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Asymmetric Synthesis of Wieland–Miescher and Hajos–Parrish Ketones Catalyzed by an Amino-Acid-Derived Chiral Primary Amine

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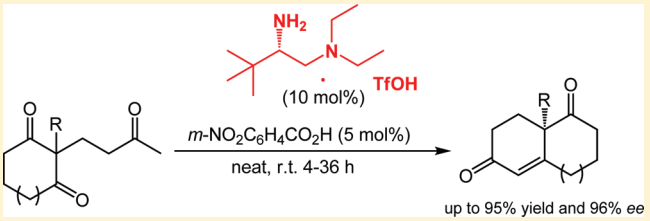
Supporting Information

ABSTRACT: This paper describes a simple chiral primary amine-catalyzed highly efficient and practical protocol for the synthesis of both Wieland–Miescher ketone and Hajos–Parrish ketone as well as their analogues. The reaction can be conducted in gram scale with 1% mol catalyst loading producing high enantioselectivity (up to 96% ee) and excellent yields (up to 98%). This procedure represents one of the most efficient methods for the synthesis of these versatile chiral building blocks.



The so-called Hajos–Parrish–Ender–Sauser–Wiechert (H–P–E–S–W) reaction, initially disclosed in the 1970s, is arguably one of the most well-known organocatalytic processes.[1] The resulting bicyclic enones, namely, Wieland–Miescher ketone (W–M ketone) and Hajos–Parrish ketone (H–P ketone), have been widely utilized in total synthesis of natural products, especially terpenoids and steroids.[2] For example, Danishefsky has utilized W–M ketone as a precursor to achieve the total synthesis of taxol.[2a] Recently, Shair accomplished the synthesis of cortistatin A starting from H–P ketone (Figure 1).[2g]

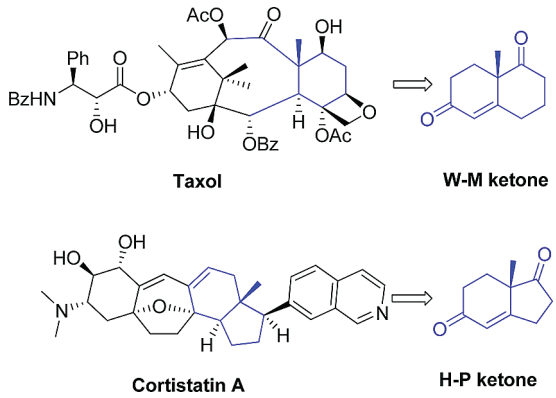
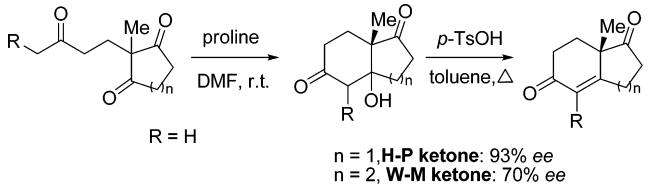


Figure 1. The applications of W–M or H–P ketones in total synthesis.

The classical H–P–E–S–W reactions use proline as a catalyst in polar aprotic solvents such as DMSO or DMF, following an intramolecular aldol and dehydration sequence (Scheme 1).[3] Though excellent enantioselectivity (93% ee) could be achieved for H–P ketone, Wieland–Miescher ketone was only obtained with moderate enantioselectivity in the classical proline protocol. The traditional methods also show some technique drawbacks such as the use of high boiling point solvents, extremely long reaction time, and multiple recrystallization at low temperature. In the following three decades, these problems had been sparsely addressed by employing chiral primary amino acids as catalysts with limited successes.[2,3]

Scheme 1. Proline-Catalyzed Intramolecular Aldol Reaction



It is not until the renaissance of organocatalysis[4] that the classical H–P–E–S–W reaction has been revisited in order to develop improved catalytic protocol. A number of chiral amine catalysts have been tested in the reactions, and notable examples include proline-catalyzed "one-pot" procedure;[5] cyclic-amino acid (1*R*,2*S*)-cispentacin,[6] short α/β-peptides,[7] bimorpholine derivatives,[8] prolinamide,[9] and chiral phosphoric acid[10] as well as monoacylated derivatives of 1,2-cyclohexanediamine[11] (Scheme 2). Among those reports, the binaphthyl-prolinamide catalyst developed by Nájera[12a] stood out with its high efficiency (94% yield and 94% ee with 2 mol % loading, Scheme 2) as well as its wide scope, and this protocol has recently been successfully applied in the total synthesis of anominine.[12b] In comparison, most of the other aminocatalsts as listed in Scheme 2 have only been applied to a few selected substrates, e.g., W–M and H–P ketones. In this context, the

