Organic LETTERS

Letter

pubs.acs.org/OrgLett

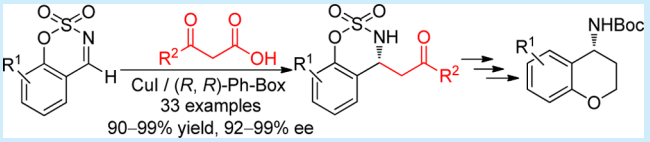
Cyclic Aldimines as Superior Electrophiles for Cu-Catalyzed Decarboxylative Mannich Reaction of β-Ketoacids with a Broad Scope and High Enantioselectivity

Heng-Xia Zhang, Jing Nie, Hua Cai, and Jun-An Ma*

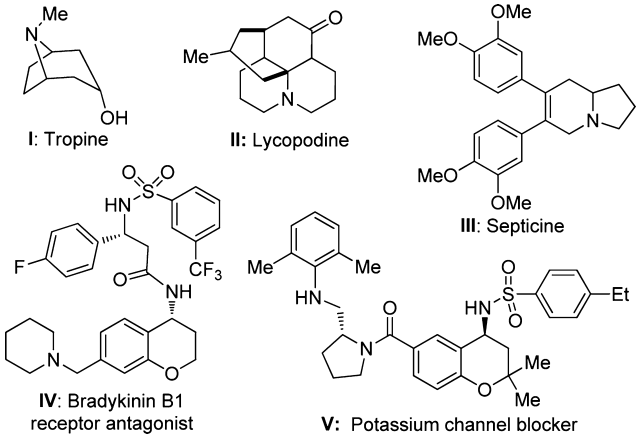
Department of Chemistry, Key Laboratory of Systems Bioengineering (the Ministry of Education), Tianjin University, and Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, P. R. of China

Supporting Information

ABSTRACT: A novel Cu-catalyzed enantioselective decarboxylative Mannich reaction of cyclic aldimines with β-ketoacids is described. The cyclic structure of these aldimines, in which the C═N bond is constrained in the Z geometry, appears to be important, allowing Mannich condensation to proceed in high yields with excellent enantioselectivities. A chiral chroman-4-amine was synthesized from the decarboxylative Mannich product in several steps without loss of enantioselectivity.

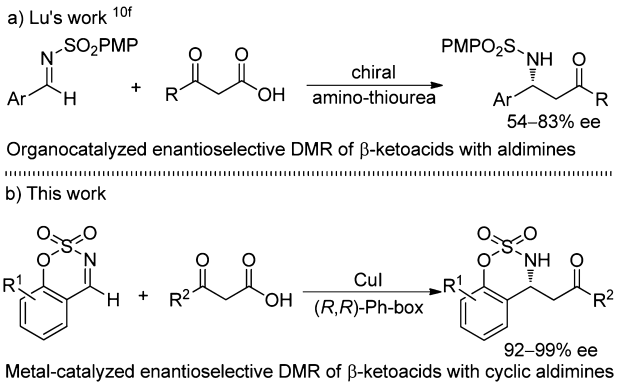


Chiral β-amino ketones are valuable synthetic intermediates, which can be easily transformed into other versatile building blocks, such as amines, β-amino alcohols, and β-amino acid derivatives.[1] Furthermore, structural motifs derived from chiral β-amino ketones can be found in a number of natural products and biologically active compounds, such as Tropine **I**,[2] Lycopodine **II**,[3] Septicine **III**,[4] the Human Bradykinin B1 receptor antagonist **IV**,[5] and potassium channel blocker **V**.[6]



