Organic LETTERS

Letter

pubs.acs.org/OrgLett

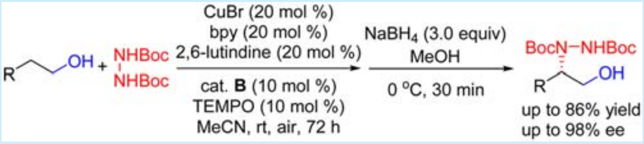
Enantioselective Synthesis of β-Hydrazino Alcohols Using Alcohols and *N*-Boc-Hydrazine as Substrates

Zhihao Cui and Da-Ming Du*

School of Chemistry and Chemical Engineering, Beijing Institute of Technology, Beijing 100081, People's Republic of China

Supporting Information

ABSTRACT: An enantioselective approach for the synthesis of α-hydrazino aldehydes is described that utilizes alcohols and *N*-Boc hydrazine instead of the conventional combination of aldehydes with azodicarboxylates. This protocol is enabled by merging *in situ* aerobic dual oxidation with asymmetric organocatalysis. This reaction also exhibits a high tolerance for varieties of substituents on the alcohol component. This approach features excellent enantiocontrol, cheap starting materials, operational simplicity, and scalability. The corresponding chiral β-hydrazino alcohols were obtained by sequential reduction with excellent enantioselectivity (up to 98% ee).



Construction of heteroatom-connected stereogenic carbon is frequently a much sought-after goal and challenge in organic chemistry[1] and the past decade has witnessed various strategies for asymmetric C–N bond formation,[2] wherein α-amination of aldehydes holds an important position. Since *in situ* generated α-hydrazino aldehydes are readily converted into β-hydrazino alcohols, oxazolidinones, β-amino alcohols, and α-amino acid derivatives, their enantioselective synthesis has been attracting tremendous attention and interest.[3] The pioneering study, made independently by the groups of List and Jørgensen in 2002, was the L-proline-catalyzed direct asymmetric α-hydrazination of aldehydes using azodicarboxylates as the electrophilic aminating agent (Scheme 1a).[3a,b] From then on, the majority of chiral amine catalysts have been exploited to construct such an amination pattern.[3] For example, Meggers and his co-workers developed a bifunctional chiral-at-metal Ir^{III} catalyst (Scheme 1b)[3k] and very recently the group of Leigh reported a mechanically driven point-chiral rotaxane catalyst that provided products in low ee (Scheme 1c).[3l] However, these advances just only concentrated on the modification or invention of the organocatalysts, and the combination of aldehydes and azodicarboxylates for gaining access to α-hydrazino aldehydes has undoubtedly never been changed to date.

Scheme 1. Asymmetric Hydrazination Reactions

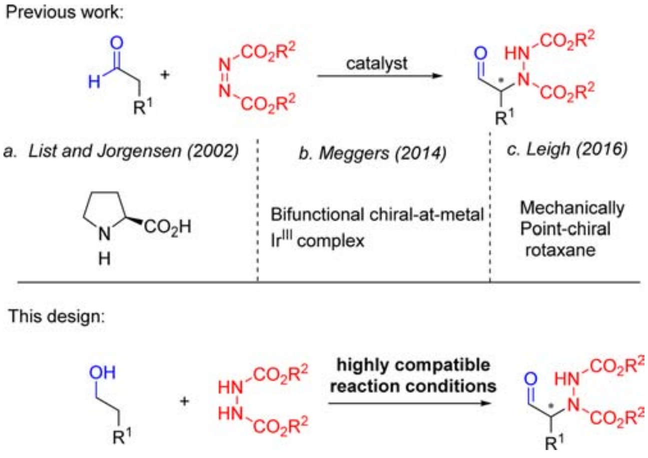
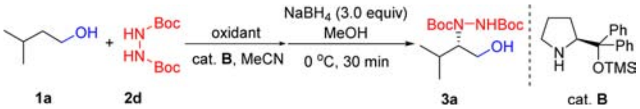


