Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Hydrogenation/Oxidative Fragmentation Cascade for Synthesis of Chiral 4,5-Dihydro-1*H*-benzo[*d*]azepin-1-ones

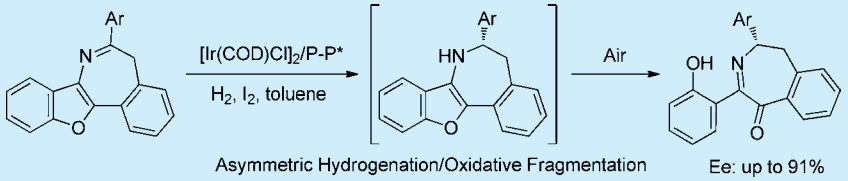
Hong-Qiang Shen,[†,‡] Xiang Gao,[†] Cong Liu,[†] Shu-Bo Hu,[†] and Yong-Gui Zhou*[,†,§]

[†]State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China

[‡]University of Chinese Academy of Sciences, Beijing 100049, P. R. China

[§]Collaborative Innovation Centre of Chemical Science and Engineering, Tianjin 300071, P. R. China

Supporting Information



ABSTRACT: An iridium-catalyzed asymmetric hydrogenation/oxidative fragmentation of 6-substituted 5*H*-benzo[*d*]benzofuro[3,2-*b*]azepines has been developed, providing an efficient access to optically active 4-substituted 4,5-dihydro-1*H*-benzo[*d*]azepin-1-ones with up to 91% ee. A possible reaction pathway includes the asymmetric hydrogenation to furnish chiral cyclic amines and oxidative fragmentation under an air atmosphere.

Benzazepines occupy a privileged position in the territory of nitrogen-containing heterocycles owing to their significantly broad bioactivity spectrum.[1] Among the diverse types of benzazepines, benzo[*d*]azepines are recognized to be particularly important due to their pharmacological properties.[1] For instance, fenoldopam acts as dopamine receptor agonists and antagonists.[2] LY-411575 is an effective γ-secretase inhibitor for the treatment of Alzheimer and Parkinson diseases.[3] 1-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines serve as selective 5-HT_{2C} receptor agonists for the treatment of obesity (Figure 1).[4] In

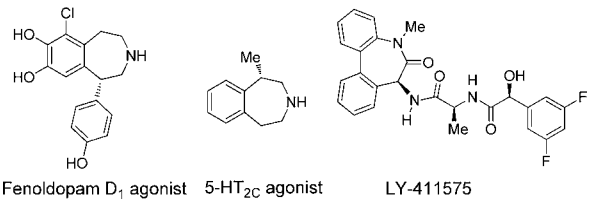


Figure 1. Selected biologically active molecules containing chiral benzo[*d*]azepine motif.

view of the remarkable significance of this framework, efficient syntheses are of contemporary interest. In 1989, Davies and co-workers developed the asymmetric intramolecular Friedel–Crafts alkylation reaction for the preparation of enantiomerically pure benzo[*d*]azepine derivatives.[5] Subsequently, starting from *o*-phenylene diacetic acid, Wünsch and co-workers successfully synthesized chiral 1-substituted tetrahydro-3-benzoazepines by employing (*R*)-phenylglycinol as a chiral auxiliary.[6] Recently, palladium-catalyzed [5 + 2] oxidative annulation of *o*-arylanilines with alkynes was disclosed by Luan's group, providing a facile access to imine-containing dibenzo[*b*,*d*]azepines in high yields and excellent diastereoselectivities.[7] Although great progress has been made to synthesize chiral benzo[*d*]azepine derivatives, the direct catalytic asymmetric protocols for the construction of these compounds are seldom mentioned. In this regard, the development of a simple and straightforward asymmetric synthetic strategy is highly desirable.

