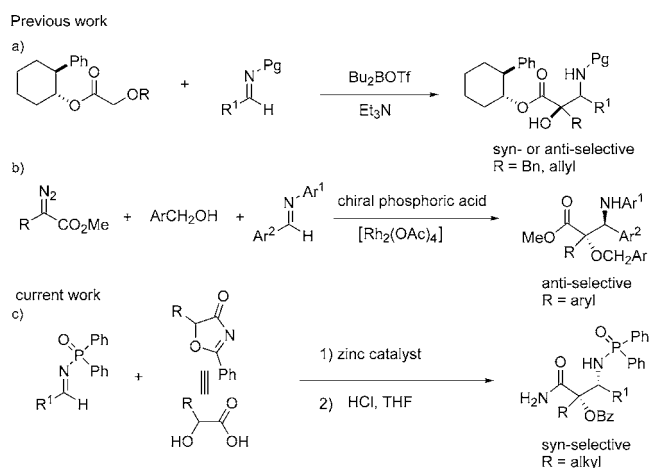


Highly Diastereo- and Enantioselective Synthesis of α -Alkyl Norstatine Derivatives: Catalytic Asymmetric Mannich Reactions of 5*H*-Oxazol-4-ones**

Depeng Zhao, Linqing Wang, Dongxu Yang, Yixin Zhang, and Rui Wang*

The catalytic asymmetric synthesis of β -amino acids^[1] has been an intense area of research in recent years as these unnatural amino acids are basic elements of peptides and peptidomimetic precursors of many physiologically active compounds.^[2] In particular, many efforts have focused on synthetic methods towards α -hydroxy β -amino acid (norstatine) derivatives,^[3] which have been used as a side chain in taxol analogues,^[4] and are observed in natural products such as leuhistin.^[5] Despite previous success, the stereoselective synthesis of α -alkyl α -hydroxy β -amino acids bearing a quaternary stereogenic center is still challenging.

In 2010, Wolfe and co-workers described an asymmetric tandem Wittig rearrangement/Mannich reaction to prepare such compounds using 2-phenylcyclohexanol as a chiral auxiliary (Scheme 1 a).^[6] With this protocol, both *syn*- and *anti*-selective products were accessed with high enantioselectivities and diastereoselectivities using specific protective groups. To date, only a few catalytic methods have been developed for α -alkyl norstatine derivatives.^[7] Hu, Gong, and co-workers reported a three-component reaction of diazo compounds with alcohols and imines catalyzed by $[\text{Rh}_2(\text{OAc})_4]$ and a chiral Brønsted acid (Scheme 1 b).^[8] In this process, *anti*- α -aryl norstatine derivatives were synthesized in high yields with excellent enantioselectivities.^[7] In view of previous failures of the direct Mannich reaction of α -alkyl α -hydroxy acids derivatives,^[8] we envisioned that the 5*H*-oxazol-4-ones^[9] **2** might serve as highly reactive equivalents of α -alkyl α -hydroxy acids and undergo an asymmetric Mannich reaction,^[10] an efficient approach to these compounds (Scheme 1 c). The high reactivity of 5*H*-oxazol-4-one compared to other equivalents of α -alkyl α -hydroxy acids is attributed to the aromatization resulting from the enolization of 5*H*-oxazol-4-one, thus enabling the intermediates to be



Scheme 1. Protocols for asymmetric synthesis of α -alkyl α -hydroxy β -amino acids.

more stable and thereby increasing the reactivity. Herein we describe our efforts on this subject, and the resulting access to a series of *syn*- α -alkyl norstatine derivatives with high enantioselectivities and diastereoselectivities.

Given our continued interest in the asymmetric synthesis of unnatural amino acids,^[11] especially oxazolones,^[12,13] we decided to investigate the asymmetric Mannich reaction of the 5*H*-oxazol-4-ones **2**. Fortunately, we found that the reaction between the N-Dpp (Dpp = diphenylphosphinoyl) imine **1a** and 5*H*-oxazol-4-one **2a** could be efficiently catalyzed by a zinc catalyst^[14] such as the salen **4**/Zn complex (Scheme 2). The Mannich adducts can be obtained with good yield and excellent diastereoselectivity, though with low enantioselectivity in the presence of salen **4**/Zn (78%, 7% *ee*, 20:1 d.r.) at room temperature. Encouraged by these results, a series of salen-type ligands, **5–7**, were synthesized including the dinuclear zinc ligand **7**. These salen/Zn catalysts were also found to be ineffective for the current Mannich reaction. In addition, the substituted binol **8** was tested and resulted in low conversion. Interestingly, when the thienyl-ProPhenol ligand **L1**^[15] was employed for the reaction, an encouraging *ee* value was obtained along with excellent diastereoselectivity. In contrast, the phenyl ligand **L2** gave low diastereoselectivity under the same reaction conditions.