Table 1. Screening of Oxidants[a]



entry	oxidant (equiv)	yield (%)[b]	ee (%)[c]
1	NMO (3.0)	n.r.	
2	BPO (2.0), TEMPO (3.0)	n.r.	
3	PhI(OAc)$_2$ (3.0)	n.r.	
4	TBHP (3.0)	n.r.	
5	DDQ (3.0)	n.r.	
6	MnO$_2$ (3.0)	trace	
7	CuCl (0.2), air	trace	
8	(bpy)CuBr (0.2), TEMPO (0.2), air	43	90

[a]Reaction conditions: BocNHNHBoc (0.2 mmol), 3-methylbutan-1-ol (0.3 mmol), cat. B (0.02 mmol), oxidant, MeCN (2.0 mL), rt, 72 h. [b]Isolated yield. [c]Enantiomeric excess detemined by chiral HPLC analysis of the corresponding ester (see Supporting Information). n.r. = no reaction.

Given that alcohols and diacylhydrazides are more widely commercially available at lower cost, we considered that it would be a better choice to use them as the starting materials.

If such design did occur as intended, it would open an easy entry into the enantioselective preparation of α-hydrazino aldehydes. However, the challenge lies in the identification of a highly compatible system, which not only can simultaneously

Received: September 21, 2016
Published: October 27, 2016

ACS Publications

DOI: 10.1021/acs.orglett.6b02841
Org. Lett. 2016, 18, 5616–5619

Table 2. Screening of Reaction Conditions[a]

entry	2	cat.	additive	yield (%)[b]	ee (%)[c]
1	**2a**	**B**	–	n.r.	
2	**2b**	**B**	–	n.r.	
3	**2c**	**B**	–	n.r.	
4	**2d**	**B**	–	43	90
5	**2e**	**B**	–	n.r.	
6	**2f**	**B**	–	n.r.	
7	**2d**	**A**	–	n.r.	
8	**2d**	**C**	–	10	
9	**2d**	**D**	–	n.r.	
10	**2d**	**B**	DMAP	n.r.	
11	**2d**	**B**	2,6-lutidine	60	96
12	**2d**	**B**	DABCO	n.r.	
13	**2d**	**B**	Et3N	43	62
14	**2d**	**B**	NMI	n.r.	
15[d]	**2d**	**B**	2,6-lutidine	71	98

[a]Reaction conditions: $RO_2CNHNHCO_2R$ (0.2 mmol), 3-methylbutan-1-ol (0.3 mmol), CuBr (0.04 mmol), bpy (0.04 mmol), cat. **B** (0.02 mmol), additive (0.04 mmol), TEMPO (0.02 mmol), solvent (2.0 mL), air, rt, 72 h. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC analysis of the corresponding ester (see Supporting Information). [d]3-Methylbutan-1-ol (0.4 mmol). n.r. = no reaction.