The transition-metal-catalyzed asymmetric hydrogenation of cyclic imines provides an efficient and straightforward access to the corresponding chiral cyclic amines.[8] Currently, some successful examples have been reported in transition-metal-catalyzed asymmetric hydrogenation of seven-membered cyclic imines. In 1993, the asymmetric hydrogenation of seven-membered cyclic imines with a chiral titanocene catalyst was reported by Buchwald and co-workers, affording the amines with excellent enantioselectivities.[9] Recently, our group focused on the development of synthesis of seven-membered cyclic chiral imines through iridium-catalyzed asymmetric hydrogenation; dibenzo[*b*,*f*][1,4]oxazepines,[10] dibenzo[*b*,*f*][1,4]-thiazepines,[11] pyrrole and indole fused benzodiazepinones, and benzodiazepines could be accessed through this strategy.[12] Meanwhile, Fan and co-workers reported a highly efficient asymmetric hydrogenation of 7-phenyl-3,4,5,6-tetrahydro-2*H*-azepine and 2,4-disubstituted 1,5-benzodiazepines using cationic ruthenium diamine catalysts.[13] Given the significance of benzo[*d*]azepines and our continuing efforts in synthesis of chiral cyclic amines via asymmetric hydrogenation,[14] we envisioned the synthesis of chiral 6-substituted 6,7-dihydro-5*H*-benzo[*d*]benzofuro[3,2-*b*]azepine by the iridium-catalyzed

Received: October 8, 2016
Published: November 4, 2016

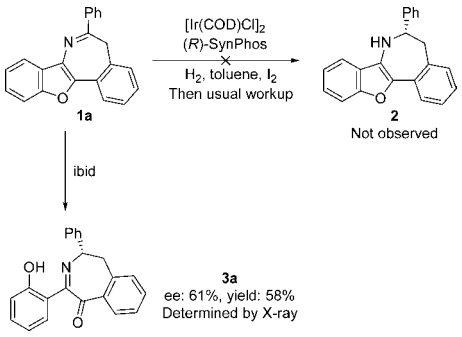
DOI: 10.1021/acs.orglett.6b03027
Org. Lett. 2016, 18, 5920–5923

asymmetric hydrogenation of the corresponding seven-membered cyclic imines.

Very recently, Zeni and co-workers reported *t*-BuOK catalyzed intramolecular anionic cyclization of (2-alkynylbenzyl)-oxy nitriles for the preparation of substituted benzofuroazepine derivatives with good yields.[15] The above work provides facile access to cyclic imine substrates for our study.

Therefore, in our initial study, the readily available 6-phenyl-5*H*-benzo[*d*]benzofuro[3,2-*b*]azepine **1a** was selected as the model substrate for condition optimization. The hydrogenation proceeded smoothly with moderate 58% yield and 61% ee by employing $[Ir(COD)Cl]_2$/(*R*)-SynPhos as the catalyst (Scheme 1). Surprisingly, the isolated product revealed to be

Scheme 1. Initial Experiment



different from the expected target product **2** evidenced by the nuclear magnetic resonance and mass spectra. Eventually, the structure of the product was determined to be 2-(2-hydroxyphenyl)-4-phenyl-4,5-dihydro-1*H*-benzo[*d*]azepin-1-one **3a** by X-ray single crystal diffraction analysis (Figure 2). We

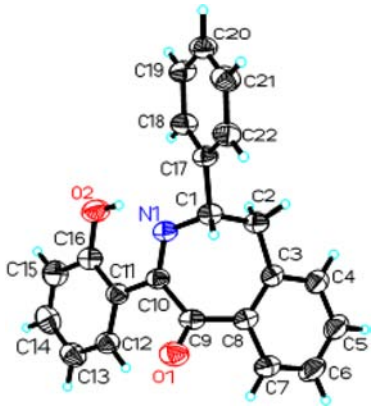
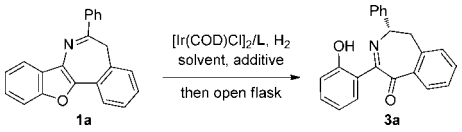


Figure 2. X-ray crystal structure of compound (*S*)-**3a**.

conjectured that an unexpected oxidative fragmentation reaction occurred in the air after the asymmetric hydrogenation (*vide infra*).[16] The unexpected reaction outcome provides an opportunity for the facile synthesis of chiral 4-substituted 4,5-dihydro-1*H*-benzo[*d*]azepin-1-ones.

