Asymmetric Catalysis

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Highly Diastereo- and Enantioselective Synthesis of 5-Substituted 3-Pyrrolidin-2-ones: Vinylogous Michael Addition under Multifunctional Catalysis**

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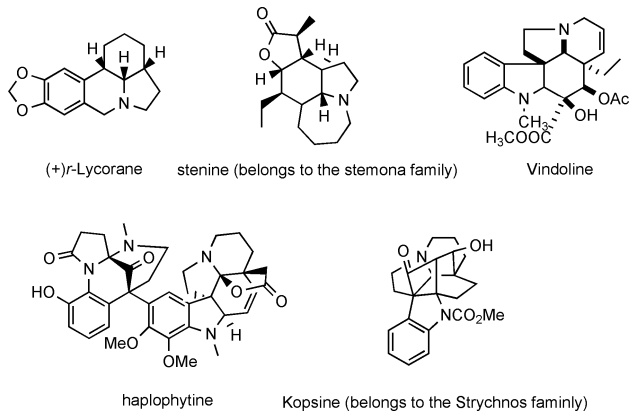
5-Substituted 3-pyrrolidin-2-ones and their structural analogues have been found as crucial fragments in a number of complex natural and non-natural compounds,[1] such as the lycorane-type alkaloids, the stemona family, and the large family of indole alkaloids including haplophytine, vindoline, and the strychnos family of alkaloids (Scheme 1). All these



Scheme 1. Several natural products that contain the fragments of 5-substituted 3-pyrrolidin-2-one derivatives.

molecules display marvelous biological properties including antiviral, pesticidal, and antitumor activity, as well as other pharmacological properties,[2] which undoubtably contribute greatly to their importance in the field of organic chemistry both in terms of their chemical synthesis and in the development of synthetic methodologies.

As one of the efficient chemical precursors to 5-substituted 3-pyrrolidin-2-one derivatives, α,β-unsaturated γ-butyrolactam has recently appeared as one of the most attractive reactants in various chemical reactions including Mannich, Aldol, Michael, and other simple transformations of either direct or Mukaiyama-type reactions.[3] Even more attractive are the diastereo- or enantioenriched products that could be further utilized as versatile building blocks towards more functionalized pyrrolidin-2-ones.[4]

However, stereoselective transformations involving this interesting molecule still remain rare, both in the field of organocatalytic synthesis and organometallic catalysis, compared with other important nucleophilic reagents. The scarcity of reactions is partially due to the difficulties in the chemoselective activation of the α, β-unsaturated vinylogous system either as a donor or as an acceptor in chemical reactions, and the challenges in the enantio- and diastereoselectivity during those processes.[5] Satisfactory results were achieved in the recent report of Shibasaki and co-workers[5a] in the asymmetric vinylogous Mannich and Michael reaction of this α,β-unsaturated γ-butyrolactam with *N*-Boc imines and nitroolefins involving a dinuclear nickel catalytic system. Furthermore, Chen and co-workers[5d] have presented an asymmetric Michael addition with α,β-unsaturated aldehydes under the well-established iminium activation using the catalyst developed by Jørgensen and Hayashi.[6] However, to the best of our knowledge, the vinylogous Michael additions of this α,β-unsaturated γ-butyrolactam to α,β-unsaturated ketones has never been reported and still represents a challenging task regarding the reactivity and stereoselectivity of the two relatively inert reactants.[7] Herein, we report our investigations on this transformation under a multifunctional catalytic system, as well as some explorations into the use of the resulting products to demonstrate the potential utility of this strategy in the pharmaceutical and organic synthesis fields.