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Scheme 2. Recent Examples on the Catalytic Asymmetric Synthesis of W−M Ketone

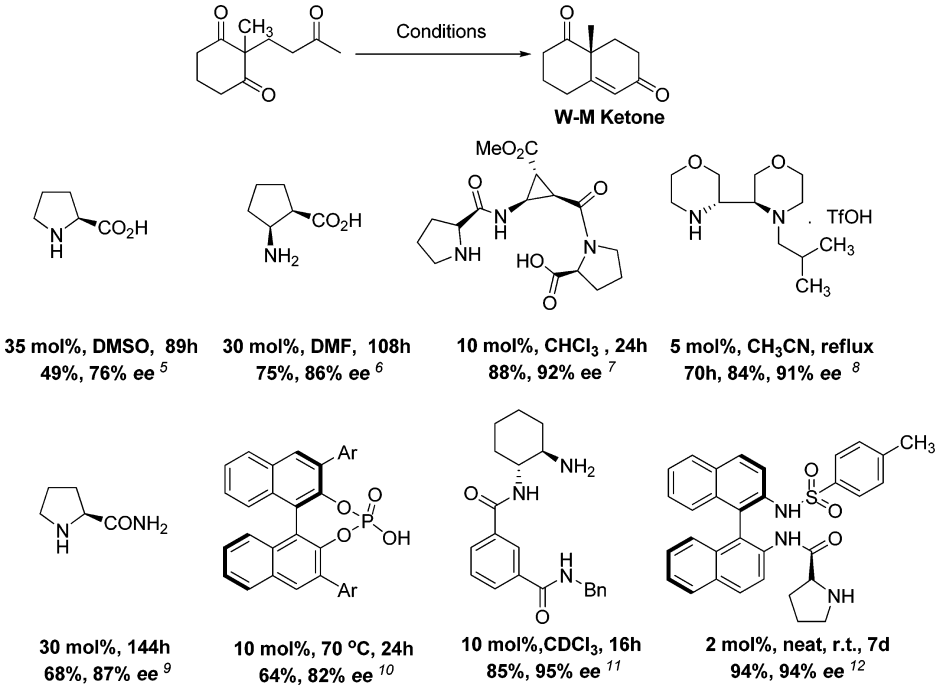
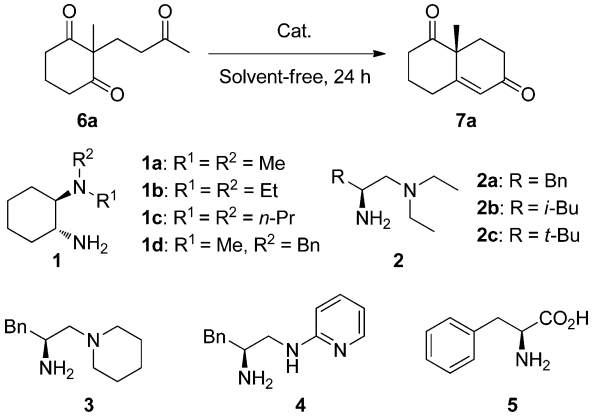


Table 1. Selected Screening and Optimization Results



entry[a]	cat (10 mol %)	additive (5 mol %)	yield (%)[b]	*ee* (%)[c]
1	**1a**/TfOH	none	88	13
2	**1b**/TfOH	none	75	65
3	**1c**/TfOH	none	88	46
4	**1d**/TfOH	none	97	46
5	**2a**/TfOH	none	94	74
6	**2b**/TfOH	none	84	62
7	**2c**/TfOH	none	95	92
8	**3**/TfOH	none	84	62
9[d]	**2c**/TfOH	*m*-$NO_2C_6H_4CO_2H$	95	92
10[d]	**2c**/TfOH	(+)-CSA	90	92
11	**4**	none	none	
12	**5**	none	none	

[a]Unless otherwise stated, all reactions were carried out on 0.1 mmol scale at ambient temperature using 10 mol % catalyst under solvent-free conditions. [b]Isolated yield. [c]Determined by chiral HPLC. [d]The reaction was completed in 12 h.

development of a simple catalyst with improved performance and wide scope is still highly desirable.