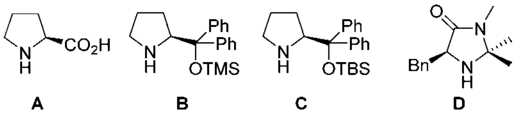


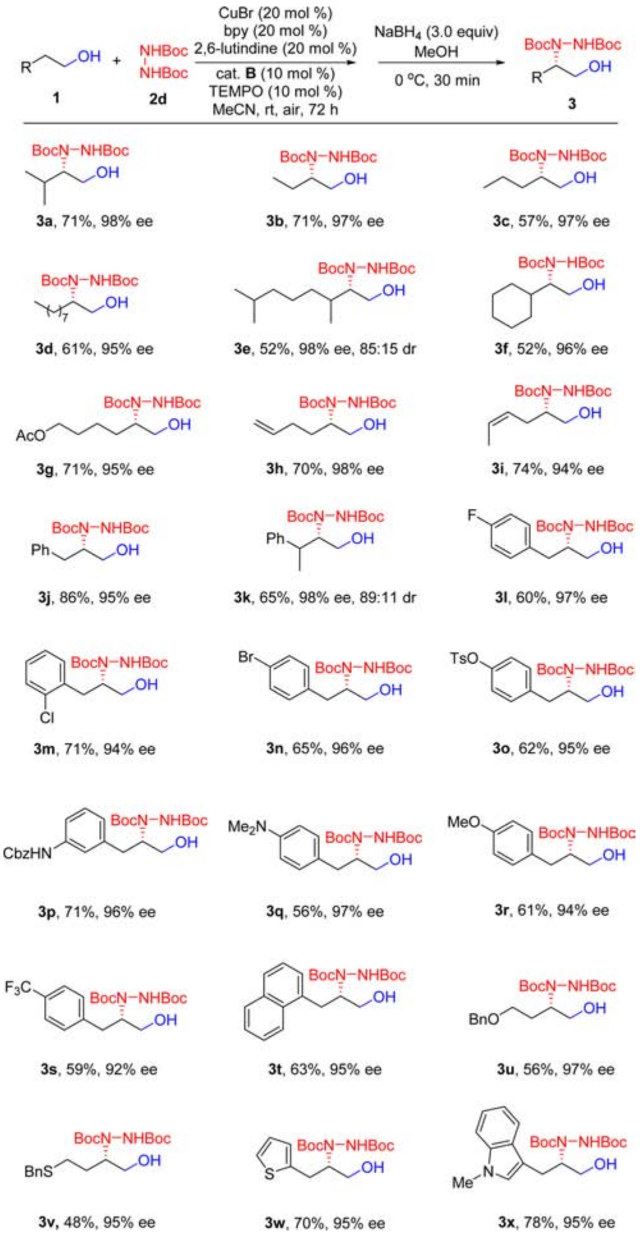
Figure 1. Organocatalysts used in this study.

oxidize the alcohols and the diacylhydrazine but also be in harmony with the asymmetric catalysis and avoid the partial racemization of the sensitive α-hydrazino aldehyde products.

Initially, we chose the reaction of 3-methylbutan-1-ol with di-*N*-Boc-hydrazine to screen different oxidants in the presence of catalyst **B**. When frequently used classic oxidants such as NMO,[4] BPO–TEMPO,[5] $PhI(OAc)_2$,[6] TBHP,[7] and DDQ[8] were employed, no desired β-hydrazino alcohol **3a** was obtained (Table 1, entries 1–5). On the other hand, either the MnO_2[9] or CuCl–air[10] oxidative system gave only trace desired hydrazination product (entries 6, 7). To our delight, the combination of (bpy)CuBr–TEMPO–air[11] met with success and product **3a** was obtained with high enantioselectivity (90% ee) albeit in low yield (43%) (entry 8).

With a viable oxidant system identified, we then investigated variations to the protecting groups (PG) in the hydrazine, in order to improve both the yield and enantioselectivity of **3a**. As shown in Table 2, and beyond our imagination was that, with the exception of the *N*-Boc hydrazine, no detectable quantity of the corresponding β-hydrazino alcohol was afforded when other hydrazine protecting groups (Cbz, *i*-$PrCO_2$, $MeCO_2$, $EtCO_2$, and Ts) were employed (entries 1–6). Although the reason is elusive, the outcome demonstrated that the protecting groups had a decisive impact on the aerobic oxidation of hydrazine. Also, an optimization of organocatalysts (**A**–**D**) (Figure 1) revealed that only the chiral pyrrolidine **B** had a high catalytic efficiency (entries 7–9). The effect of a wide spectrum of additives on this reaction was established as well. When DMAP, DABCO, or NMI was added into the reaction system, these individual reagents would completely suppress the reaction and provide an unknown side product (entries 10, 12, 14). The addition of Et_3N furnished **3a** with dramatically decreased enantioselectivity. A good yield and excellent enantioselectivity were accessed when 2, 6-lutidine was used (entry 11). Also, optimization of the copper salt and solvent showed that CuBr outmatched other copper catalysts and MeCN gave the best outcomes (for details, see Supporting Information). Especially, with an increase of the amount of alcohol to 0.4 mmol, both the yield (71%) and enantioselectivity (98%) of **3a** were improved (entry 15).