Our initial investigations were carried out using a series of catalysts (**1**–**3**) for the model reaction of benzalacetone **4a** and α,β-unsaturated γ-butyrolactam **5a** in CH_2Cl_2 at room temperature (Table 1, entries 1–11). Experimental data showed that the cyclohexane-1,2-diamine catalysts **1a** and **1b** could promote the reaction more effectively than other types of catalysts, with conversions of up to 93% after 72 hours, but with low stereoselectivity (entries 1 and 2). The 9-amino-epiquinine **2a** and its derivative **2b** afforded the products with slightly increased *ee* values, but still with unsatisfactory reaction conversions or stereoselectivity (entries 3 and 4). Then our attention turned to another type of iminium-activation catalyst bearing a chiral 1,2-diphenylethane-1,2-diamine fragment with the hope that it would provide an improvement in this transformation. Attractive *ee* values were attained using the simple (*R*,*R*)-1,2-diphenyl-

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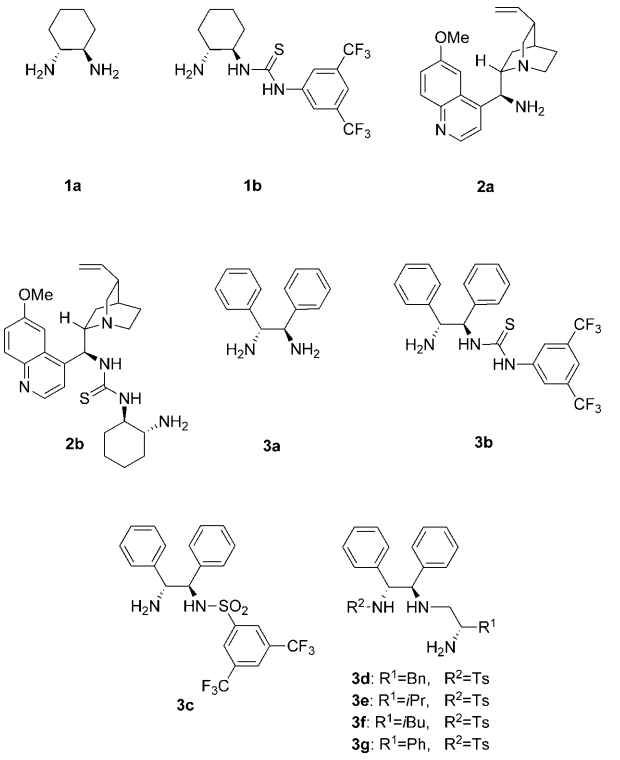
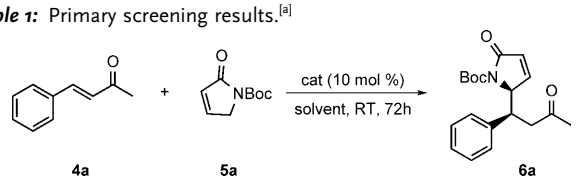


Table 1: Primary screening results.[a]



Entry	Cat.	Solvent	Acid additive	Conv. [%][b]	d.r.[b]	*ee* [%][c,d]
1	**1a**	CH_2Cl_2	none	93	2:1	50(27)
2	**1b**	CH_2Cl_2	none	58	2:1	0(31)
3	**2a**	CH_2Cl_2	none	30	2:1	48(66)
4	**2b**	CH_2Cl_2	none	71	2.5:1	77(72)
5	**3a**	CH_2Cl_2	none	16	1:1.5	77(90)
6	**3b**	CH_2Cl_2	none	13	1:1.5	20(8)
7	**3c**	CH_2Cl_2	none	0	–	–
8	**3d**	CH_2Cl_2	none	63	2:1	6(36)
9	**3e**	CH_2Cl_2	none	66	1:2.5	21(0)
10	**3f**	CH_2Cl_2	none	65	1:1	11(21)
11	**3g**	CH_2Cl_2	none	42	1.5:1	25(11)
12	**3e**[e]	$CHCl_3$[f]	*N*-Boc-L-Trp	93	15:1	98