Recently, we have developed bioinspired chiral primary amine catalysts that enable a full range of aldol reactions including direct aldol reactions with aliphatic ketones,[13a] hydroxyacetones,[13b] dihydroxyacetone,[13c] pyruvic acetal,[13d] acetoacetals,[13e] aliphatic aldehydes,[13f] and acetaldehyde,[13g] as well as asymmetric retro aldol reactions[13h] and transfer aldol reactions.[13i] In our continuing studies, we found that the simple primary tertiary diamines derived from α-amino acid turned out

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to be an effective catalyst for the H−P−E−S−W reactions, formulating one of the most practical catalytic protocols for this classical reaction.[14]

We chose triketone **6a** as a model substrate to test our previously developed primary amine catalysts. Indeed, the cyclohexanediamine-based primary amines **1** in concert with TfOH showed good activity in the reactions, albeit with moderate enantioselectivity (Table 1, entries 1−4). Taking advantage of the liquid nature of the primary amine catalysts such as **1**, the reactions can be conveniently conducted under solvent-free conditions, resulting in a much faster reaction than that in solution (24 vs 48 h in CH_2Cl_2 for completed conversion). Under solvent-free conditions, other diamine catalysts have been examined. To our delight, the vicinal diamines **2** derived from α-amino acids were found to provide much higher enantioselectivity (Table 1, entries 5−7), and the optimal results were obtained with *tert*-leucine derivative **2c** (95% yield, 92% ee; Table 1, entry 7). The use of other primary amine catalysts gave inferior results in terms of both activity and enantioselectivity (for examples, see entries 8, 11−12). Consistent with our previous observations,[13] the addition of a second weak acid *m*-nitrobenzoic acid led to remarkable rate enhancement with completed conversion in 12 h (Table 1, entry 9) in the presence of 10 mol % of **2c**/TfOH.

Under the optimized conditions (solvent-free and ambient temperature), the generality of this protocol was examined (Table 2). The reactions accommodate different substituted triketones to afford the desired W−M ketones with good isolated yields and high enantioselectivity (Table 2, entries 1−6). The phenyl-substituted **7g** and ester-containing **7h** are first applied in this reaction, showing good reactivity and enantioselectivity (Table 2, entries 7 and 8). The current catalyst can also be applied to the synthesis of H−P ketone, affording 95% yield and 92% ee in 12 h (Table 2, entry 9). A benzo-conjugated H−P ketone **7j** can also be accessed with good yield and moderate 65% ee (Table 2, entry 10).

To further demonstrate the applicability of our primary aminocatalytic process, gram-scale reactions were attempted with only 1 mol % of catalyst. Under this condition, the reaction of **6a** proceeded to completion in 4 days to afford the desired W−M ketone in 98% isolated yield with 91% ee. These results represent those of the best that have been reported for the synthesis of W−M ketones without additional manipulation (e.g., recrystallization).[13c] Similarly, H−P ketone can also be isolated in 90% yield and 96% ee in gram-scale with 1 mol % of catalyst (Scheme 3).

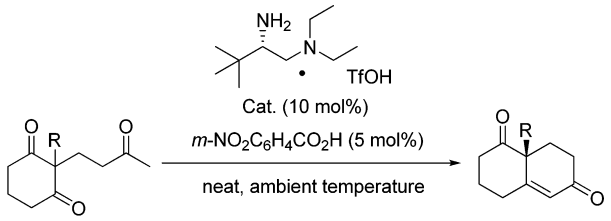
In conclusion, we have presented a highly enantioselective and efficient protocol for the synthesis of both H−P ketone and W−M ketone as well as their analogues catalyzed by a simple chiral primary amine catalyst. The loading of catalyst can be reduced to 1 mol % with good reactivity and selectivity. In addition, the primary amine catalyst is structurally simple and readily available. These notable features promise significant synthetic applications of the current catalytic protocol.

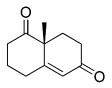
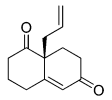
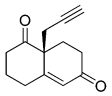
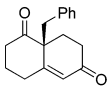
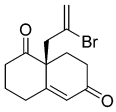
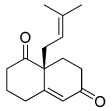
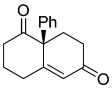
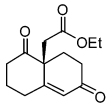
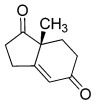
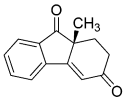
EXPERIMENTAL SECTION

General Procedure for the Preparation of Triketone.[12a] To 2-methyl-1,3-cyclohexadione (6.3 g, 50 mmol) in a standard glass vial with stirrer bar was added methyl vinyl ketone (4.5 mL, 55 mmol) followed by Et_3N (69 μL, 0.50 mmol). The initial thick suspension slowly became more fluid as the solid slowly dissolved to give a yellow/orange solution/oil. After 5 h, the mixture was absorbed onto silica and purified by column chromatography to give the triketone **6a** as colorless oil (9.6 g, 98% yield). The NMR data obtained for **6a** are identical to those previously reported. Triketones **6a−6f**,[12a] **6h−6j**[10,12a] are known compounds.