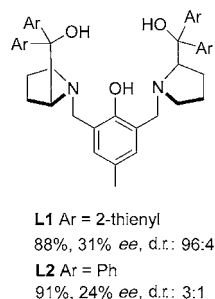
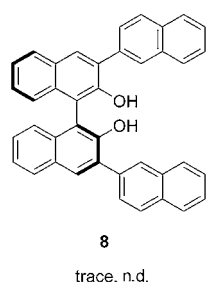
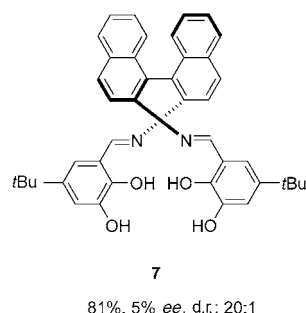
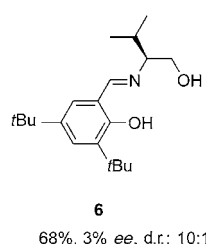
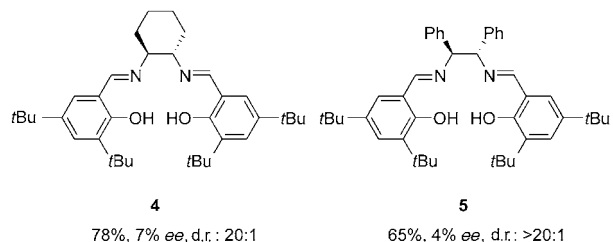
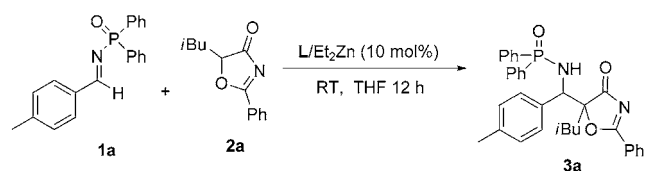
With these results in hand, we then tried to optimize the Mannich reaction with **L1**/Et₂Zn by changing variables such as reaction temperature and solvent. In running the reaction at lower temperatures, we were satisfied to find that the *ee* value increased to 50% at 0°C and 67% at –20°C with

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Scheme 2. Preliminary ligand screening. [a] All reactions were carried out with **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), and L/Et₂Zn (10 mol%) in 2.0 mL solvent at RT. For **4**, **5**, **6**, and **8**, L/Et₂Zn = 1:1; for **7**, **L1**, and **L2**, L/Et₂Zn = 1:2.

excellent diastereoselectivities (Table 1, entries 1 and 2). The *ee* value increased at lower temperature at the expense of conversion. A screening of solvents (Table 1, entries 3–5) showed that THF was the best solvent with respect to enantioselectivity. After careful examination of the structure of the 5*H*-oxazol-4-ones, we found that they could be viewed as cyclic *N*-acyl imines, which might have a dual binding mode to the metal. So we assume 5*H*-oxazol-4-one can adopt two different dual binding modes with regard to the L₁/Et₂Zn complex, that is, an independent binding: 5*H*-oxazol-4-one binds to only one zinc center of the catalyst, and cross-binding: 5*H*-oxazol-4-one binds to the two zinc centers (**E**; see Scheme 4). We believe the cross-binding is not conducive to the final enantioselectivity. Therefore, we considered using Lewis-basic additives, which might be able to coordinate to

Table 1: Optimization of the Mannich reaction.