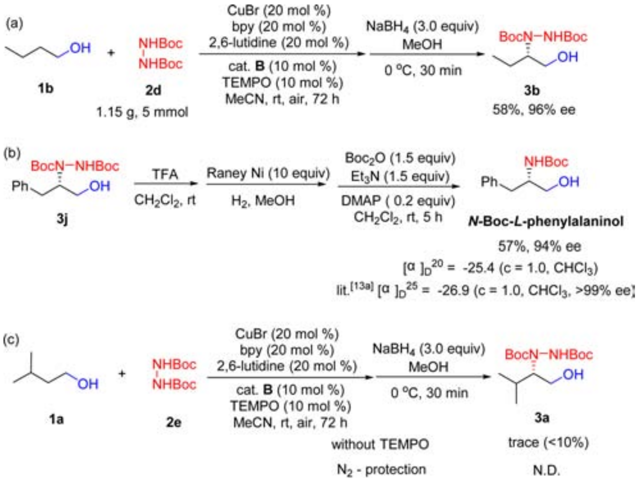
Scheme 2. Substrate Scope of the Asymmetric Amination of Alcohols[a,b,c]



[a]Reaction conditions: BocNHNHBoc (0.2 mmol), alcohol (0.4 mmol), CuBr (0.04 mmol), bpy (0.04 mmol), cat. **B** (0.02 mmol), 2,6-lutidine (0.04 mmol), TEMPO (0.02 mmol), MeCN (2.0 mL), air, rt, 72 h. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC analysis of the corresponding ester (see Supporting Information).

We then made an investigation of the scope of different alcohols as shown in Scheme 2. A range of alkane chains on the

Scheme 3. (a) Gram-Scale Preparation; (b) Facile Synthesis of *N*-Boc-l-Phenylalaninol; (c) Control Experiment



alcohol component were tolerated, even those with sterically demanding substituents (**3b**, **3f**). Additionally, alcohols **1** attached with internal and terminal olefins smoothly underwent enantioselective hydrazination without further oxidation or degradation (**3h**, **3i**). This protocol also accommodated a wide range of alcohols **1** containing aromatics. The absolute configuration of **3j** was assigned as ***S*** by analogy.[3k] In spite of the steric hindrance, 3-phenylbutan-1-ol still gave the hydrazination product **3k** with moderate yield and excellent enantioselectivity. Aromatic halides, such as fluorine, chlorine, and bromine on the alcohol component, were amenable to this hydrazination process and so were aromatics with tosyloxy, amide, and methoxy (**3l**, **3r**). Surprisingly, aniline, which readily undergoes aerobic oxidative dehydrogenative coupling with nucleophiles under copper-catalyzed conditions, as many reports have demonstrated,[12] also underwent the hydrazination reaction (**3q**). Moreover, alcohol **1v** bearing the readily oxidizable thioether also furnished the enantioenriched adduct **3v**. This reaction proceeded well with alcohols possessing heterocycles (**1w**, **1x**), to provide a new entry to complicated building blocks.

To demonstrate the practical utility of this protocol, *n*-butyl alcohol was hydrazinated on a multigram scale and the product **3b** was obtained with moderate yield (58%) and high enantioselectivity (96% ee) (Scheme 3a). Of particular note is that this reaction procedure was operationally simple and no precautions were needed with regards to moisture exclusion. Furthermore, the simple transformation method of product **3j** to l-phenylalaninol was established. Deprotection of the Boc group of **3j**, followed by reduction cleavage of the N–N bond with the aid of Raney Ni and H_2, and finally protection by Boc group furnished the *N*-Boc-l-phenylalaninol in 57% yield with the unchanged enantiopurity over three steps (Scheme 3b). The absolute configuration of *N*-Boc-l-phenylalaninol was assigned as (*S*).[13] Control experiments showed that the absence of TEMPO did not make the reaction run successfully and only trace product **3a** was achieved when the reaction was performed under a N_2 atmosphere, substantiating that air was the actual oxidant (Scheme 3c). A plausible synergistic catalytic mechanism merging of aerobic dual oxidation with asymmetric enamine catalysis is proposed (see Supporting Information).