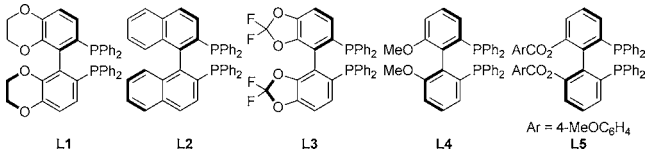
Intrigued by the above result, the evaluation of reaction parameters was carried out. As shown in Table 1, initially, with iodine as an additive, various kinds of solvents were examined, and it was found that the solvent effect played a crucial role in reactivity and enantioselectivity. Solvent screening revealed that toluene was optimal (Table 1, entries 1−4). Then, the effect of

Table 1. Evaluation of Reaction Parameters[a]



entry	solvent	additive	ligand	yield (%)[b]	ee (%)[c]
1	toluene	I_2	**L1**	58	61
2	THF	I_2	**L1**	86	−19
3	MeOH	I_2	**L1**	61	−1
4	EtOAc	I_2	**L1**	73	11
5	toluene	NCS	**L1**	46	14
6	toluene	NBS	**L1**	49	52
7	toluene	NIS	**L1**	28	18
8[d]	toluene	I_2	**L1**	52	80
9[d,e]	toluene	I_2	**L1**	61	80
10[d,e]	toluene	I_2	**L2**	40	68
11[d,e]	toluene	I_2	**L3**	73	84
12[d,e]	toluene	I_2	**L4**	87	82
13[d,e]	toluene	I_2	**L5**	86	87

[a]Conditions: **1a** (0.10 mmol), $[Ir(COD)Cl]_2$ (2.0 mol %), **L** (4.4 mol %), solvent (3.0 mL), additive (10 mol %), H_2 (700 psi), 30 °C, 24 h. [b]Isolated yields. [c]Determined by chiral HPLC. [d]0 °C. [e]H_2 (1000 psi), 36 h.



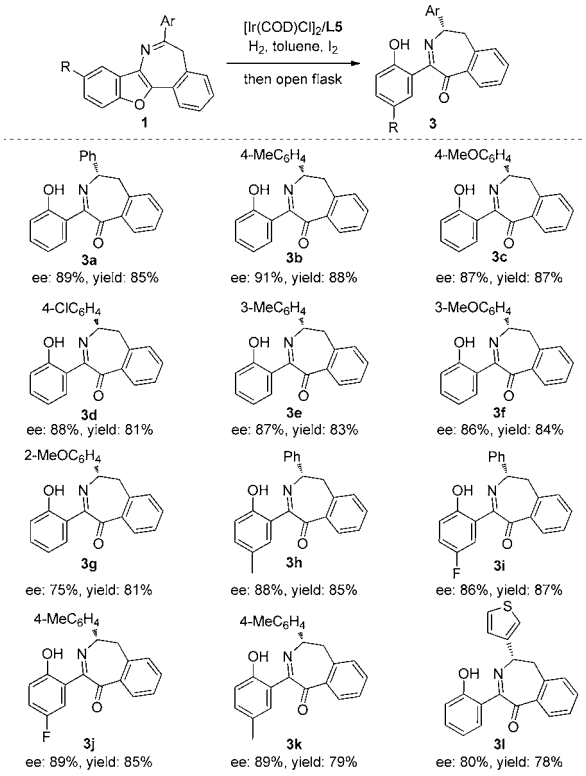
other additives, including NBS, NCS, and NIS, was surveyed in toluene (entries 5−7). To our disappointment, no additive gave a better result than iodine. When the reaction temperature was reduced to 0 °C, the ee value was enhanced to 80% (entry 8). To further improve the reactivity, we tried to increase the hydrogen pressure and prolong the reaction time, and the yield slightly increased (Table 1, entry 9).