Entry ^[a]	Additive (mol %)	Solvent	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1	–	THF	89	97:3	50
2	–	THF	65	96:4	67 ^[e]
3	–	toluene	83	98:2	34
4	–	CPME	73	90:10	48
5	–	DME	75	97:3	37
6	9a (10)	THF	85	99:1	86
7	9b (10)	THF	79	99:1	83
8	9c (10)	THF	85	99:1	86
9	9d (10)	THF	80	98:2	89
10	9e (10)	THF	91	99:1	89
11	9e (20)	THF	92	> 99:1	92
12	9e (30)	THF	92	> 99:1	95
13	(<i>S</i>)- 9f (30)	THF	70	98:2	76
14	(<i>R</i>)- 9f (30)	THF	56	94:6	23
15	10 (30)	THF	trace	–	–
16	11 , POPh ₃ (30)	THF	85	95:5	69

[a] Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), and L₁/Et₂Zn (10 mol%) in 2.0 mL solvent at 0°C for 24 h. [b] Yield of isolated product. [c] Determined by ¹H and ³¹P NMR spectroscopic analysis. [d] The enantiomeric excess was determined by HPLC analysis. [e] The reaction was carried out at –20°C. CPME = cyclopentylmethyl ether, THF = tetrahydrofuran.

the metal center either permanently or temporarily, and thereby prevent the unfavorable cross-binding pathway. Fortunately, after screening a large number of potential candidates, we successfully identified the diphenylphosphoramidate **9a** as an effective ligand (Table 1, entry 6). The enantioselectivity increased remarkably to 85% together with the diastereoselectivity (99:1) by using 10 mol % of **9a**. Inspired by this result, a series of analogues, dialkyl phosphoramidates **9b–e**, were prepared and tested in the current Mannich reaction (Table 1, entries 7–10). The results suggested the diethyl phosphoramidate **9e** was the most effective of the series with respect to both *ee* and d.r. values (Table 1, entry 10). Then the amount of the diethyl phosphoramidate **9e** was investigated and we were pleased to find that the best result was obtained with 30 mol % of **9e** (Table 1, entry 12). Two chiral phosphoramidates, (*R*)-**9f** and (*S*)-**9f**, derived from binol were also tested and proved not to be as effective as the achiral ones (Table 1, entries 13 and 14). In addition, low conversion was observed when the diphenylphosphinic acid **10** was subjected to the system, possibly because the catalyst decomposed under the acidic conditions. The unsatisfactory results obtained with triphenylphosphine oxide **11** also emphasized the essential role of the amide group of the phosphoramidate.

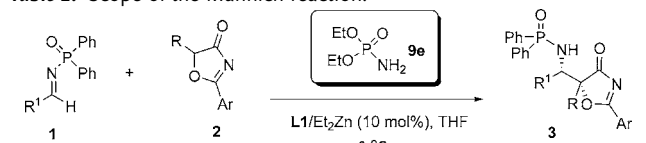
With the established optimized reaction conditions as indicated in entry 12 of Table 1, the substrate scope of the

Mannich reaction using various 5*H*-oxazol-4-ones **2** and Dpp-imines **1** was examined. Initially, a series of 5*H*-oxazol-4-one derivatives bearing alkyl groups at the C5-position were investigated with **1a** (Table 2). The results showed that 5*H*-oxazol-4-ones **2a–f** were amenable to the catalysis and the alkyl group had no obvious effect on the yield and stereoselectivities (Table 2, entries 1–5). We also tested the Mannich reaction with (*S,S*)-**L1**, and as expected, the product enantiomers were obtained with similar results (Table 2, entries 1–5). Subsequently, the aromatic Dpp-imines **1** bearing various substituents and imines with condensed rings or heteroaryl units were examined with **2a** (Table 2, entries 7–17). In general excellent results were achieved, except for **1f** and

11, which resulted in lower enantioselectivities (Table 2, entries 11 and 17). In view of the synthetic utility of the product, the reaction was also conducted with the aliphatic imine **11** and reasonable results were observed (Table 2, entry 18). Importantly, a preformed complex of **L1/9e/Et₂Zn** was also investigated in the Mannich reaction of **1a** and **2a** (Table 2, entry 19). With the preformed air-stable complex of **L1/9e/Et₂Zn**, the reaction could be performed without the protection of argon atmosphere and gave identical results. This improvement greatly facilitates the operation of the experiment.