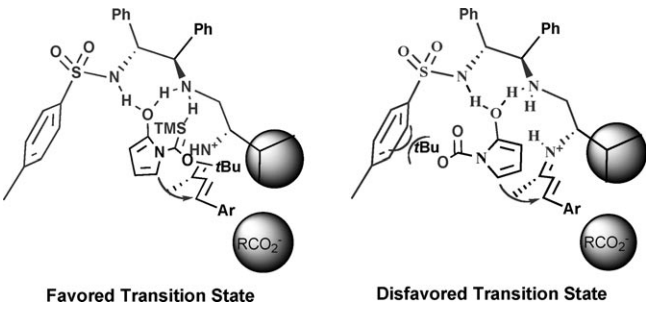
[a] Unless noted otherwise the following reaction conditions were used: **5a** (1.0 equiv, 0.10 mmol, 0.5 M), **4a** (1.3 equiv), catalyst (0.10 equiv), and acid additive (0.10 equiv). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC on a chiral stationary phase. [d] The data in the parentheses are the *ee* values of the other diastereomer. [e] 0.15 equiv of **3e** was employed. [f] The reaction was carried out at 35 °C. Boc = *tert*-butoxycarbonyl.

ethane-1,2-diamine (**3a**), but the conversion and diastereoselectivity were disappointing (entry 5). So a series of **3a** derivatives were sequentially examined to find the suitable catalyst. However, the stereoselectivity did not even show marginal improvements, albeit with some improvements in the reaction conversions (entries 6–11). A bulky acid partner was crucial for the stereocontrol,[8] so a series of commercially available bulky *N*-Boc amino acids were surveyed in combination with the organocatalysts. The diastereoselectivity decreased with **3a**, **3b**, and **3c** as catalysts in the presence of the bulky *N*-Boc-L-Phe. However, bulky *N*-Boc amino acids improved the diastereoselectivity significantly with catalysts **3d**–**3g**. To our delight, both excellent enantio- and diastereoselectivity could be achieved using the catalytic system consisting of **3e** and *N*-Boc-L-Trp. Furthermore, investigations showed that the amount of acidic additives had little effect, and the reaction could proceed well in many different solvents to give excellent *ee* values and good to excellent d.r. values.[9] Finally, the reaction conversion could be improved to 93% with high d.r. and *ee* values when the reaction was run at 35 °C in $CHCl_3$ (entry 12).

With the optimized reaction conditions in hand, the scope of this organocatalytic asymmetric vinylogous Michael addition was exploited to check the substrate generality of this strategy (Table 2). To our great delight, this well-established approach could be utilized for a large variety of α,β-unsaturated ketones bearing either electron-donating (entries 1–10) or electron-withdrawing (entries 11–18) groups. All the Michael products could be acquired in excellent yields with excellent enantio- and diastereoselectivity. Notably, the Michael receptors could be extended to aliphatic α,β-unsaturated ketones (entries 22–31), including various cyclic vinyl ketones, to result in complete enantioselectivity and favorable d.r. values with excellent product yields (entries 30 and 31).

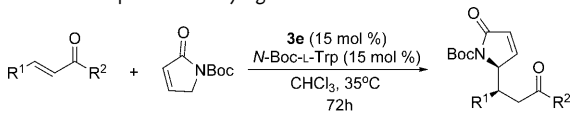
The bromide product **6r** was recrystallized and the corresponding single crystal was subjected to X-ray analysis to determine the absolute structure.[10] On the basis of this result and our previous work,[8] a plausible catalytic mechanism involving multisite interactions was assumed to explain the high stereoselectivity of this process (Scheme 2).

Having successfully extended this strategy to a large variety of vinyl ketones, we then devoted our efforts to exploring some additional transformations of the enantio- and diastereopure Michael products, which are important fragments in the structure of many biologically active molecules. The malonate group can be introduced into the 5-substituted 3-pyrrolidin-2-ones under sodium hydride and TMSCl conditions. Highly stereoselective dihydroxylation of the 5-substituted 3-pyrrolidin-2-ones proceed well with

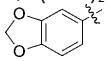


Scheme 2. Proposed transition state in the vinylogous Michael reaction.

