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Highly Enantioselective and Efficient Organocatalytic Aldol Reaction of Acetone and β,γ-Unsaturated α-Keto Ester

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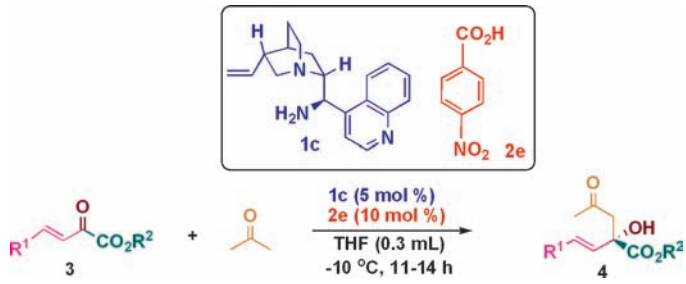
ABSTRACT



An effective organocatalytic asymmetric aldol reaction of acetone to β,γ-unsaturated α-keto ester has been developed. In the presence of 5 mol % of 9-amino (9-deoxy)-epicinchona alkaloid and 10 mol % of 4-nitrobenzoic acid, the aldol adducts containing a chiral tertiary alcohol moiety were obtained in excellent yields and enantioselectivities.

Asymmetric aldol reaction has been successful and captured considerable attention as one of the most powerful synthetic tools for the carbon−carbon bond-forming reaction.[1] This method provides a beneficial route to access chiral β-hydroxy carbonyl compounds which are versatile synthetic motifs for biologically active natural products and pharmaceutically attractive intermediates.[2] In particular, the application of an α-keto ester[3] as an electrophilic partner has recently become the focus of research leading to products bearing a chiral quaternary carbon center which comprises several functional groups (e.g., hydroxy, ester, etc.) that are synthetically useful.[4] In addition to the role of a Michael acceptor,[5] β,γ-unsaturated α-keto ester has also been applied in the hetero-Diels−Alder reaction to afford remarkable results.[6]

Yet, there are still only a few examples of the catalytic asymmetric aldol reaction of β,γ-unsaturated α-keto ester.[7] Highly attractive and inexpensive acetone has been broadly used in the aldolization of aldehyde to afford chiral β-hydroxy carbonyl compounds with excellent results.[8] In fact, the asymmetric reaction between unsaturated α-keto ester and ketone remains sporadically studied as this protocol is highly challenging. It should be noted that only two examples

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(1) For selected reference books, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry*; Wiley: New York, 1982; Vol. 13. (b) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004, Vols. *1 and 2*. For selected reviews, see: (c) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem.—Eur. J.* **1998**, *4*, 1137. (d) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (e) Denmark, S.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (f) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (g) List, B. *Tetrahedron* **2002**, *58*, 5573. (h) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (i) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570. (j) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580.

(2) For selected books, see: (a) Trost, B. M.; Fleming, I.; Heathcock, C. H. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 2. (b) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. *Houben-Weyl: Methods of Organic Chemistry*; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21. For some selected references, see: (c) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819. (d) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283. (e) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647. (f) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231. (g) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 10497.

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of the catalytic asymmetric aldol reaction of acetone and β,γ-unsaturated α-keto ester were reported with no more than 45% ee.[7,9]

Herein, we report a highly efficient and enantioseletive aldol reaction of acetone and β,γ-unsaturated α-keto ester for constructing a chiral quaternary carbon center. This protocol offers the aldol adducts containing hydroxy, carbon−carbon double bond, ester, and carbonyl functional groups in a single molecule.

In the past few years, the primary amine has emerged as a powerful organocatalyst to afford impressive results in the asymmetric reactions,[10] and an exciting development has also been achieved in the field of organocatalytic aldol reaction when the primary amine is employed as catalyst.[11,12] The potential of modified cinchona alkaloids as efficient and enantioselective organocatalysts for asymmetric synthesis has been demonstrated.[13] As one of the typical primary amino catalysts, 9-animo (9-deoxy)-epicinchona alkaloids have been successfully applied in the asymmetric reactions,[14] and it turned out that the acid cocatalyst significantly influenced both the reactivity and enantioselectivity of the reaction.