Furthermore, when the Mannich reaction of the 5*H*-oxazol-4-one **2g** was performed on a gram scale, **3ag** was obtained with 89% yield (1.92 g), greater than 99:1 d.r., and 92% ee (Table 2, entry 20). The additional transformation of the product into α -alkyl α -hydroxy β -amino acid derivatives was exemplified by conversion of **3ag**. As shown in Scheme 3,

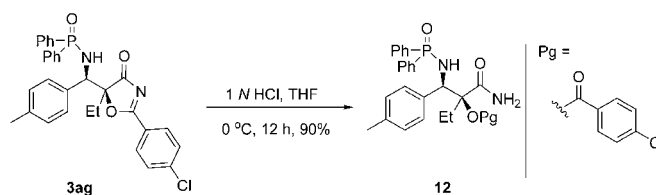
Table 2: Scope of the Mannich reaction.



2b, R = Me, Ar = Ph
2c, R = Et, Ar = Ph
2d, R = Pr, Ar = Ph
2e, R = Bu, Ar = Ph
2f, R = Bn, Ar = Ph
2g, R = Et, Ar = *p*-ClC₆H₄

Entry ^[a]	R ¹	2	3	Yield [%] ^[b]	d.r. ^[c,e]	ee [%] ^[d,e]
1	4-MeC ₆ H ₄	2a	3a	92 (93)	> 99:1 (>99:1)	95 (96) ^[f]
2	4-MeC ₆ H ₄	2b	3ab	91 (89)	> 99:1 (>99:1)	92 (94)
3	4-MeC ₆ H ₄	2c	3ac	91 (93)	> 99:1 (>99:1)	90 (91)
4	4-MeC ₆ H ₄	2d	3ad	90 (87)	98:2 (98:2)	94 (91)
5	4-MeC ₆ H ₄	2e	3ae	88 (89)	> 99:1 (>99:1)	94 (92)
6	4-MeC ₆ H ₄	2f	3af	92 (87)	99:1 (99:1)	91 (93)
7	Ph	2a	3b	87	> 99:1	94
8	4-FC ₆ H ₄	2a	3c	89	99:1	93
9	4-ClC ₆ H ₄	2a	3d	85	> 99:1	90
10	4-BrC ₆ H ₄	2a	3e	87	98:2	93
11	3-ClC ₆ H ₄	2a	3f	88	98:2	85
12	3-MeC ₆ H ₄	2a	3g	91	99:1	92
13	4-MeOC ₆ H ₄	2a	3h	90	99:1	96
14	3-MeOC ₆ H ₄	2a	3i	88	> 99:1	92
15		2a	3j	92	98:2	94
16	2-naphthyl	2a	3k	93	99:1	90
17	3-furyl	2a	3l	92	> 99:1	86
18	cyclopropyl	2f	3m	91	81:19	80
19	4-MeC ₆ H ₄	2f	3af	93	99:1	91 ^[g]
20	4-MeC ₆ H ₄	2g	3ag	89	> 99:1	92 ^[h]

[a] Unless otherwise noted, reactions were carried out with **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), and **L1/Et₂Zn** (10 mol %) in 2.0 mL THF at 0 °C for 24 h. [b] Yield of isolated product. [c] Determined by ¹H and ³¹P NMR spectroscopic analysis. [d] The enantiomeric excess was determined by HPLC analysis. [e] In parentheses are results obtained from (*S,S*)-**L1**. [f] The absolute configuration of **3a** from (*S,S*)-**L1** was determined by X-ray analysis^[16] and the other products were assigned by analogy. [g] The reaction was conducted with a preformed complex of **L1/9e/Et₂Zn**. For details, see the Supporting Information. [h] The reaction was performed on 4.0 mmol scale.