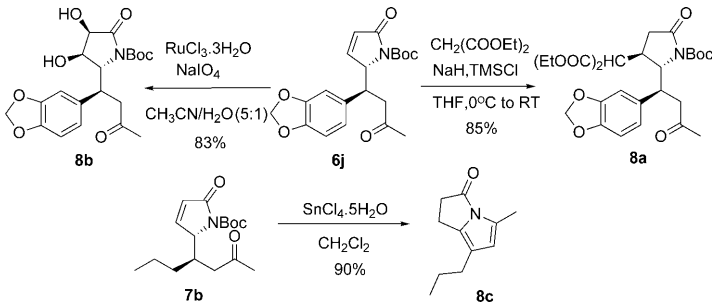
Table 2: The scope of the vinylogous Michael reaction.[a]



4 5a 6 or 7

Entry	R^1	R^2	Adduct	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	C_6H_5	Me	**6a**	86	15:1	98
2	2-$MeOC_6H_4$	Me	**6b**	88	25:1	98
3	3-$MeOC_6H_4$	Me	**6c**	86	15:1	95
4	4-$MeOC_6H_4$	Me	**6d**	83	14:1	98
5	2-MeC_6H_4	Me	**6e**	83	15:1	99
6	3-MeC_6H_4	Me	**6f**	84	17:1	99
7	4-MeC_6H_4	Me	**6g**	75	15:1	98
8	2,3-$(MeO)_2C_6H_3$	Me	**6h**	90	18:1	99
9	2,4-$(MeO)_2C_6H_3$	Me	**6i**	88	19:1	98
10		Me	**6j**	82	15:1	98
11	2-FC_6H_4	Me	**6k**	88	16:1	99
12	3-FC_6H_4	Me	**6l**	80	13:1	98
12	4-FC_6H_4	Me	**6m**	81	12:1	98
14	2-ClC_6H_4	Me	**6n**	82	20:1	99
15	3-ClC_6H_4	Me	**6o**	76	12:1	98
16	4-ClC_6H_4	Me	**6p**	81	12:1	96
17	3-BrC_6H_4	Me	**6q**	83	16:1	98
18	4-BrC_6H_4	Me	**6r**	85	14:1	98
19	2-naphthyl	Me	**6s**	81	13:1	98
20	2-furanyl	Me	**6t**	83	>30:1	99
21	2-thiopenyl	Me	**6u**	85	>30:1	99
22	Me	Me	**7a**	85	>20:1	98
23	*n*Pr	Me	**7b**	81	>20:1	98
24	*n*Bu	Me	**7c**	84	>20:1	98
25	pentyl	Me	**7d**	86	>20:1	98
26	hexyl	Me	**7e**	83	>20:1	98
27	Me	Bu	**7f**	80	>20:1	98
28	$C_6H_5CH_2CH_2$	Me	**7g**	78	>20:1	99
29	$C_6H_5CH{=}CH$	Me	**7h**	81	18:1	98
30	-$(CH_2)_2$-		**7i**	79	4:1	99
31	-$(CH_2)_4$-		**7j**	83	10:1	99

[a] All reactions were carried out using the following reaction conditions: **5a** (1.0 equiv, 0.50 mmol, 0.5 M), α,β-unsaturated ketone **4** (1.3 equiv), catalyst **3e** (0.15 equiv), and *N*-Boc-L-Trp in $CHCl_3$. [b] Yield of the isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase.



Scheme 3. Several examples of the transformations of the corresponding Michael products. THF = tetrahydrofuran, TMS = trimethylsilyl.

$RuCl_3{\cdot}H_2O$ and $NaIO_4$.[5b] The transformations are summarized in Scheme 3.

In summary, a direct organocatalytic asymmetric vinylogous Michael reaction of α,β-unsaturated γ-butyrolactam with α,β-unsaturated ketones has been developed. The corresponding Michael products could be obtained with excellent enantio- (95% to 99% *ee*) and diastereoselectivity (4:1–30:1 d.r.) in excellent yields (75–90%). Moreover, those enantiopure products could serve as important fragments in a number of biologically active natural and non-natural compounds, and might be of importance in both natural product synthesis and pharmaceutical research because of their potential utility towards construction of attractive molecules. Additional investigations involving the application of this catalytic approach are currently under way in our group and will be reported in due course.

