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Stereoselective Synthesis of Fused Aziridines via One-Pot Sequential Decarboxylative Mannich Reaction and Oxidative C−H Amination of Cyclic Imines with β-Ketoacids

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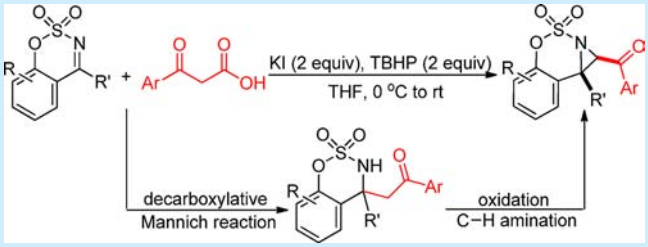
Supporting Information

ABSTRACT: A novel one-pot sequential transformation via decarboxylative Mannich reaction (DMR) and oxidative C−H amination of cyclic imines with β-ketoacids is described. This methodology has been utilized to provide access to fused aziridines with excellent diastereoselectivity. Several examples of catalytic enantioselective sequential transformation are presented.



Aziridines, an important class of three-membered aza-heterocycles, are widely used in organic chemistry.[1] Furthermore, the aziridine skeleton occurs in many natural products and compounds of pharmaceutical significance (Figure 1).[2] Thus, the construction of these three-membered ring motifs has been an active research area in organic synthesis and drug chemistry. Traditionally, the main approaches to the construction of aziridines include the nitrogen-olefin additions, the carbon-imine cyclizations, the dihydrotriazole ring contractions, and the azirine transformations.[3] Despite these impressive advances, the development of new synthetic transformations for the construction of diverse aziridines is still in great demand. Over the past several years, direct intramolecular C−H amination has advanced as a general technology for chemical synthesis.[4]

However, very few direct C−H activation methods have been developed for the preparation of ring strain aziridines. Only one recent report by Gaunt and co-workers has addressed a powerful palladium-catalyzed C−H bond activation strategy for

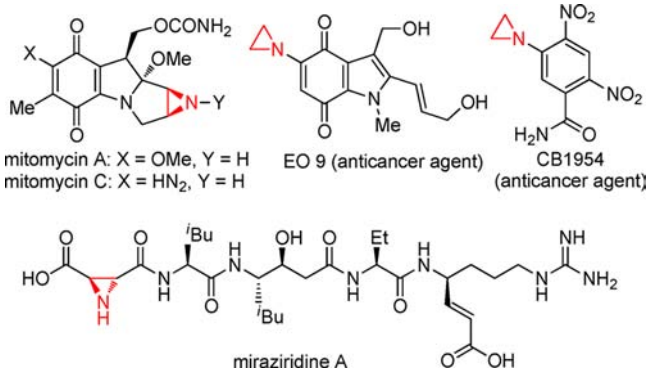


Figure 1. Aziridine-containing natural products and drugs.

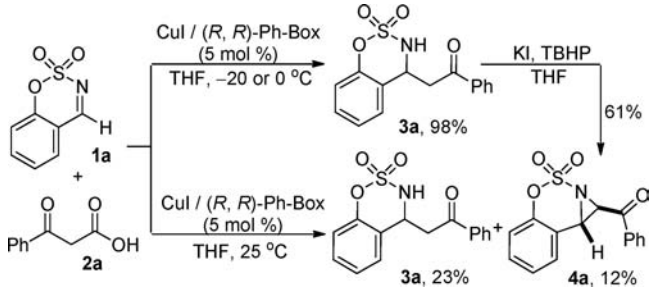


Figure 2. Reaction of cyclic imine **1a** with β-ketoacid **2a** and further transformation of the Mannich adduct **3a** into aziridine **4a**.

the synthesis of aziridine derivatives starting from amino-lactones.[5] Herein, we report our efforts in developing a novel one-pot decarboxylative Mannich reaction and oxidative C−H amination sequence of cyclic imines with β-ketoacids for the construction of the fused aziridines. This sequential reaction can be conducted under mild conditions without the need for any transition metals.