Over the past decades, common methods for the construction of chiral β-amino ketones have focused on the Mukaiyama–Mannich reactions of silyl enol ethers[7] and the organocatalytic Mannich reactions of inactivated ketones[8] with various imines. Accordingly, the former requires the corresponding silyl enol ethers to be prepared beforehand, whereas the latter is limited to the use of only acetone and cyclic alkyl ketones. Noteworthily, the decarboxylative Mannich reaction (DMR) of β-ketoacids with imines provides an alternative means of accessing β-amino ketones, and many DMRs have been successfully applied as the key step for the efficient synthesis of natural products and compounds of pharmaceutical significance.[9] Furthermore, the relevance has stimulated the recent development of catalytic asymmetric DMRs leading to the formation of chiral nonracemic β-amino ketones.[10] However, the use of aldimines in asymmetric DMRs of β-ketoacids suffers from a limited substrate scope and/or unsatisfactory stereoselectivity. For example, Lu and co-workers described an organocatalytic asymmetric DMR of β-ketoacids with acyclic aldimines to afford β-amino ketones with a maximum ee value of 83% (Scheme 1a).[10f] Herein, we report a novel approach that utilizes cyclic aldimines as superior electrophiles and copper-bisoxazoline (Box) complexes as chiral catalysts to deliver high yields of β-amino ketones in excellent enantioselectivity (Scheme 1b).[11,12] The cyclic structure of these aldimines, in which the C═N bond is constrained in the Z

Scheme 1. Catalytic Enantioselective DMRs of β-Ketoacids with Aldimines



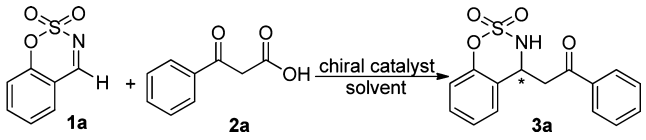
Received: March 28, 2014
Published: April 24, 2014

dx.doi.org/10.1021/ol500929d | Org. Lett. 2014, 16, 2542–2545

geometry, appears to be very important for the success of the reactions.

In the initial study, the reaction between benzoxathiazine-2,2-dioxide **1a** and benzoylacetic acid **2a** was performed in tetrahydrofuran (THF) at room temperature with a 5 mol % loading of a Lewis acid catalyst prepared in situ from a copper salt and a chiral bisoxazoline ligand. Excellent enantioselectivity but a very low yield of the decarboxylative Mannich product **3a** was obtained in the presence of the CuI/(*R*,*R*)-Ph-Box (**L1**) complex (Table 1, entry 1). The major byproduct was acetophenone,

Table 1. Optimization of Reaction Conditions for Cu-Catalyzed DMR of Cyclic Aldimine 1a with β-Ketoacid 2a[a]



entry	catalyst (mol %)	solvent	temp (°C)/ time (h)	yield (%)[b]	ee (%)[c]
1	CuI/**L1** (5)	THF	25/12	23	94
2	CuI/**L1** (5)	THF	0/12	98	95
3	CuI/**L1** (5)	THF	−20/12	98	97
4	CuI/**L2** (5)	THF	−20/16	99	92
5	CuI/**L3** (5)	THF	−20/60	90	78
6	CuI/**L4** (5)	THF	−20/16	97	77
7	CuI/**L5** (5)	THF	−20/72	93	3
8	CuBr/**L1** (5)	THF	−20/12	97	94
9	CuCl/**L1** (5)	THF	−20/36	98	96
10	CuTPC/**L1** (5)	THF	−20/72	95	94
11	$Cu(OTf)_2$/**L1** (5)	THF	−20/36	90	30
12	$Cu(OAc)_2$/**L1** (5)	THF	−20/36	95	76
13	CuI/**L1** (5)	Et_2O	25/36	96	96
14	CuI/**L1** (5)	CH_3CN	25/36	98	94
15	CuI/**L1** (5)	CH_2Cl_2	25/120	85	30
16	CuI/**L1** (5)	toluene	25/120	90	80
17	CuI/**L1** (5)	MeOH	25/60	98	63
18	CuI/**L1** (1)	THF	25/24	98	93

[a]General reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), and catalyst (1−5 mol %) in solvent for the stated time. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.

which results from decarboxylative protonation of **2a**. Mindful of this detrimental background reaction which could lead to the observed low yield, the reaction was performed at a lower temperature, and as expected, the yield was improved from 23% to 98% (entries 2 and 3). A subsequent investigation of ligands (Figure 1) confirmed that **L1** provided higher ee's than other substituted bidentate ligands **L2**−**L4** (entries 4−6). The use of tridentate ligand **L5** led to the formation of an almost racemic product (entry 7). A series of other copper salts were then evaluated in THF using **L1** as the chiral ligand. Interestingly, all