Subsequently, chiral diphosphine ligands were examined. Initially, lower enantioselectivity and yield were observed with BINAP **L2** (Table 1, entry 10). The electron-deficient ligand **L3** gave good enantioselectivity and yield (Table 1, entry 11). For the commercially available ligand MeO-Biphep **L4**, 82% ee and 87% yield were observed (Table 1, entry 12). When the electron-withdrawing aroyl group was introduced to replace the methyl group of **L4**, which was synthesized by the Zhou group,[17] the highest 87% ee was obtained (Table 1, entry 13). Therefore, the optimal conditions were established as $[Ir(COD)Cl]_2$/**L5**/0 °C/toluene.

With the optimized reaction conditions in hand, we then investigated the substrate scope of the reaction (Scheme 2). The iridium-catalyzed protocol was compatible with electron-donating as well as electron-withdrawing groups at the 4-position of the phenyl ring of **1**, delivering the corresponding products in good yields and high enantioselectivities (**3b**−**3d**). The substituents at the 3-position of the phenyl ring of **1** were tolerable. The methoxyl at the 2-position of the phenyl ring of **1** led to slight erosion of the ee (**3g**), which was possibly caused by the steric hindrance of the *ortho* methoxyl group. In addition, introduction of the methyl group and fluoro atom in the benzofuran moiety barely had any effect on the yields and enantioselectivities (**3h**−**3k**). Notably, the thienyl substituted product **3l** could be obtained with 80% ee. Unfortunately,

DOI: 10.1021/acs.orglett.6b03027
Org. Lett. 2016, 18, 5920−5923

Scheme 2. Substrate Scope[a]

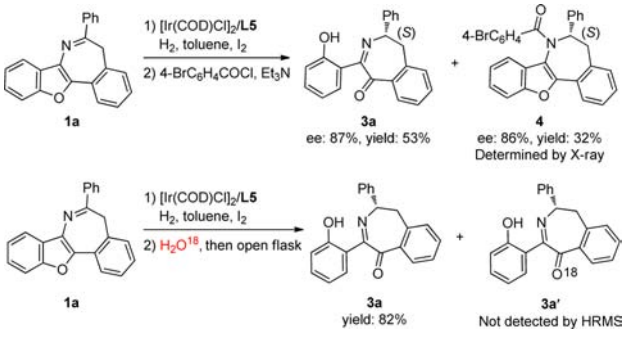


[a]Conditions: **1** (0.20 mmol), $[Ir(COD)Cl]_2$ (2.0 mol %), **L5** (4.4 mol %), I_2 (10 mol %), toluene (3.0 mL), H_2 (1000 psi), 0 °C, 36 h.

because the 6-alkyl-5*H*-benzo[*d*]benzofuro[3,2-*b*]azepine derivatives were inaccessible following the aforementioned method, we were unable to utilize these substrates in our iridium-catalyzed protocol. The absolute configuration of the product **3a** was unambiguously assigned to be *S* by X-ray crystallographic analysis after a simple recrystallization with ethyl acetate and *n*-hexane (Figure 2).

To get more insight into the reaction mechanism, we performed the following control experiments (Scheme 3).

Scheme 3. Control Experiments



Initially, we conjectured that an unexpected oxidative fragmentation reaction occurred in the air after the asymmetric hydrogenation. In order to determine the existence of the hydrogenation product **2**, we transferred the reaction flask quickly from the autoclave into the glovebox after asymmetric hydrogenation. Then, 4-bromobenzoyl chloride and triethylamine were added to the mixture. The solution was stirred at room temperature for 24 h and purified with a silica gel column; the protected hydrogenation product **4** was obtained with 86% ee. The absolute configuration of the product **4** was determined to be *S* by X-ray crystallographic analysis after a simple recrystallization with ethyl acetate and *n*-hexane (Figure 3). The compounds **3a** and **4** have the identical ee and absolute