The utility of β-ketoacids as ketone enolate equivalents in the catalytic asymmetric decarboxylative transformations[6] has been well established by our group[7] and others.[8] During the course of our studies on the decarboxylative Mannich reactions of cyclic imine **1a** with β-ketoacid **2a**,[7d] we found that at relatively low temperatures the Mannich product **3a** was obtained in high yield, whereas at room temperature a novel fused aziridine **4a** was isolated in 12% yield (Figure 2). Variation of other standard reaction parameters (solvent, temperature, and catalyst loading) failed to increase the yield of aziridine **4a**. The generation of aziridine led us to examine the oxidative C−

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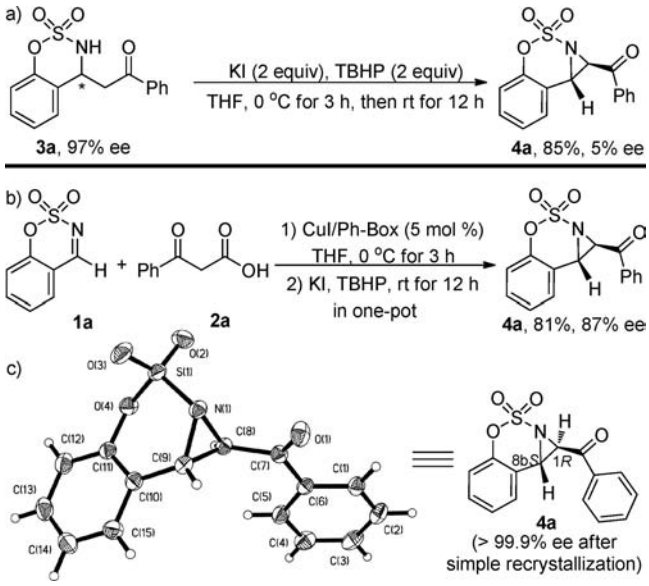
Table 1. Optimization of Reaction Conditions for One-Pot Sequential Transformation of Cyclic Imine 1a and β-Ketoacid 2a[a]

entry	reaction conditions[a]	yield (%)[b]
1	KI (1 equiv), TBHP (1 equiv), 0 °C for 3 h then 25 °C for 16 h	59
2	KI (1 equiv), TBHP (2 equiv), 0 °C for 3 h then 25 °C for 16 h	63
3	KI (2 equiv), TBHP (2 equiv), 0 °C for 3 h then 25 °C for 16 h	78
4	KI (2 equiv), H_2O_2 (2 equiv), 0 °C for 3 h then 25 °C for 24 h	8
5	KI (2 equiv), PhIO (2 equiv), 0 °C for 3 h then 25 °C for 24 h	15
6	NaI (2 equiv), TBHP (2 equiv), 0 °C for 3 h then 25 °C for 24 h	0
7	*n*-Bu_4NI (2 equiv), TBHP (2 equiv), 0 °C for 3 h then 25 °C for 24 h	32

[a]**1a** (0.2 mmol) and **2a** (0.3 mmol) were used. [b]Yields of isolated product averaged over two runs.