Therefore, we initially investigated the aldolization of acetone to methyl 2-oxo-4-phenylbut-3-enoate (**3a**) catalyzed by 9-amino (9-deoxy)-epicinchona alkaloids (**1**) and acid additives **2**. The representative results were compiled in Table 1. When 9-amino (9-deoxy)-epiquinine (**1a**) was used as a catalyst without acidic additive, poor results were obtained (7% yield and 51% ee) (Table 1, entry 1). A remarkable enhancement was achieved when an acidic additive, 3-hydroxy-2-naphthoic acid (**2a**), was introduced into the reaction system (Table 1, entry 2). In the presence of **2a**, a variety of 9-amino (9-deoxy)-epicinchona alkaloids (**1b**−**1d**) catalyzed the aldol reaction of acetone to **3a**. To our delight, all the aldolizations proceeded well to afford adducts with good enantioselectivities (Table 1, entries 3−5). In particular, **1c** gave the best product enantioselectivity among ligands screened (Table 1, entry 4).

Having identified the best catalyst (**1c**), optimization of reaction conditions was investigated. The screening of acid additives was first carried out. All attempted aldol reactions of acetone to **3a** were efficiently catalyzed by **1c** with the association of **2**, to provide the aldol adducts in good to excellent yields and good ee (except acetic acid (**2b**) and trifluoroacetic acid (**2c**)) (Table 1, entries 6−12). The best results, 99% product yield, and 86% ee were obtained in the presence of **1c** and 4-nitrobenzoic acid (**2e**) (Table 1,

(3) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (b) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (c) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103. (d) Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263. (e) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532. (f) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442. (g) Dodda, R.; Zhao, C.-G. *Synlett* **2007**, 1605. (h) Xu, X.-Y.; Tang, Z.; Wang, Y.-Z.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Org. Chem.* **2007**, *72*, 9905. (i) Wang, F.; Xiong, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 2665. (j) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950. (k) Yanagisawa, A.; Terajima, Y.; Sugita, K.; Yoshida, K. *Adv. Synth. Catal.* **2009**, *351*, 1757. (l) Jiang, Z.; Lu, Y. *Tetrahedron Lett.* **2010**, *51*, 1884.

(4) For selected reviews, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

(5) (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (b) Jørgensen, K. A. *Synthesis* **2003**, *7*, 1117. (c) Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067. (d) Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, 2843. (e) Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303. (f) Xiong, X.; Ovens, C.; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 565. (g) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Zhu, C.-Y.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408. (h) Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205. (i) Liu, Y.; Shang, D.; Zhou, X.; Zhu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 180.

(6) (a) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2404. (b) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372. (c) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487. (d) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (e) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3417. (f) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (g) Gohier, F.; Bouhadjera, K.; Faye, D.; Gaulon, C.; Maisonneuve, V.; Dujardin, G.; Dhal, R. *Org. Lett.* **2007**, *9*, 211. (h) Samanta, S.; Krause, J.; Mandal, T.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 2745. (i) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817. (j) Gallier, F.; Hussain, H.; Martel, A.; Kirschning, A.; Dujardin, G. *Org. Lett.* **2009**, *11*, 3060. (k) Yao, W.; Pan, L.; Wu, Y.; Ma, C. *Org. Lett.* **2010**, *12*, 2422. (l) Xu, D.; Zhang, Y.; Ma, D. *Tetrahedron Lett.* **2010**, *51*, 3827.

(7) Zheng, C.; Wu, Y.; Wang, X.; Zhao, G. *Adv. Synth. Catal.* **2008**, *350*, 2690.

(8) For selected references, see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (d) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (e) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755. (f) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (g) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321. (h) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074.

(9) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151.

(10) For selected reviews, see: (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (d) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. (e) Chen, Y.-C. *Synlett* **2008**, 1919. (f) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807.