2-(3-Oxobutyl)-2-phenylcyclohexane-1,3-dione (6g). The starting 2-phenyl cyclohexane-1,3-dione was synthesized following a reported procedure.[15] Pale yellow syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.28 (m, 3H), 7.00 (d, J = 7.8 Hz, 2H), 2.75 (ddd, J = 15.5, 9.6, 5.8 Hz, 2H), 2.55 (dt, J = 16.3, 5.6 Hz, 2H), 2.41−2.27 (m, 2H), 2.22 (dt, J = 11.9, 6.0 Hz, 2H), 2.05 (d, J = 2.8 Hz, 3H), 1.95−1.81 (m, 1H), 1.71 (ddd, J = 18.9, 9.6, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.54, 204.5, 135.0, 126.9, 125.4, 123.8, 72.1, 37.1, 36.3,

Table 2. Substrate Scope



entry [a]	product	t (h)	yield (%) [b]	*ee* (%) [c]
1		12	**7a**/95	92
2		24	**7b**/95	92
3		24	**7c**/90	92
4		36	**7d**/80	87
5		24	**7e**/75	90
6		24	**7f**/90	89
7		4	**7g**/92	79
8		36	**7h**/82	86
9		12	**7i**/95	96
10		24	**7j**/95	65

[a]Unless otherwise noted, all reactions were conducted on 0.1 mmol scale with 10 mol % primary amine and 5 mol % *m*-$NO_2C_6H_4CO_2H$ under solvent-free conditions at ambient temperature. [b]Isolated yields. [c]Determined by chiral HPLC.

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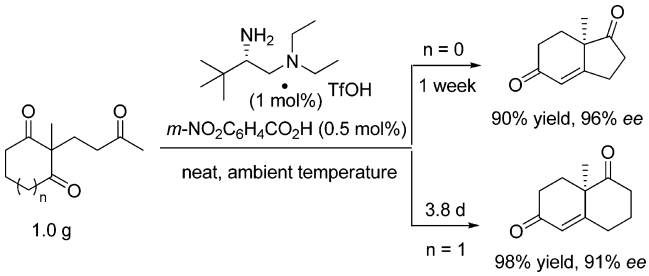
Scheme 3. Gram Scale Experiments



27.1, 26.2, 14.8; HRMS(EI) Calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1260.

General Procedure for the Synthesis of Wieland–Miescher and Hajos–Parrish Ketones. To 2-alkylcyclohexane-1,3-dione (0.1 mmol) were added chiral amine catalyst (3.2 mg, 0.01 mmol) and *m*-$NO_2C_6H_4CO_2H$ (0.8 mg, 0.005 mmol) under solvent-free conditions at ambient temperature. The reaction was monitored by ^{1}H NMR and stopped in the given time. The reaction mixture was directly isolated by flash chromatography to give the pure product. Products **7a–7f**, **7i**, and **7j** are known compounds.[10,12]

(*S*)-8a-Phenyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (7g). The reaction was carried out with slight modification of standard conditions. Dicholormethane (0.5 mL) was added to first dissolve the catalyst and **6g**, and the resulting homogeneous solution was concentrated under a vacuum to remove DCM. The obtained residue was kept at room temperature. After 4 h, when the reaction was completed as monitored by TLC, the reaction mixture was directly purified by flash chromatography to give **7g** as a colorless syrup: 92% yield, 79% *ee*; $[\alpha]_D^{20}$ = 16 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.29 (m, 3H), 7.17 (dd, *J* = 5.3, 3.2 Hz, 2H), 6.23 (s, 1H), 2.79–2.55 (m, 2H), 2.55–2.38 (m, 3H), 2.38–2.17 (m, 2H), 2.11–1.95 (m, 2H), 1.89–1.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 195.9, 159.9, 135.0, 126.8, 126.7, 125.2, 124.1, 57.8, 36.3, 30.7, 30.2, 30.1, 20.8; HRMS(EI) Calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1153. The *ee* value was determined by chiral HPLC [Daicel Chiralpak OD-H column, λ = 254 nm, 2-propanol/*n*-hexane = 3:97, flow rate = 0.8 mL min^{-1}]: t_R = 21.97 min (minor), t_R = 24.11 min (major).