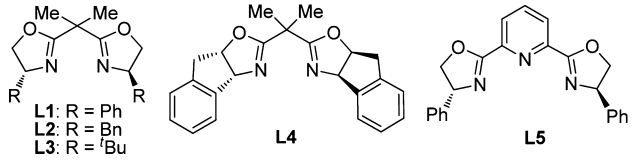
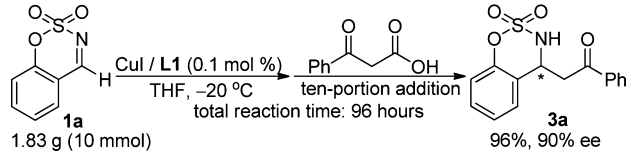


Figure 1. Ligand structures tested in the model reaction.

of copper(I) complexes could induce high enantioselectivity (entries 8−10), whereas the use of copper(II) complexes caused a significant drop in stereoselectivity (entries 11 and 12). In addition, the solvent was found to have an important effect on the reactivity and enantioselectivity (entries 13−17). Among the solvents tested, THF was found to be the solvent of choice for this decarboxylative Mannich reaction with respect to both catalytic activity and asymmetric induction. The effect of catalyst loading was next examined, and excellent results were still obtained when the catalyst loading was lowered to 1 mol % (entry 18).

Remarkably, even at a loading of 0.1 mol %, the CuI/(*R*,*R*)-Ph-Box (**L1**) complex could also deliver comparable results (95% yield and 90% ee) when the reaction was run on a gram scale for an extended reaction time by sequential addition of benzoylacetic acid **2a** (Scheme 2). In contrast, a one-portion addition of 1.5 equiv of β-ketoacid resulted in the formation of the mass of acetophenone byproduct.

