Paixao, M. W.; Holub, N.; Vila, C.; Nielsen, M.; Jøgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 7338. (q) Qiao, Z.; Shafiq, Z.; Liu, L.; Yu, Z.-B.; Zheng, Q.-Y.; Wang, D.; Chen, Y.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7294.

The examination of solvent effects revealed that $ClCH_2$-CH_2Cl was the best reaction media for this reaction, which could facilitate the reaction to produce the corresponding product in 64% yield with 82% ee (Table 1, entry 18). Decreasing the catalyst loading to 10 and 5 mol % had a negative impact on both the yields and the enantioselectivities (Table 1, entries 19–20). Additionally, the optically pure **4a** was obtained upon recrystallization, the absolute configuration was determined to be *S* by means of X-ray crystallographic analysis (Figure 1),[13] and the absolute configuration of the corresponding product **5a** could also be determined to be *S*.

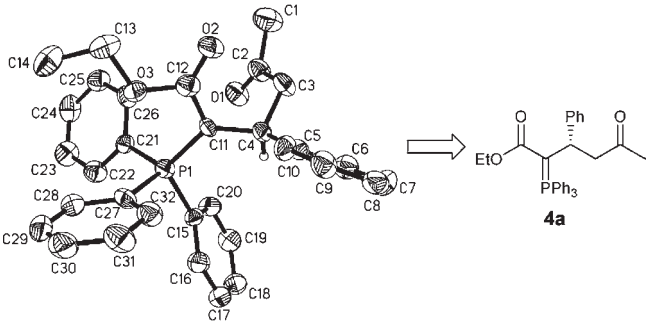


Figure 1. X-ray structure of enantiopure **4a**. Thermal ellipsoids are shown at 30% probability.

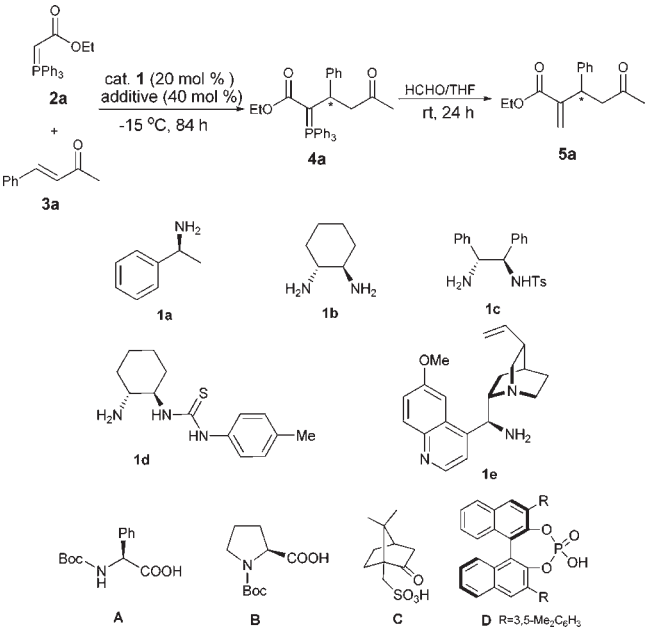
Having established the optimal reaction conditions, we then examined a spectrum of P-ylide **2** and α,*β*-unsaturated ketones **3** to explore the generality of this new asymmetric successive Michael-type/Wittig reaction. The reactions were conducted in 0.5 mL of $ClCH_2CH_2Cl$ with 20 mol % of catalyst **1e** and 40 mol % of L-*N*-Boc-proline (**B**) at −15 °C for 84 h. The results are summarized in Table 2. Based on entries 1–4 of Table 2, the enantioselectivities were slightly dependent on the substituted ester groups of the P-ylide **2**. The electronic properties of the phenyl ring of the α,*β*-unsaturated ketones did not influence the level of the enantioselectivity markedly, and all these substrates accomplished the reaction smoothly (Table 2, entries 5–11). Moreover, when 2-thienyl-substituted ketone was used as the substrate, the corresponding product **5l** was obtained in 55% yield with 88% ee (Table 2, entry 12). *β*-Alkyl-substituted ketone was also tested; luckily, the reaction was completed with 83% ee (Table 2, entry 13).

As is evident from entries 1–3 of Table 3, an exchange of the methyl group of the ketone to an ethyl group or a propyl group improved the enantioselectivity of the reaction, with product **5n** and **5o** obtained with 92% ee and 94% ee, respectively. However, a further increase of the steric bulk at the R^3-position to an isopropyl group slowed down the reaction and a very low conversion (< 5%) was observed. These results revealed that a longer chain ketone could engender higher enantioselectivity. Then a series of long chain ketones were synthesized and utilized in this reaction; all of the corresponding products were obtained with excellent enantioselectivities, and the ee values ranged from 94% to 95% (Table 3, entries 4–11).

Based on the above results, we proposed a transition state for the catalytic asymmetric Michael-type reaction.

(13) CCDC 827398 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data_request/cif.