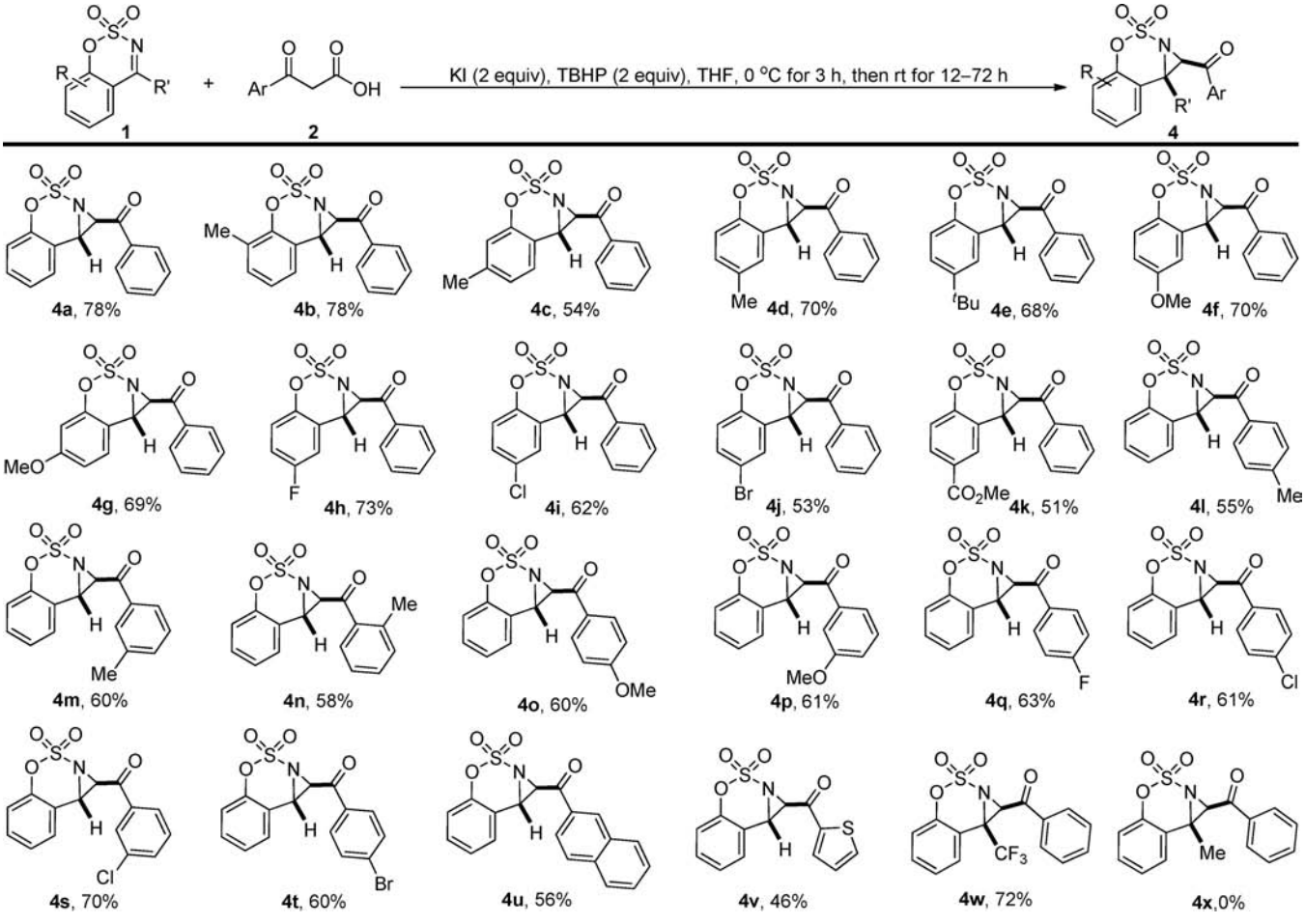
H amination of the Mannich product **3a**. By screening of various oxidation systems,[9] it was found that oxidation of **3a** with the combination of KI and *tert*-butylhydroperoxide (TBHP) gave rise to the formation of aziridine **4a** in 61% yield. Next, a sequential transformation of the decarboxylative Mannich reaction and oxidative C−H amination was conducted in one pot, and the results were shown in Table 1. In the

Scheme 2. (a) Oxidative C−H Amination of Chiral Nonracemic 3a; (b) One-Pot Asymmetric Synthesis of Aziridine 4a; (c) X-ray Crystal Structure of the Stereoisomer of 4a



presence of KI and TBHP, this sequential reaction proceeded to afford the fused aziridine **4a** as a single diastereoisomer in

Scheme 1. Scope for One-Pot Sequential Reaction of Cyclic Imines 1 and β-Ketoacids 2