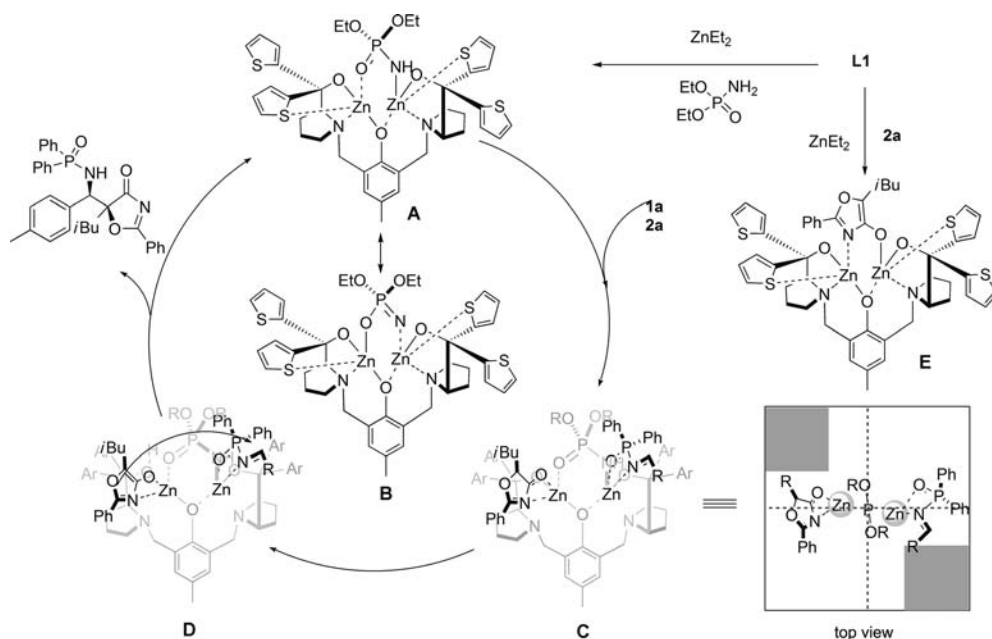


Scheme 3. Transformation of the Mannich adducts.

the product **3ag** can be readily hydrolyzed to the α -alkyl α -hydroxy β -amino acid derivative **12** under acidic conditions.

A plausible mechanism is on the basis of the absolute configuration of **3a** that was obtained from using (*S,S*)-**L1**. The first step may involve the formation of complex **A** (Scheme 4) with participation of **L1**, **9e**, and Et₂Zn. In this process, the bifunctional diethyl phosphoramidate **9e** might function as a Brønsted acid and a Lewis base, which is possibly involved in deprotonation and coordination with the metal center. This aspect can be ascertained by previous reports from Hoveyda and co-workers,^[17] who found that diethyl phosphoramidate reacted with Et₂Zn and greatly improved enantioselectivities of the products. The covalent bond enables its tight binding to the two zinc atoms. The two substrates then bind to the two zinc atoms independently through dual-mode binding (Scheme 4, complex **C**). Afterwards, the 5*H*-oxazol-4-ones **2a** is enolized and undergoes the stereospecific addition. High diastereoselectivities were supposed to be attributed to the repulsion between the Dpp group and the phenyl group of the 5*H*-oxazol-4-one. In the absence of phosphoramidates, a competitive pathway, in which the 5*H*-oxazol-4-one binds to both of the zinc centers of the catalyst, may occur (**E**; Scheme 4). This cross-binding of **2a** to the catalyst is disadvantageous as this mode impedes the coordination of the Dpp imine and both the *Re* and *Si* faces of the 5*H*-oxazol-4-one are open.

In conclusion, we have developed a highly diastereo- and enantioselective zinc-catalyzed Mannich reaction of 5*H*-oxazol-4-ones, which leads to the first catalytic asymmetric synthesis of *syn*- α -alkyl norstatine derivatives. Excellent



Scheme 4. Proposed mechanism of the Mannich reaction.

enantioselectivities and diastereoselectivities were achieved with a series of *N*-Dpp imines and 5*H*-oxazol-4-ones. Importantly, the combination of the ProPhenol ligand **L1**, dialkyl phosphoramidate, and Et₂Zn was found to be a unique catalyst. Additional studies on the application of the catalyst system to other reactions and the synthetic utilities of the Mannich adducts are underway.