Scheme 2. Scaled-up DMR of Aldimine 1a with β-Ketoacid 2a



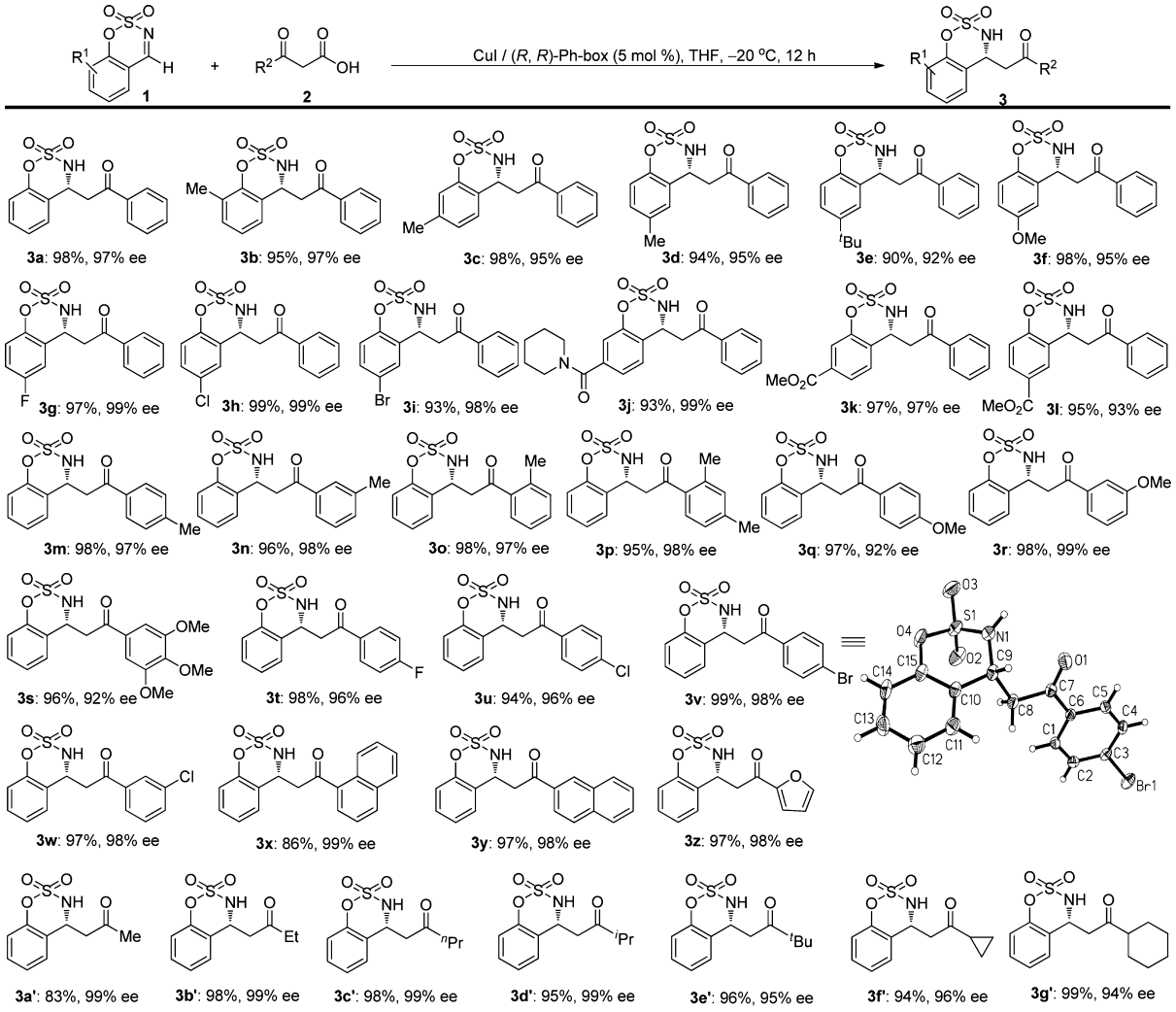
With the optimized conditions in hand, we turned our focus to the substrate scope and generality of this decarboxylative Mannich reaction (Scheme 3). First, a series of cyclic aldimines **1** were examined for their reactions with benzoylacetic acid **2a**. The introduction of electron-donating and -withdrawing groups on the phenyl ring had little influence on enantioselectivity. The corresponding products **3a**−**3l** were obtained in high yields with excellent enantioselectivity. Subsequently, the β-ketoacid substrate scope was investigated. In the presence of 5 mol % CuI/(*R*,*R*)-Ph-Box complex, the reaction of *ortho*-, *meta*-, and *para*-substituted phenyl β-ketoacids with benzoxathiazine-2,2-dioxide **1a** all proceeded smoothly, thus generating the Mannich adducts **3m**−**3w** in consistently high yield (94−99%) and enantioselectivity (92−99% ee). The product **3v** was isolated as a crystalline compound, and the structure was characterized by X-ray crystallographic analysis. The absolute configuration for the stereogenic carbon center formed in the reaction is of *R* stereochemistry (see the Supporting Information).[13] Fused-ring aryl or heteroaryl-substituted β-ketoacids could also be used as the nucleophilic partners, thus providing β-amino ketones **3x**−**3z** in high yields with excellent ee values. Additionally, it is found that linear, branched, and cyclic alkyl substituted β-ketoacids could also be used as the substrates, and excellent results were obtained for the condensation products **3a′**−**3g′**. Notably, in all cases the reaction can be conducted under mild reaction conditions without the need for inert gas protection.

The stereochemical outcome can be explained using a transition-state model as shown in Figure 2. The [Cu((*R*,*R*)-Ph-box)]I catalyst undergoes coordination with the enol of β-ketoacid to form a square-planar complex, and the chelation of the sulfonyl oxygen of the imine to copper creates a more compact reaction sphere. The sterically favored intermediate **B** allows the nucleophilic approach of β-ketoacid from the *Re* face of cyclic aldimine which generates the *R* enantiomer.

The chroman-4-amines are important intermediates in the construction of several biological active compounds.[5,6] A short

dx.doi.org/10.1021/ol500929d | *Org. Lett.* 2014, 16, 2542−2545

Scheme 3. Scope for Copper-Catalyzed Enantioselective DMR of Cyclic Aldimines 1 with β-Ketoacids 2



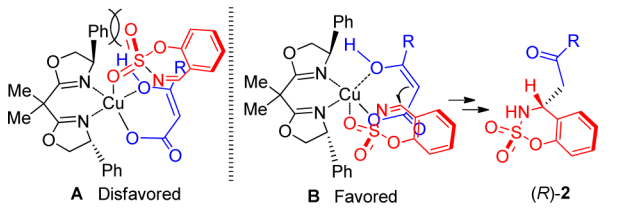
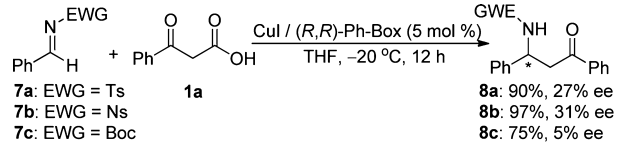


Figure 2. Stereochemical model.