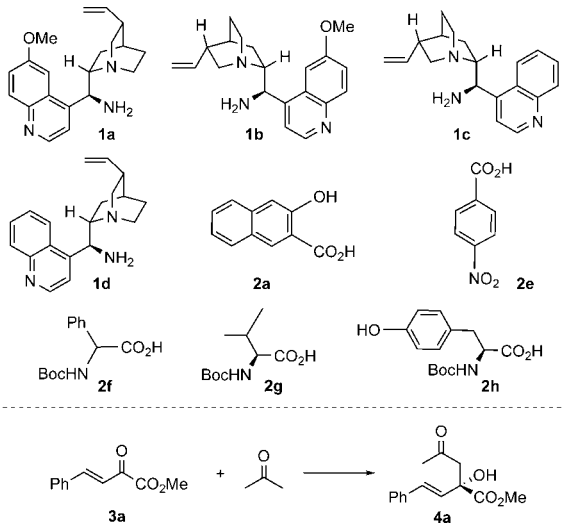
(11) For selected references on the primary amino acid catalytic aldol reactions, see: (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586. (b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sunden, H.; Córdova, A. *Chem. Commun.* **2005**, 4946. (c) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028. (d) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem.—Eur. J.* **2006**, *12*, 5383. (e) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801. (f) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812.

(12) For other selected references on the primary amino catalytic aldol reactions, see: (a) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (b) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247. (c) Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199. (d) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654. (e) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656.

(13) For reviews, see: (a) Chen, Y.; Mcdaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Mcdaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

(14) For selected references, see: (a) 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. (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413. (c) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816. (d) Zheng, B.-L.; Liu, Q.-Z.; Guo, C.-S.; Wang, X.-L.; He, L. *Org. Biomol. Chem.* **2007**, *5*, 2913. (e) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (f) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (g) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (h) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49.

Table 1. Screening of Catalyst and Reaction Conditions for Aldolization between Acetone and **3a**[a]



entry	1	additives	solvent	yield (%)[b]	ee (%)[c]
1	**1a**	–	MeCN	7	51
2	**1a**	**2a**	MeCN	99	69
3	**1b**	**2a**	MeCN	90	80
4	**1c**	**2a**	MeCN	93	84
5	**1d**	**2a**	MeCN	99	82
6	**1c**	AcOH, **2b**	MeCN	34	82
7	**1c**	TFA, **2c**	MeCN	54	86
8	**1c**	Me_3CCO_2H, **2d**	MeCN	87	80
9	**1c**	**2e**	MeCN	99	86
10	**1c**	**2f**	MeCN	96	81
11	**1c**	**2g**	MeCN	97	82
12	**1c**	**2h**	MeCN	85	80
13	**1c**	**2e**	CH_2Cl_2	98	87
14	**1c**	**2e**	$CHCl_3$	92	88
15	**1c**	**2e**	toluene	89	91
16	**1c**	**2e**	EtOAc	94	91
17	**1c**	**2e**	Et_2O	90	90
18	**1c**	**2e**	THF	99	93
19	**1c**	**2e** (20 mol %)	THF	94	90
20	**1c**	**2e** (60 mol %)	THF	98	92
21	**1c**	**2e** (80 mol %)	THF	97	92
22[d]	**1c**	**2e**	THF	83	92
23[e]	**1c**	**2e**	THF	89	92
24[f]	**1c**	**2e**	THF	95	92
25[g]	**1c**	**2e**	THF	97	93
26[h]	**1c**	**2e**	THF	89	93
27[i]	**1c**	**2e**	THF	81	94
28[j]	**1c**	**2e**	THF	98	92
29[k]	**1c**	**2e**	THF	69	92

[a] Unless otherwise noted, all the reactions were carried out at −10 °C for 11 h, **3a** (0.1 mmol), acetone (0.2 mL), **1** (20 mol %), and **2** (40 mol %) in solvent (0.3 mL). [b] Isolated product. [c] Determined by chiral HPLC analysis. [d] **1c** (10 mol %), **2e** (20 mol %) in THF (0.1 mL) for 4 h. [e] **1c** (10 mol %), **2e** (20 mol %) in THF (0.2 mL) for 4 h. [f] **1c** (10 mol %), **2e** (20 mol %) in THF (0.3 mL) for 7 h. [g] **1c** (10 mol %), **2e** (20 mol %) in THF (0.4 mL) for 7 h. [h] **1c** (10 mol %), **2e** (20 mol %) in THF (0.5 mL) for 11 h. [i] **1c** (5 mol %), **2e** (10 mol %) in THF (0.4 mL). [j] **1c** (5 mol %), **2e** (10 mol %) in THF (0.2 mL). [k] **1c** (1 mol %), **2e** (2 mol %) in THF (0.2 mL) for 28 h.

entry 9). Amino acids as acid additives could also be applied into this reaction system, while the configuration of amino acid essentially had no effect on the asymmetric induction to the desired aldol product (Table 1, entries 10−12).