Experimental Section

General procedure: α,β-Unsaturated γ-butyrolactam **5a** (0.5 mmol, 1.0 equiv) was added to a mixture of catalyst **3e** (0.075 mmol, 0.15 equiv), *N*-Boc-L-Trp (0.075 mmol, 0.15 equiv), and α,β-unsaturated ketones **4** (0.65 mmol, 1.3 equiv) in $CHCl_3$ (1.0 mL) at 35°C. The reaction mixture was maintained at this temperature for 3 days and then the solvent was removed under vacuum. The residue was purified by chromatography on silica gel to yield the desired addition product. The enantiomeric ratio was determined by HPLC on a chiral stationary phase.

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[1] a) G. Casiraghi, F. Zanardi, L. Battistini, G. Rassu, *Synlett* **2009**, 1525; b) L. Dong, Y.-J. Xu, L.-F. Cun, X. Cui, A.-Q. Mi, Y. Z. Jiang, L.-Z. Gong, *Org. Lett.* **2005**, *7*, 4285; c) J. W. Ward, K. Dodd, C. L. Rigby, C. D. Savib, D. J. Dixon, *Chem. Commun.* **2010**, *46*, 1691; d) L. A. Sharp, S. Z. Zard, *Org. Lett.* **2006**, *8*, 831; e) C.-A. Fan, Y.-Q. Tu, Z.-L. Song, E. Zhang, L. Shi, M. Wang, B. Wang, S.-Y. Zhang, *Org. Lett.* **2004**, *6*, 4691; f) Q. Wang, A. Padwa, *Org. Lett.* **2004**, *6*, 2189; g) L. D. Miranda, S. Z. Zard, *Org. Lett.* **2002**, *4*, 1135; h) J. D. Ginn A. Padwa, *Org. Lett.* **2002**, *4*, 1515; i) B. D. Chapsal, I. Ojima, *Org. Lett.* **2006**, *8*, 1395; j) G. D. Wilkie, G. I. Elliott, B. S. J. Blagg, S. E. Wolkenberg, D. R. Soenen, M. M. Miller, S. Pollack, D. L. Boger, *J. Am. Chem. Soc.* **2002**, *124*, 11292; k) P. Magnus, T. Katoh, I. R. Matthews, J. C. Huffman, *J. Am. Chem. Soc.* **1989**, *111*, 6707; l) S. E. Denmark, Y.-C. Moon, C. B. W. Senanayake, *J. Am. Chem. Soc.* **1990**, *112*, 311; m) J. P. Marino, M. B. Rubio, G. Cao, A. Dios, *J. Am. Chem. Soc.* **2002**, *124*, 13398; n) H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 10596; o) K. C. Nicolaou, S. M. Dalby, U. Majumder, *J. Am. Chem. Soc.* **2008**, *130*, 14942; p) K. C. Nicolaou, U. Majumder, S. P. Roche, D. Y.-K. Chen, *Angew. Chem.* **2007**, *119*, 4799; *Angew. Chem. Int. Ed.* **2007**, *46*, 4715.

[2] a) G. R. Pettit, S. Freeman, M. J. Simpson, M. A. Thompson, M. R. Boyd, M. D. Williams, G. R. Pettit, D. L. Doubek, *Anti-Cancer Drug Des.* **1995**, *10*, 243; b) K. Sakata, K. Aoki, C. F. Chang, A. Sakurai, S. Tamura, S. Murakoshi, *Agric. Biol. Chem.* **1978**, *42*, 457; c) M.

Tereda, M. Sano, A. I. Ishii, H. Kino, S. Fukushima, T. J. Noro, *Pharm. Soc. Jpn.* **1982**, *79*, 93; d) H. Shinozaki, M. Ishida, *Brain Res.* **1985**, *334*, 33.