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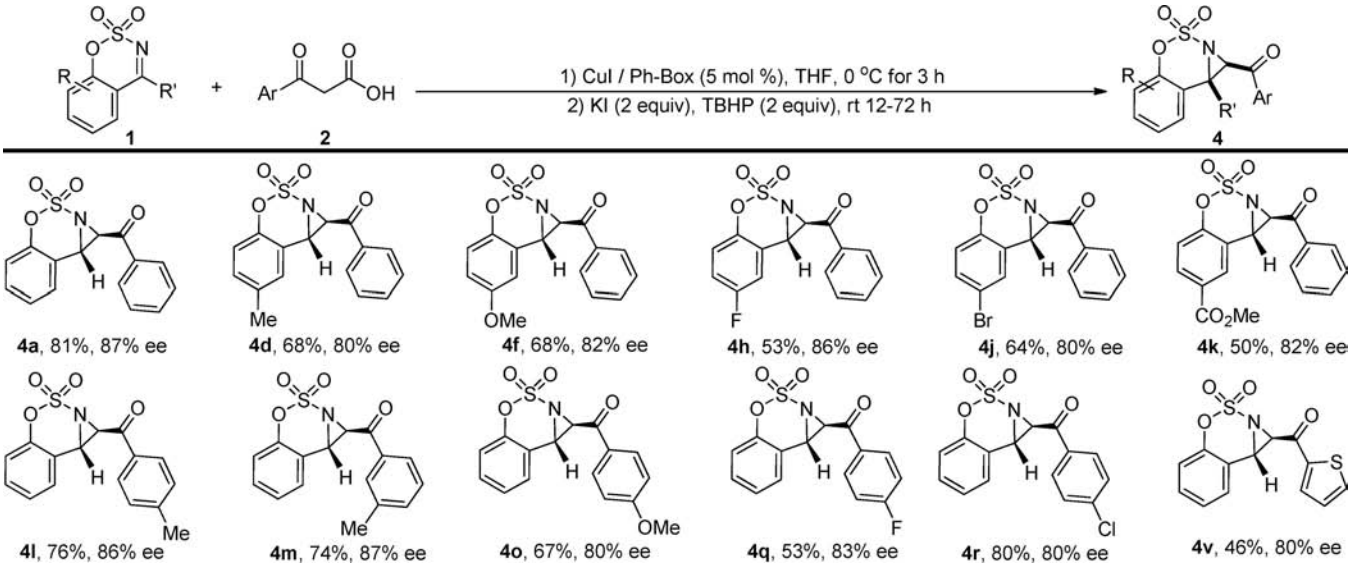
Scheme 3. Enantioselective Synthesis of Fused Aziridines through One-Pot Sequential Transformation



59% yield (entry 1). The use of excess KI and TBHP was essential for the efficiency of this reaction (entries 2 and 3), and the yield of **4a** could be further improved to 78%. In addition, all the other combinations tested resulted in poor yields (entries 4−7).

With the optimized reaction conditions in hand, we next investigated the substrate scope of this one-pot sequential reaction of cyclic imines **1** with *β*-ketoacids **2**, and the results are summarized in Scheme 1. We first tested the reaction of a series of cyclic aldimines with 3-oxo-3-phenylpropanoic acid **2a** under the established conditions. The corresponding fused aziridines **4a−k** were obtained in moderate to good yields (51−78%). Subsequently, the *β*-ketoacid substrate scope was investigated by the reaction with cyclic aldimine **1a** under the optimal conditions. It was found that a broad range of phenyl-substituted *β*-ketoacids with substituents in the *ortho*-, *meta*-, or *para*-position of the phenyl ring proceeded well to furnish the desired aziridines **4l−t** in 55−70% yields. Other aryl-substituted *β*-ketoacids such as 3-(naphthalen-2-yl)-3-oxopropanoic acid and 3-oxo-3-(thiophen-2-yl)propanoic acid could also be successfully employed in this one-pot sequential reaction, furnishing the desired products (**4u** and **4v**) in 56% and 46% yields, respectively. It is noteworthy that all these substrates displayed uniformly excellent diastereoselectivity. In addition, we investigated the use of alkyl-substituted *β*-ketoacids and found that these substrates were not suitable for this one-pot sequential reaction and no desired products were observed. To further define the scope of this methodology, the reactions of cyclic ketimines with 3-oxo-3-phenylpropanoic acid **2a** were tested. Notably, the trifluoromethylated cyclic ketimine delivered the expected aziridine **4w** in 72% yield, whereas the methylated aziridine **4x** was not obtained under identical conditions. These results indicated that the strong electron-withdrawing trifluoromethyl group could be critical for this one-pot sequential reaction of cyclic ketimines to occur.