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- [1] For reviews on the asymmetric synthesis of β -amino acids, see: a) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, 39, 1656; b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, 58, 7991; c) *Enantioselective Synthesis of β -Amino Acids* (Eds.: E. Juaristi, V. Soloshnok), Wiley, Hoboken, **2005**; d) J. A. Ma, *Angew. Chem.* **2003**, 115, 4426; *Angew. Chem. Int. Ed.* **2003**, 42, 4290.
- [2] a) R. P. Cheng, S. H. Gellman, W. F. deGrado, *Chem. Rev.* **2001**, 101, 3219; b) P. A. Magriotis, *Angew. Chem.* **2001**, 113, 4507; *Angew. Chem. Int. Ed.* **2001**, 40, 4377; c) J. L. Matthews in *Synthesis of Peptides and Peptidomimetics*, Houben-Weyl (Eds.: A. Felix, L. Morodor, C. Toniolo), Georg Thieme, Stuttgart, **2003**, Vol. E22c, p. 552; d) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, 41, 1366.
- [3] For selected examples, see: a) I. Ibrahim, A. Córdova, *Tetrahedron Lett.* **2005**, 46, 2839; b) P. Dziedzic, J. Vesely, A. Córdova, *Tetrahedron Lett.* **2008**, 49, 6631; c) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, 117, 4439; *Angew. Chem. Int. Ed.* **2005**, 44, 4365; *Angew. Chem.* **2005**, 117, 4439; *Angew. Chem. Int. Ed.* **2005**, 44, 4365; d) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, 125, 338.
- [4] a) I. Ojima, S. Lin, T. Wang, *Curr. Med. Chem.* **1999**, 6, 927; b) I. Ojima, T. Wang, F. Delaloge, *Tetrahedron Lett.* **1998**, 39, 3663; c) J. Kant, W. S. Schwartz, C. Fairchild, Q. Gao, S. Huang, B. H. Long, J. F. Kadow, D. R. Langley, V. Farina, D. Vyas, *Tetrahedron Lett.* **1996**, 37, 6495.
- [5] a) S. J. Hecker, K. M. Werner, *J. Org. Chem.* **1993**, 58, 1762; b) B. Bauvois, D. Dauzonne, *Med. Res. Rev.* **2006**, 26, 88.
- [6] N. C. Giampietro, J. P. Wolf, *Angew. Chem.* **2010**, 122, 2984; *Angew. Chem. Int. Ed.* **2010**, 49, 2922.
- [7] a) W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.-X. Huang, J. Hu, L.-P. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, 130, 7782; b) X. Xu, J. Zhou, L. Yang, W. Hu, *Chem. Commun.* **2008**, 6564–6566.
- [8] a) A. Guerrini, G. Varchi, R. Daniele, C. Samori, A. Battaglia, *Tetrahedron* **2007**, 63, 7949; b) A. Guerrini, G. Varchi, A. Battaglia, *J. Org. Chem.* **2006**, 71, 6785; c) A. Battaglia, A. Guerrini, C. Bertucci, *J. Org. Chem.* **2004**, 69, 9055; d) A. M. Nocioni, C. Papa, C. Tomasini, *Tetrahedron Lett.* **1999**, 40, 8453.
- [9] a) B. M. Trost, K. Dogra, M. Franzini, *J. Am. Chem. Soc.* **2004**, 126, 1944; b) T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, 133, 5695; c) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, 132, 6286; d) H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, 48, 461.
- [10] For recent reviews on the asymmetric Mannich Reaction, see: a) R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, 38, 1940; b) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, 37, 29; c) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797; d) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, 111, 2626.
- [11] a) G. Zhang, Y. Zhang, *Angew. Chem.* **2011**, 123, 10613; *Angew. Chem. Int. Ed.* **2011**, 50, 10429; b) D. Zhao, Y. Wang, L. Mao, R. Wang, *Chem. Eur. J.* **2009**, 15, 10983; c) D. Zhao, D. Yang, Y.-J. Wang, Y. Wang, L. Wang, L. Mao, R. Wang, *Chem. Sci.* **2011**, 2, 1918.
- [12] a) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, 13, 1494; b) X. Liu, L. Deng, Xi. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, 12, 8.
- [13] For a recent review on oxazolones, see: A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, 6, 720.
- [14] For zinc-catalyzed asymmetric Mannich reactions, see: a) S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2003**, 9, 6145; b) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 4712; c) S.

- Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777; d) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 3985; e) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003. See also ref. [1d].
- [15] a) D. Zhao, L. Mao, D. Yang, R. Wang, *J. Org. Chem.* **2010**, *75*, 6756; b) D. Zhao, L. Mao, L. Wang, D. Yang, R. Wang, *Chem. Commun.* **2012**, 48, 889.
- [16] CCDC 869370 (**3a** obtained from (S,S)-**L1**) 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.
- [17] a) D. K. Friel, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 9942; b) L. C. Wieland, H. Deng, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 15453.
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