[3] For limited examples, see: a) X. Feng, H.-L. Cui, S. Xu, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 10309; b) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666; c) C. Curti, A. Sartori, L. Battistini, G. Rassu, P. Burreddu, F. Zanardi, G. Casiraghi, *J. Org. Chem.* **2008**, *73*, 5446; d) A. Sartori, C. Curti, L. Battistini, P. Burreddu, G. Rassu, G. Pelosi, G. Casiraghi, F. Zanardi, *Tetrahedron* **2008**, *64*, 11697; e) C. Curti, A. Sartori, L. Battistini, G. Rassu, F. Zanardi, G. Casiraghi, *Tetrahedron Lett.* **2009**, *50*, 3428; f) H. Suga, H. Takemoto, A. Kakehi, *Heterocycles* **2007**, *71*, 361; g) D. M. Barnes, L. Bhagavatula, J. DeMattei, A. Gupta, D. R. Hill, S. Manna, M. A. McLaughlin, P. Nichols, R. Premchandran, M. W. Rasmussen, Z. Tian, S. J. Wittenberger, *Tetrahedron Asymmetry* **2003**, *14*, 3541.

[4] A. Gheorghe, M. Schulte, O. Reiser, *J. Org. Chem.* **2006**, *71*, 2173.

[5] For selected recent examples of direct vinylogous reaction of γ-butyrolactones, see: a) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319; b) B. M. Trost, J. Hitce, *J. Am. Chem. Soc.* **2009**, *131*, 4572; c) A. M. Hyde, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 2663; d) J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 720; e) J. Wang, C. Qi, Z. Ge, T. Cheng, R. Li, *Chem. Commun.* **2010**, *46*, 2124; f) Y. Zhang, C. Yu, Y. Ji, W. Wang, *Chem. Asian J.* **2010**, *5*, 1303; g) Y. Yang, K. Zheng, J. Zhao, J. Shi, X. Liu, X. Feng, *J. Org. Chem.* **2010**, *75*, 5382; h) H. Ube, N. Shimada, M. Terada, *Angew. Chem.* **2010**, *122*, 1902; *Angew. Chem. Int. Ed.* **2010**, *49*, 1858; for selected recent examples of direct vinylogous reaction of γ-butyrolactams, see: Ref. [3a,b,c].

[6] For the original studies involving this type of catalyst, see: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[7] For selected examples of organocatalyzed asymmetric Michael addition of enones, see: a) M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520; b) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; c) P. McDaid, Y. Chen, L. Deng, *Angew. Chem.* **2002**, *114*, 348; *Angew. Chem. Int. Ed.* **2002**, *41*, 338; d) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685; *Angew. Chem. Int. Ed.* **2003**, *42*, 661; e) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955; f) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; g) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621; h) M. T. Hechevarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 4048; *Angew. Chem. Int. Ed.* **2004**, *43*, 3958; i) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897; j) J. Yang, M. T. Hechevarria FonsecaFonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036; k) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem.* **2006**, *118*, 961; *Angew. Chem. Int. Ed.* **2006**, *45*, 947; l) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66; m) J. Xie, W. Chen, R. Li, W. Du, Y. Chen, Y. Wu, J. Zhu, J. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; n) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49; o) Z. Jiang, W. Ye, Y. Yang, C. Tan, *Adv. Synth. Catal.* **2008**, *350*, 2345; p) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422; q) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070; r) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134; s) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112; t) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302; u) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang, J. Ye, *Org. Lett.* **2009**, *11*, 753; v) S. Wen, P. Li, H. Wu, F. Yu, X. Liang, J. Ye, *Chem. Commun.* **2010**, *46*, 4806; w) J. Yang, W. Li, Z. Jin, X. Liang, J. Ye, *Org. Lett.* **2010**, *12*, 5218; x) X. Sun, F. Yu, T. Ye, X. Liang, J. Ye, *Chem. Eur. J.* **2011**, *17*, 430.

[8] H. Huang, F. Yu, Z. Jin, W. Li, W. Wu, X. Liang, J. Ye, *Chem. Commun.* **2010**, *46*, 5957.

[9] For details, see the Supporting Information.

[10] CCDC 804551 (**6r**) 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.