(*S*)-Ethyl 2-(4,7-Dioxo-1,2,3,4,4a,5,6,7-octahydronaphthalen-4a-yl)acetate (7h). The reaction was conducted following the procedure of **7g**. Colorless syrup: 82% yield, 86% *ee*, $[\alpha]_D^{20}$ = −11 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (d, *J* = 1.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.05–2.68 (m, 4H), 2.68–2.32 (m, 4H), 2.27–2.05 (m, 3H), 1.72 (ddd, *J* = 17.9, 13.4, 9.0 Hz, 2H), 1.24 (d, *J* = 7.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 197.7, 169.1, 163.4, 127.2, 61.3, 52.8, 40.4, 38.0, 33.4, 31.7, 26.9, 23.6, 14.0; HRMS(EI) Calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1208. The *ee* value was determined by chiral HPLC [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol/*n*-hexane = 1:9, flow rate = 1.0 mL min^{-1}]: t_R = 13.09 min (major), t_R = 15.21 min (minor).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and HPLC spectra for all the final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239. (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (d) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675. (e) Hajos, Z. G.; Parrish, D. R. *Organic Synthesis*; Wiley: New York, 1990; Collect. Vol. *VII*, p 363. (f) Bradshaw, B.; Bonjoch, J. *Synlett* **2011**, DOI: 10.1055/s-0031-1290107.

(2) For examples, see: (a) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; DiGrandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (b) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764. (c) Paquette, L. A.; Wang, T. Z.; Philippo, C. M. G.; Wang, S. P. *J. Am. Chem. Soc.* **1994**, *116*, 3367. (d) Smith, A. B. III; Kingerywood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438. (e) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.* **2001**, *123*, 11586. (f) Waters, S. P.; Tian, Y.; Li, Y. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514. (g) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864.

(3) (a) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53. (b) Clemente, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 11294 and references therein. (c) Mander, L. N.; Turner, J. V. *Tetrahedron Lett.* **1981**, *22*, 3683. (d) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308. (e) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429.

(4) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.

(5) (a) Bui, T.; Barbas, C. F. III *Tetrahedron Lett.* **2000**, *41*, 6951. (b) Rajagopal, D.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron: Asymmetry* **1996**, *7*, 2189. (c) Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* **2001**, *42*, 4887.

(6) Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005**, 3802.

(7) D'Elia, V.; Zwicknagl, H.; Oliver, R. *J. Org. Chem.* **2008**, *73*, 3262.

(8) Kanger, T.; Kriis, K.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *J. Org. Chem.* **2007**, *72*, 5168.

(9) Zhang, X. M.; Wang, M.; Tu, Y. Q.; Fan, C. A.; Jiang, Y. J.; Zhang, S. Y.; Zhang, F. M. *Synlett* **2008**, 2831.

(10) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652.

(11) Fuentes de Arriba, A. L.; Seisdedos, D. G.; Simón, L.; Alcázar, V.; Raposo, C.; Morán, J. R *J. Org. Chem.* **2010**, *75*, 8303.

(12) (a) Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C. *Adv. Synth. Catal.* **2009**, *351*, 2482. (b) Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010**, *132*, 5966. (c) Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C. *Org. Synth.* **2011**, *88*, 330.

(13) (a) Luo, S. Z.; Xu, H.; Li, J. Y.; Zhang, L.; Cheng, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (b) Luo, S. Z.; Xu, H.; Zhang, L.; Li, J. Y.; Cheng, J. P. *Org. Lett.* **2008**, *10*, 653. (c) Li, J. Y.; Luo, S. Z.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 1747. (d) Luo, S. Z.; Xu, H.; Chen, L. J.; Cheng, J. P. *Org. Lett.* **2008**, *10*, 1775. (e) Luo, S.; Qiao, Y.; Zhang, L.; Li, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 9521. (f) Li, J. Y.; Fu, N. K.; Li, X.; Luo, S. Z.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 4501. (g) Hu, S. S.; Zhang, L.; Li, J. Y.; Luo, S. Z.; Cheng, J.-P. *Eur. J. Org. Chem.* **2011**, *75*, 3347. (h) Luo, S. Z.; Zhou, P. X.; Li, J. Y.; Cheng, J. P. *Chem.—Eur. J.* **2010**, *16*, 4457. (i) Zhou, P. X.; Luo, S. Z.; Cheng, J. P. *Org. Biomol. Chem.* **2011**, *9*, 1784.

(14) For recent reviews for primary amine catalysis, see: (a) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1−13. (b) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807−1821. (c) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047−2053. (d) Chen, Y.-C. *Synlett* **2008**, 1919.
(15) Gér Rousseau, G.; Robert, F.; Landais, Y. *Synthesis* **2010**, 1223.