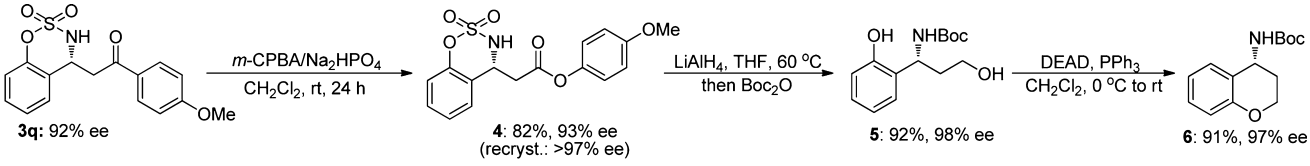
synthesis of chiral nonracemic chroman-4-amine **6** was conducted from the decarboxylative Mannich product (Scheme 4). In the presence of *m*-chlorobenzoperoxoic acid (*m*-CBPA) and Na_2HPO_4, the Baeyer–Villiger oxidation of **3q** afforded the corresponding ester **4** in 82% yield. Reduction of **4** with $LiAlH_4$ at reflux[14] and subsequent protection with Boc_2O provided carbamate **5**, which was then converted into chroman-4-amine **6** by means of a Mitsunobu cyclization. In all of the processes, no loss of enantiomeric purity was observed.

For a comparison with cyclic aldimines, we examined the decarboxylative Mannich reaction of acyclic benzaldimines **7a–c** with β-ketoacid **1a** under the standard reaction conditions (Scheme 5). The corresponding Mannich products **8a–c** were

Scheme 5. Catalytic Enantioselective DMRs of β-Ketoacids with Acyclic Benzaldimines



Scheme 4. Further Synthetic Transformation of the Decarboxylative Mannich Product 3q into the Chroman-4-amine 6



dx.doi.org/10.1021/ol500929d | Org. Lett. 2014, 16, 2542–2545

obtained in good to high yields, albeit with low enantioselectivities. These results show that the *E* geometry of acyclic aldimines could have a negative impact upon stereoselectivity.

In summary, a new catalytic asymmetric decarboxylative Mannich reaction of β-ketoacids with cyclic aldimines in the presence of chiral CuI−bisoxazoline complexes has been presented. The cyclic structure of these aldimines, in which the C═N bond is constrained in the Z geometry, appears to be important, allowing Mannich condensation to proceed in high yields (90−99%) with excellent enantioselectivities (92−99% ee). Moreover, the products obtained can be converted into optically active chroman-4-amines. Further development and application of this reaction, as well as study of the mechanism, is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data of all the new compounds, and the CIF information on **3v**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: majun_an68@tju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 21172170 and 21225208) and the National Basic Research Program of China (973 Program, 2014CB745100).

■ REFERENCES

(1) (a) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (c) Greco, S. J.; Lacerda, J. V.; Santos, R. B. *Aldrichimica Acta* **2011**, *44*, 15.

(2) (a) O'Hagan, D.; Humphrey, A. J. *Nat. Prod. Rep.* **2001**, *18*, 494. (b) Gadzikowska, M.; Grynkiewicz, G. *Acta Polym. Pharm.* **2002**, *59*, 149. (c) Grynkiewicz, G.; Gadzikowska, M. *Pharmacol. Rep.* **2008**, *60*, 439.

(3) (a) Hemscheidt, T. *Top. Curr. Chem.* **2000**, *209*, 175. (b) Ma, X.-Q.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752. (c) Wang, L.; Lin, C.-W. *Chin. J. Org. Chem.* **2008**, *28*, 755.

(4) (a) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50. (b) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365. (c) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2.