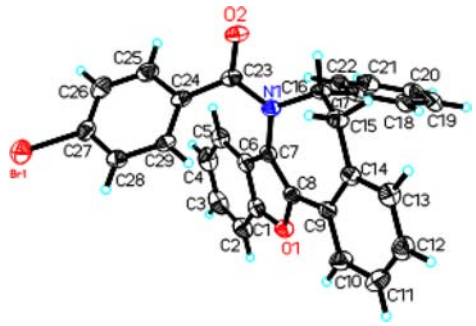
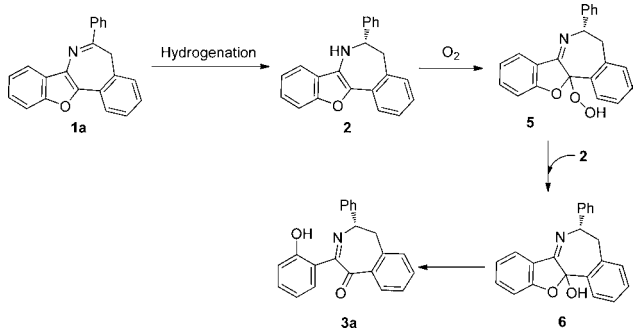


Figure 3. X-ray crystal structure of compound (*S*)-**4**.

configuration. In addition, H_2O^{18} was added to the mixture of the hydrogenation reaction to determine the source of oxygen of the carbonyl of compound **3a**; O^{18} incorporated product **3a′** was not detected in this reaction mixture by high resolution mass spectrometry analysis. This result accorded with our conjecture that the oxygen of the carbonyl of compound **2** is from air rather than water.

The use of molecular oxygen as an oxidant and oxygen atom source for oxygen incorporation in organic synthesis has attracted considerable attention owing to its inexpensive, abundant, and environmentally benign nature.[18] The reaction mechanism generally involved the formation of hydroperoxide compounds by oxidation in the air, and then, the hydroperoxide compound was reduced to generate product.[19] Based on the above experimental results and putative mechanism on the oxidation with air, a plausible mechanism is outlined in Scheme 4. Initially, the hydrogenation product **2** was obtained by the

Scheme 4. Possible Mechanism



asymmetric hydrogenation of **1a**. Subsequently, **2** reacted with oxygen gas to generate the intermediate hydroperoxide **5** via a radical pathway. The intermediate **5** would then undergo reduction by compound **2** or decomposition to give the hemiketal **6**. Finally, the isolated product **3a** could be obtained via ring-opening reaction of compound **6**.

In summary, we have discovered an unexpected iridium-catalyzed asymmetric hydrogenation/oxidative fragmentation of 6-substituted 5*H*-benzo[*d*]benzofuro[3,2-*b*]azepines, giving an efficient access to optically active 4-substituted 4,5-dihydro-1*H*-benzo[*d*]azepin-1-ones with up to 91% ee. In addition, based

DOI: 10.1021/acs.orglett.6b03027
Org. Lett. 2016, 18, 5920−5923

on the control experiments, a possible reaction pathway is tentatively proposed. Further research about the detailed reaction mechanism and asymmetric hydrogenation of other functionalized benzo[*d*]azepines are 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.6b03027.

General procedures; NMR spectra of obtained compounds (PDF)
X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **4** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ygzhou@dicp.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21532006 and 21372220) and Dalian Institute of Chemical Physics (DMTO201501) is acknowledged.

■ REFERENCES

(1) For reviews, see: (a) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 931. (b) Kawase, M.; Saito, S.; Motohashi, N. *Int. J. Antimicrob. Agents* **2000**, *14*, 193. (c) Hoyt, S. B.; London, C.; Gorin, D.; Wyvratt, M. J.; Fisher, M. H.; Abbadie, C.; Felix, J. P.; Garcia, M. L.; Li, X.; Lyons, K. A.; McGowan, E.; MacIntyre, D. E.; Martin, W. J.; Priest, B. T.; Ritter, A.; Smith, M. M.; Warren, V. A.; Williams, B. S.; Kaczorowski, G. J.; Parsons, W. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4630.

(2) (a) Ladd, D. L.; Weinstock, J.; Wise, M.; Gessner, G. W.; Sawyer, J. L.; Flaim, K. E. *J. Med. Chem.* **1986**, *29*, 1904. (b) Pettersson, I.; Liljefors, T.; Boegesoe, K. *J. Med. Chem.* **1990**, *33*, 2197. (c) Kaiser, C.; Dandridge, P. A.; Garvey, E.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Bass, L. S.; Clardy, J. *J. Med. Chem.* **1982**, *25*, 697. (d) Husain, S. M.; Fröhlich, R.; Schepmann, D.; Wünsch, B. *J. Org. Chem.* **2009**, *74*, 2788.