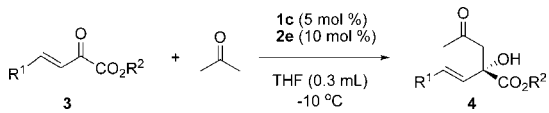
The effect of solvent for the aldolization of acetone and **3a** was also surveyed. As shown in Table 1, the reaction media had a little effect on the yield and enantioselectivity. CH_2Cl_2 solvent gave the aldol adducts in 98% yield with 87% ee (Table 1, entry 13). Similar results were obtained in $CHCl_3$ (Table 1, entry 14). Up to 91% ee with 89% yield was obtained in toluene (Table 1, entry 15). It should be noted that EtOAc, Et_2O, and THF provided a high level of enantioselectivities (>90% yields and ee) (Table 1, entries 16−18), and the best results (99% of yield and 93% ee) were obtained in THF (Table 1, entry 18).

A further study was carried out with a different amount of **2e** and solvent (Table 1, entries 19−26). After detailed screening, **1c** (20 mol %) together with **2e** (40 mol %) enabled the efficient formation of aldol adduct in 97% yield and 93% ee, in 0.4 mL of THF after 7 h (Table 1, entry 25). Lowering the catalyst loading could still afford satisfactory results after an extended reaction time. For example, 81% product yield with 94% ee could be obtained when **1c** (5 mol %) and **2e** (10 mol %) were used in 0.4 mL of THF after 11 h (Table 1, entry 27). Importantly, the yield could be increased up to 98% with 92% ee when the reaction was performed in 0.2 mL of THF (Table 1, entry 28). When the catalyst loading was reduced to 1 mol %, the reaction resulted in 69% yield. However, the enantioselectivity still remained up to 92% (Table 1, entry 29).

Under the optimal reaction conditions, the aldolizations of acetone to a variety of β,γ-unsaturated α-keto esters were surveyed, and the results were presented in Table 2. In general, the ester group slightly affected the yields and ee as a result of steric hindrance. In the presence of **1c** and **2e**, all the β,γ-unsaturated α-keto esters **3a**−**n** reacted smoothly with acetone to afford the corresponding aldol adducts **4a**−**n** in excellent yields and ee (Table 2, entries 1−3). Particularly noteworthy was that the aldolization of more sterically congested **3c** also resulted in good yield and enantioselectivity (83% yield and 92% ee) (Table 2, entry 3). No significant electronic effect on the aromatic moiety was observed. The electron-withdrawing (Table 2, entries 4−9, 12−16) and electron-donating substituents (Table 2, entries 10−11, 17−18) could be introduced into the aromatic ring, with only a small effect on the yield and asymmetric induction. Thus, substituted aromatic β,γ-unsaturated α-keto esters **3f**−**o** reacted efficiently, and the aldol adducts **4f**−**o** were formed in more than 90% of both yields and ee (Table 2, entries 6−15). The adduct **4p** was formed in excellent yield with a slightly dropped ee (Table 2, entry 16). The heteroaromatic β,γ-unsaturated α-keto ester **3s** was found to be compatible under these reaction conditions and was successfully transformed to aldol adduct with 91% yield and 91% ee (Table 2, entry 19).

When the primary amine catalyst **1c** was changed to **1d**, the absolute configuration of the aldol adduct was reversed (Table 2, entries 20 and 21). These results indicated that the chirality transfer to product is originally from the chiral amine.

Table 2. Aldol Reaction between Acetone and **3**[a]