(5) Biswas, K.; Li, A.; Chen, J. J.; D'Amico, D. C.; Fotsch, C.; Han, N.; Human, J.; Liu, Q.; Norman, M. H.; Riahi, B.; Yuan, C.; Suzuki, H.; Mareska, D. A.; Zhan, J.; Clarke, D. E.; Toro, A.; Groneberg, R. D.; Burgess, L. E.; Lester-Zeiner, D.; Biddlecome, G.; Manning, B. H.; Arik, L.; Dong, H.; Huang, M.; Kamassah, A.; Loeloff, R.; Sun, H.; Hsieh, F.-Y.; Kumar, G.; Ng, G. Y.; Hungate, R. W.; Askew, B. C.; Johnson, E. *J. Med. Chem.* **2007**, *50*, 2200.

(6) Lloyd, J.; Atwal, K. S.; Finlay, H. J.; Huynh, M. T.; Bhandaru, R.; Kover, A.; Schmidt, J.; Vaccaro, W.; Conder, M. L.; Jenkins-West, T.; Levesque, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3271.

(7) For selected examples, see: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (c) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (d) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (e) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. (f) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (g) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (h) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (i) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (j) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640. (k) Hamda, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768.

(8) For selected reviews, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (b) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (e) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465. (f) Verkade, J. M. M.; Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (g) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

(9) (a) Robinson, R. *J. Chem. Soc.* **1917**, 762. (b) Robinson, R. *J. Chem. Soc.* **1917**, 876. (c) Herbert, R. B.; Jackson, F. B.; Nicolson, I. T. *J. Chem. Soc., Chem. Commun.* **1976**, 450. (d) Herbert, R. B.; Jackson, F. B. *J. Chem. Soc., Chem. Commun.* **1977**, 955. (e) Herbert, R. B. *J. Chem. Soc., Chem. Commun.* **1978**, 794. (f) Mangla, V. K.; Bhakuni, D. S. *Tetrahedron.* **1980**, *36*, 2489. (g) Bhakuni, D. S.; Mangla, V. K. *Tetrahedron* **1981**, *37*, 401. (h) Baxter, G.; Melville, J. C.; Robins, D. J. *Synlett.* **1991**, 359. (i) Hemscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1993**, *115*, 3020. (j) Hemscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1996**, *118*, 1799.

(10) For reviews on the asymmetric decarboxylative reactions of β-ketoacids, see: (a) Wang, Z.-L. *Adv. Synth. Catal.* **2013**, *355*, 2745. (b) Nakamura, S. *Org. Biomol. Chem.* **2014**, *12*, 394. For recent examples on the asymmetric decarboxylative reactions of β-ketoacids, see: (c) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583. (d) Zheng, Y.; Xiong, H.-Y.; Nie, J.; Hua, M.-Q.; Ma, J.-A. *Chem. Commun.* **2012**, *48*, 4308. (e) Yang, C.-F.; Shen, C.; Wang, J.-R.; Tian, S.-K. *Org. Lett.* **2012**, *14*, 3092. (f) Jiang, C.; Zhong, F.; Lu, Y. *Beilstein J. Org. Chem.* **2012**, *8*, 1279. (g) Zhong, F.; Yao, W.; Dou, X.; Lu, Y. *Org. Lett.* **2012**, *14*, 4018. (h) Zuo, J.; Liao, Y.-H.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2012**, *77*, 11325. (i) Moon, H. W.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 6569. (j) Yuan, H.-N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3869. (k) Kang, Y. K.; Lee, H. J.; Moon, H. W.; Kim, D. Y. *RSC Adv.* **2013**, *3*, 1332. (l) Suh, C. W.; Chang, C. W.; Choi, K. W.; Lim, Y. J.; Kim, D. Y. *Tetrahedron Lett.* **2013**, *54*, 3651.

(11) For recent examples on the use of benzoxathiazine-2,2-dioxide as cyclic aldimine substrates, see: (a) Tripathi, M.; Dhar, D. N. *J. Heterocycl. Chem.* **1988**, *25*, 1191. (b) Zhu, B.-H.; Zheng, J.-C.; Yu, C.-B.; Sun, X.-L.; Zhou, Y.-G.; Shen, Q.; Tang, Y. *Org. Lett.* **2010**, *12*, 504. (c) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762. (d) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309.

(12) For reviews on chiral metal-bisoxazoline complexes, see: (a) Ghosh, A. K.; Packiarajan, M.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467. (c) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151. (d) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505. (e) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2011**, *111*, PR284.

(13) CCDC 990136 (**3v**) 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.

(14) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, *10*, 2071.