The direct oxidative C−H amination of chiral nonracemic intermediate **3a** was examined next, and an unexpected result was obtained. Treatment of **3a** with KI and TBHP in THF at room temperature led to the racemic product **4a** in 85% yield (Scheme 2a). However, it was noteworthy that the decarboxylative Mannich reaction of **1a** and **2a** with the chiral CuI-(*R*,*R*)-Ph-Box complex proceeded normally,[7a] and subsequent addition of KI and TBHP in one pot gave rise to the corresponding aziridine **4a** in 81% yield with 87% ee (Scheme 2b). Furthermore, an improvement of the enantiopurity of **4a** (>99.9% ee) could be achieved by simple recrystallization, and the absolute configuration of two adjacent stereogenic centers was determined to be (1*R*, 8b*S*) by means of X-ray crystallographic analysis (Scheme 2c).[10]

Based on these preliminary results, we performed the enantioselective sequential transformation between cyclic imines and *β*-ketoacids in THF by using 5 mol % of chiral CuI-(*R*,*R*)-Ph-Box complex in one pot. As highlighted in Scheme 3, a wide range of functional groups, including alkyl, methoxy, halogen, and/or ester groups, can be readily tolerated on the phenyl rings of both substrates. Good enantioselectivities of more than 80% ee were obtained, and the enantioenriched aziridines were formed in moderate to good yields (50−81%). Furthermore, 3-oxo-3-(thiophen-2-yl)-propanoic acid also delivered the desired product **4v** in 46% yield with 80% ee.

In summary, we have developed a novel one-pot sequential transformation via the decarboxylative Mannich reaction and the oxidative C−H amination of cyclic imines and *β*-ketoacids for the preparation of fused aziridine derivatives. This process proceeds with excellent diastereoselectivity and creates two new stereocenters. The stereocenters of sequential products can be controlled by a chiral catalyst. Further studies on the application of these fused aziridine compounds to other areas of chemistry and chemical synthesis are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03551.

Experimental details, spectral data of all the new compounds (PDF)

CIF information for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Botuha, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A. *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 3−39. (c) Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H. J. *Chem. Soc. Rev.* **2012**, *41*, 643.

(2) (a) Sartorelli, A. C.; Hodnick, W. F.; Belcourt, M. F.; Tomasz, M.; Haffty, B.; Fischer, J. J.; Rockwell, S.; Mitomycin, C. *Oncol. Res.* **1994**, *6*, 501. (b) Moody, C. J.; O'Sullivan, N.; Stratford, I. J.; Stephens, M. A.; Workman, P.; Bailey, S. M.; Lewis, A. *Anti-Cancer Drugs* **1994**, *5*, 367. (c) Knox, R. J.; Boland, M. P.; Friedlos, F.; Coles, B.; Southan, C.; Roberts, J. J. *Biochem. Pharmacol.* **1988**, *37*, 4671. (d) Westphal, E. M.; Ge, J.; Catchpole, J. R.; Ford, M.; Kenney, S. C. *Cancer Gene Ther.* **2000**, *7*, 97. (e) Denny, W. A. *Curr. Pharm. Des.* **2002**, *8*, 99. (f) Nakao, Y.; Fujita, M.; Warabi, K.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **2000**, *122*, 10462.