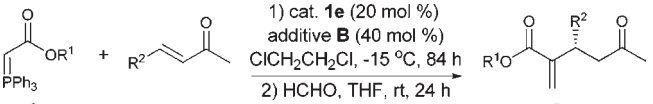
Table 1. Screening Studies of the Michael-Type Reaction Conditions and Subsequent Synthesis of α-Methylene-*δ*-Ketoester[a]



entry	cat.	additive	solvent	yield (%)[b]	ee (%)[c]
1	**1a**	AcOH	DCM	41	8
2	**1b**	AcOH	DCM	35	15
3	**1c**	AcOH	DCM	39	21
4	**1d**	AcOH	DCM	45	18
5	**1e**	AcOH	DCM	55	63
6	**1e**	TFA	DCM	42	57
7	**1e**	*p*-NO_2PhCOOH	DCM	50	61
8	**1e**	TsOH	DCM	38	55
9	**1e**	**A**	DCM	51	76
10	**1e**	**B**	DCM	56	80
11	**1e**	**C**	DCM	47	75
12	**1e**	**D**	DCM	40	78
13	**1e**	**B**	DCM	67	71[d]
14	**1e**	**B**	DCM	33	84[e]
15	**1e**	**B**	CH_3CN	42	61
16	**1e**	**B**	THF	trace	n.d[f]
17	**1e**	**B**	$CHCl_3$	35	49
18	**1e**	**B**	DCE	64	82
19	**1e**	**B**	DCE	51	75[g]
20	**1e**	**B**	DCE	39	64[h]

[a] The reaction was carried out with 0.20 mmol of **2a**, 0.30 mmol of **3a**, and 20 mol % of catalyst **1** in combination with 40 mol % of additive in 0.5 mL of solvent at −15 °C for 84 h. [b] Isolated yield for two steps. [c] Ee values were determined by chiral HPLC analysis. [d] 0 °C reaction temperature. [e] −30 °C reaction temperature. [f] Not determined. [g] 10 mol % of catalyst **1e** was used. [h] 5 mol % of catalyst **1e** was used.

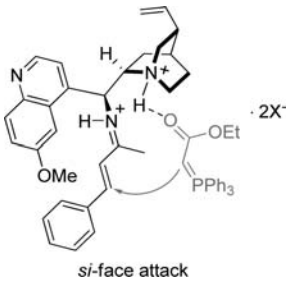
Table 2. Asymmetric Synthesis of α-Methylene-δ-Ketoesters via Successive Michael-Type/Wittig Reaction[a]



2 3 5

entry	2 (R^1)	3 (R^2)	yield (%)[b]	ee (%)[c]
1	Et	Ph	64 (**5a**)	82
2	Me	Ph	67 (**5b**)	78
3	*i*-Pr	Ph	54 (**5c**)	73
4	Bn	Ph	60 (**5d**)	81
5	Et	4-FPh	53 (**5e**)	80
6	Et	4-ClPh	61 (**5f**)	78
7	Et	3-ClPh	67 (**5g**)	81
8	Et	4-BrPh	58 (**5h**)	81
9	Et	4-MePh	50 (**5i**)	82
10	Et	4-MeOPh	48 (**5j**)	80
11	Et	4-NO_2Ph	71 (**5k**)	72
12	Et	2-thienyl	55 (**5l**)	88
13	Bn	*n*-Bu	65 (**5m**)	83

[a] The reaction was carried out with 0.20 mmol of **2**, 0.30 mmol of **3**, and 20 mol % of catalyst **1e** in combination with 40 mol % of **B** in 0.5 mL of $ClCH_2CH_2Cl$ at −15 °C for 84 h. [b] Isolated yield for two steps. [c] Ee values were determined by chiral HPLC analysis.

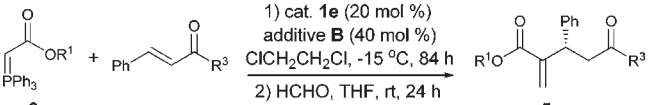


si-face attack

Figure 2. Proposed transition state for the Michael-type reaction of phosphorus ylides and α,β-unsaturated ketones.

The interaction between ketone and amine would adopt a *trans* conformation. The phosphorus ylide is much more accessible to attack the active iminium from the *Si* face, affording the corresponding product as *S* (Figure 2).

Table 3. Asymmetric Synthesis of α-Methylene-δ-Ketoesters via Successive Michael-Type/Wittig Reaction[a]



2 3 5

entry	2 (R^1)	3 (R^3)	yield (%)[b]	ee (%)[c]
1	Et	Me	64 (**5a**)	82
2	Et	Et	58 (**5n**)	92
3	Et	*n*-Pr	54 (**5o**)	94
4	Et	*n*-Bu	56 (**5p**)	95
5	Et	*n*-Pen	49 (**5q**)	95
6	Et	*n*-Hex	52 (**5r**)	95
7	Et	*n*-Hep	47 (**5s**)	95
8	Et	*n*-Oct	50 (**5t**)	95
9	Me	*n*-Pen	62 (**5u**)	94
10	*i*-Pr	*n*-Pen	53 (**5v**)	94
11	Bn	*n*-Pen	46 (**5w**)	95

[a] The reaction was carried out with 0.20 mmol of **2**, 0.30 mmol of **3**, and 20 mol % of catalyst **1e** in combination with 40 mol % of **B** in 0.5 mL of $ClCH_2CH_2Cl$ at −15 °C for 84 h. [b] Isolated yield for two steps. [c] Ee values were determined by chiral HPLC analysis.

In summary, we have provided an organocatalytic Michael-type addition of phosphorus ylides and α,β-unsaturated ketones using a chiral ion pair catalyst. And the catalyst was easily prepared by mixing 9-amino-(9-deoxy)-*epi*-quinine with L-*N*-Boc-proline. The reaction proceeded with a great diversity of α,β-unsaturated ketones with good to excellent enantioselectivities (up to 95% ee). Following a Wittig reaction with formaldehyde, the scope of the reaction was demonstrated by the synthesis of chiral α-methylene-δ-ketoesters. Further exploration of using phosphorus ylides as the nucleophiles in asymmetric reactions is now in progress in our laboratory.

Acknowledgment. We gratefully acknowledge the National Natural Science Foundation of China (20832001, 20972065, 21074054) and the National Basic Research Program of China (2007CB925103, 2010CB923303) for their financial support.

Supporting Information Available. Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products. This material is available free of charge via the Internet at http://pubs.acs.org.