(3) Wong, G. T.; Manfra, D.; Poulet, F. M.; Josien, H.; Zhang, Q.; Bara, T.; Engstrom, L.; Pinzon-Ortiz, M.; Fine, J. S.; Lee, H.-J. J.; Zhang, L.; Higgins, G. A.; Parker, E. M. *J. Biol. Chem.* **2004**, *279*, 12876.

(4) (a) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Thomsen, W. J.; Saldana, H. R.; Whelan, K. T.; Menzaghi, F.; Webb, R. R.; Beeley, N. R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1467. (b) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Dosa, P. I.; Covel, J. A.; Ren, A.; Webb, R. R.; Beeley, N. R. A.; Martin, M.; Morgan, M.; Espitia, S.; Saldana, H. R.; Bjenning, C.; Whelan, K. T.; Grottick, A. J.; Menzaghi, F.; Thomsen, W. J. *J. Med. Chem.* **2008**, *51*, 305.

(5) (a) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron Lett.* **1989**, *30*, 3581. (b) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 33.

(6) Wirt, U.; Fröhlich, R.; Wünsch, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2199.

(7) Zuo, Z.; Liu, J.; Nan, J.; Fan, L.; Sun, W.; Wang, Y.; Luan, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 15385.

(8) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (c) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340. (d) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (e) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev.* **2013**, *42*, 497.

(9) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627.

(10) Gao, K.; Yu, C.-B.; Li, W.; Zhou, Y.-G.; Zhang, X. *Chem. Commun.* **2011**, *47*, 7845.

(11) Guo, R.-N.; Gao, K.; Ye, Z.-S.; Shi, L.; Li, Y.; Zhou, Y.-G. *Pure Appl. Chem.* **2013**, *85*, 843.

(12) Gao, K.; Wu, B.; Yu, C.-B.; Chen, Q.-A.; Ye, Z.-S.; Zhou, Y.-G. *Org. Lett.* **2012**, *14*, 3890.

(13) (a) Chen, F.; Ding, Z.; Qin, J.; Wang, T.; He, Y.; Fan, Q.-H. *Org. Lett.* **2011**, *13*, 4348. (b) Ding, Z.-Y.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5706.

(14) (a) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260. (b) Ye, Z.-S.; Chen, M.-W.; Chen, Q.-A.; Shi, L.; Duan, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 10181. (c) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 8286. (d) Ye, Z.-S.; Guo, R.-N.; Cai, X.-F.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2013**, *52*, 3685. (e) Ji, Y.; Shi, L.; Chen, M.-W.; Feng, G.-S.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2015**, *137*, 10496.

(15) Gai, R.; Back, D. F.; Zeni, G. *J. Org. Chem.* **2015**, *80*, 10278.

(16) (a) Adam, W.; Sauter, M. *Tetrahedron* **1994**, *50*, 8393. (b) Sauter, M.; Adam, W. *Acc. Chem. Res.* **1995**, *28*, 289. (c) More, A. A.; Ramana, C. V. *Org. Lett.* **2016**, *18*, 612.

(17) Zhang, D.-Y.; Wang, D.-S.; Wang, M.-C.; Yu, C.-B.; Gao, K.; Zhou, Y.-G. *Synthesis* **2011**, *2011*, 2796.

(18) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(19) (a) Yang, Y.; Moinodeen, F.; Chin, W.; Ma, T.; Jiang, Z.; Tan, C.-H. *Org. Lett.* **2012**, *14*, 4762. (b) Liang, Y.-F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548. (c) Bai, M.; You, Y.; Chen, Y.-Z.; Xiang, G.-Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Biomol. Chem.* **2016**, *14*, 1395. (d) Chen, C.-X.; Liu, L.; Yang, D.-P.; Wang, D.; Chen, Y.-J. *Synlett* **2005**, 2047.

DOI: 10.1021/acs.orglett.6b03027
Org. Lett. 2016, 18, 5920−5923