(3) (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (b) Sweeney, J. *Eur. J. Org. Chem.* **2009**, *2009*, 4911. (c) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509.

(4) For reviews, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

(5) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129.

(6) For reviews, see: (a) Pan, Y.; Tan, C.-H. *Synthesis* **2011**, *2011*, 2044. (b) Bernardi, L.; Fochi, M.; Franchini, M. C.; Ricci, A. *Org. Biomol. Chem.* **2012**, *10*, 2911. (c) Wang, Z.-L. *Adv. Synth. Catal.* **2013**, *355*, 2745. (d) Nakamura, S. *Org. Biomol. Chem.* **2014**, *12*, 394.

(7) (a) Li, X.-J.; Xiong, H.-Y.; Hua, M.-Q.; Nie, J.; Ma, J.-A. *Tetrahedron Lett.* **2012**, *53*, 2117. (b) Zheng, Y.; Xiong, H.-Y.; Nie, J.; Hua, M.-Q.; Ma, J.-A. *Chem. Commun.* **2012**, *48*, 4308. (c) Yuan, H.-N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3869. (d) Xiong, H.-Y.; Yang, Z.-Y.; Chen, Z.; Zeng, J.-L.; Nie, J.; Ma, J.-A. *Chem. - Eur. J.* **2014**, *20*, 8325. (e) Zhang, H.-X.; Nie, J.; Cai, H.; Ma, J.-A. *Org. Lett.* **2014**, *16*, 2542. (f) Tang, X.-D.; Li, S.; Guo, R.; Nie, J.; Ma, J.-A. *Org. Lett.* **2015**, *17*, 1389.

(8) For recent examples, see: (a) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583. (b) Rohr, K.; Mahrwald, R. *Org. Lett.* **2011**, *13*, 1878. (c) Yang, C.-F.; Shen, C.; Wang, J.-R.; Tian, S.-K. *Org. Lett.* **2012**, *14*, 3092. (d) Zhong, F.; Yao, W.; Dou, X.; Lu, Y. *Org. Lett.* **2012**, *14*, 4018. (e) Jiang, C.; Zhong, F.; Lu, Y. *Beilstein J. Org. Chem.* **2012**, *8*, 1279. (f) Moon, H. W.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 6569. (g) Zuo, J.; Liao, Y.-H.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2012**, *77*, 11325. (h) Suh, C. W.; Chang, C. W.; Choi, K. W.; Lim, Y. J.; Kim, D. Y. *Tetrahedron Lett.* **2013**, *54*, 3651. (i) Duan, Z.; Han, J.; Qian, P.; Zhang, Z.; Wang, Y.; Pan, Y. *Org. Biomol. Chem.* **2013**, *11*, 6456. (j) Kang, Y. K.; Lee, H. J.; Moon, H. W.; Kim, D. Y. *RSC Adv.* **2013**, *3*, 1332. (k) Duan, Z.; Han, J.; Qian, P.; Zhang, Z.; Wang, Y.; Pan, Y. *Beilstein J. Org. Chem.* **2014**, *10*, 969. (l) Zhu, F.-L.; Wang, Y.-H.; Zhang, D.-Y.; Hu, X.-H.; Chen, S.; Hou, C.-J.; Xu, J.; Hua, X.-P. *Adv. Synth. Catal.* **2014**, *356*, 3231.

(9) (a) Fan, R.; Wang, L.; Ye, Y.; Zhang, J. *Tetrahedron Lett.* **2009**, *50*, 3857. (b) Fan, R.; Wang, H.; Ye, Y.; Gan, J. *Tetrahedron Lett.* **2010**, *51*, 453. (c) Tang, S.; Wu, Y.; Liao, W.; Bai, R.; Liu, C.; Lei, A. *Chem. Commun.* **2014**, *50*, 4496. (d) Dian, L.; Wang, S.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Chem. Commun.* **2014**, *50*, 11738.

(10) CCDC 1439978 contains the supplementary crystallographic data for the compound **4a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/deposit/.

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