3 **4**

entry	R^1	R^2	time (h)	product	yield (%)[b]	ee (%)[c]
1	Ph (**3a**)	Me	11	**4a**	98	92
2	Ph (**3b**)	Et	11	**4b**	92	92
3	Ph (**3c**)	*i*-Pr	12	**4c**	83	92
4	2-ClPh (**3d**)	Et	11	**4d**	86	85
5	2-BrPh (**3e**)	Et	11	**4e**	91	86
6	3-ClPh (**3f**)	Et	11	**4f**	95	92
7	3-BrPh (**3g**)	Et	11	**4g**	99	92
8	3-NO_2Ph (**3h**)	Me	11	**4h**	98	94
9	3-NO_2Ph (**3i**)	Et	11	**4i**	94	93
10	3-MePh (**3j**)	Et	12	**4j**	91	91
11	3-MeOPh (**3k**)	Et	11	**4k**	98	92
12	4-FPh (**3l**)	Et	11	**4l**	97	92
13	4-ClPh (**3m**)	Et	11	**4m**	97	92
14	4-BrPh (**3n**)	Et	11	**4n**	98	92
15	4-NO_2Ph (**3o**)	Me	11	**4o**	98	93
16	4-NO_2Ph (**3p**)	Et	11	**4p**	98	87
17	4-MePh (**3q**)	Et	11	**4q**	88	92
18	4-MeOPh (**3r**)	Et	11	**4r**	56	92
19	5-Me-2-thienyl (**3s**)	Et	14	**4s**	91	91
20[d]	Ph (**3a**)	Me	11	**4t**	60	−90
21[d]	3-BrPh (**3g**)	Et	11	**4u**	73	−90
22[e]	4-ClPh (**3m**)	Et	11	**4m**	91	92
23[e]	4-BrPh (**3n**)	Et	11	**4n**	94	92

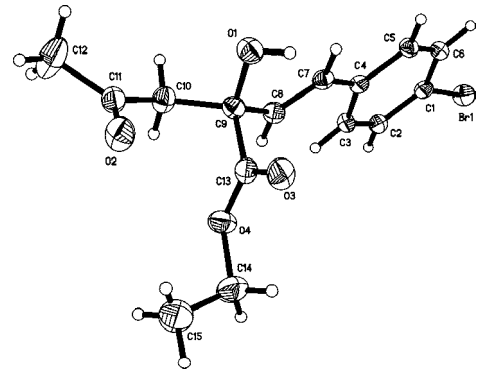
[a] Unless otherwise noted, all the reactions were carried out at −10 °C for 11 h, **3** (0.1 mmol), acetone (0.2 mL), **1c** (5 mol %), and **2e** (10 mol %) in THF (0.3 mL). [b] Isolated product. [c] Determined by chiral HPLC analysis. [d] **1d** was used as catalyst. [e] In 1.0 mmol scale: **3** (1.0 mmol), acetone (2.0 mL), **1c** (5 mol %), **2e** (10 mol %), THF (2.0 mL).

To exploit the potential of the current catalyst system, the reaction was scaled up to 1 mmol of the starting material. The corresponding products could be obtained in constant yields of 91−94% without a deleterious effect on the enantioselectivities (Table 2, entries 22 and 23).

Apart from acetone, we have also attempted to explore our **1c**/**2e** system to other ketones. Preliminary studies showed that cyclohexanone afforded moderate yield with dr = 82:18 (95% ee of major product). 2-Butanone furnished a mixture of regioselective products with moderate to good ee.[15]

The absolute configuration of **4n**, based on a **1c**-catalyzed aldol reaction, was found to be *S*-configuration, as unambiguously determined by single-crystal X-ray crystallography (Scheme 1).

Scheme 1. X-ray Structure of Aldol Adduct **4n**



In conclusion, we have developed a new organocatalytic methodology for the asymmetric aldol reaction of acetone to β,γ-unsaturated α-keto ester in the presence of 9-amino (9-deoxy)-epicinchona alkaloid and acidic additives. This highly enantioselective protocol gives a chiral quaternary carbon center together with tertiary alcohol, alkenyl motif, ester, and carbonyl functional group. A wide spectrum of β,γ-unsaturated α-keto esters reacts smoothly with acetone to afford the corresponding aldol adducts in excellent yields and ee. Particularly noteworthy is that the product enantioselectivities obtained by this catalytic system represent the highest level achieved so far in this type of aldol reaction. We anticipate that this protocol would be of high potential in preparing optically active six-membered ring organic molecules with functionality.

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Supporting Information Available: Detailed experimental procedures and characterization, copies of CSP-HPLC chromatograms, and ^1H and ^{13}C NMR spectra of aldol adducts, and X-ray crystallographic data of **4n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We thank reviewers for suggesting cyclohexanone and 2-butanone for further substrate scope investigations.