In summary, we have developed a new approach to prepare enantioenriched *β*-hydrazino alcohols using alcohols and *N*-Boc-hydrazine as cheap starting materials. In comparison to conventional methods, this approach represents great progress from the perspective of step- and atom-economy. This reaction is highly compatible with alcohols bearing alkanes, alkenes, aromatics with varieties of substituents, and even heterocycles. Meanwhile, this reaction is scalable and very operationally simple without any elaborate procedures. The corresponding *β*-hydrazino alcohols could be obtained by sequential reduction in excellent enantioselectivity (up to 98% ee). We hope that this mild and efficient method will facilitate the late-stage asymmetric hydrazination of complicated molecules as well as pharmaceuticals. To clarify the mechanism, further investigations are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02841.

> Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra and HPLC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dudm@bit.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from National Natural Science Foundation of China (Grant No. 21272024).

■ REFERENCES

(1) For selected examples of construction of a heteroatom-connected stereogenic carbon: (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688. (c) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (d) De Faveri, G.; Ilyashenko, G.; Watkinson, M. *Chem. Soc. Rev.* **2011**, *40*, 1722.

(2) For selected reviews of various strategies for the asymmetric C–N bond formation, see: (a) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (b) Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630. (c) Verkade, J.; Hemert, L.; Quaedflieg, P.; Rutjes, F. P. J. *Chem. Soc. Rev.* **2008**, *37*, 29. (d) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J. *Chem. Soc. Rev.* **2010**, *39*, 1656.

(3) (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (c) Franzen, J.; Marigo, M.; Jørgensen, K. R. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (d) Baumann, T.; Bachle, M.; Hartmann, C.; Brase, S. *Eur. J. Org. Chem.* **2008**, *2008*, 2207. (e) Quintard, A.; Belot, S.; Marchal, E.; Alexakis, A. *Eur. J. Org. Chem.* **2010**, *2010*, 927. (f) Liu, P.-M.; Magar, D. R.; Chen, K. *Eur. J. Org. Chem.* **2010**, *2010*, 5705. (g) Hein, J.; Bures, J.; Lam, Y.-H.; Hughes, M.; Houk, K. N.; Armstrong, A. A.; Blackmond, D. *Org. Lett.* **2011**, *13*, 5644. (h) Kumar, B. S.; Venkataramasubramanian, V.; Sudalai, A. *Org. Lett.* **2012**, *14*, 2468. (i) Fan, X.; Sayalero, S.; Pericas, M. A. *Adv. Synth. Catal.* **2012**, *354*, 2971. (j) Theodorou, A.; Papadopoulos, G. N.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 5438. (k) Huo, H.; Fu, C.; Wang, C.; Harms, K.; Meggers, E. *Chem. Commun.* **2014**, *50*, 10409. (l) Cakmak, Y.; Erbas-Cakmak, S.; Leigh, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 1749. (m) Jovanovic, P.; Petkovic, M.; Simic, M.; Ivkovic, B.; Savic, V. *Org. Biomol. Chem.* **2016**, *14*, 6712.

(4) (a) Rivero, M. R.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992. (b) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342.

(5) (a) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638. (b) Kano, T.; Shirozu, F.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 18036.

(6) (a) Muangkaew, C.; Katrun, P.; Kanchanarugee, P.; Kuhakam, C. *Tetrahedron* **2013**, *69*, 8847. (b) Zhan, Z.; Cheng, X.; Zheng, Y.; Wu, Y. *RSC Adv.* **2015**, *5*, 82800.

(7) For reviews, see: (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(8) For reviews, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.

(9) (a) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8714. (b) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14472. (c) Kano, T.; Shirozu, F.; Maruoka, K. *Org. Lett.* **2014**, *16*, 1530.

(10) (a) Frazier, C. P.; Engelking, J. R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2011**, *133*, 10430. (b) Sandoval, D.; Frazier, C. P.; Bugarin, A.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2012**, *134*, 18948. (c) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. *Org. Lett.* **2012**, *14*, 3620. (d) Frazier, C. P.; Sandoval, D.; Palmer, L. I.; Read de Alaniz, J. *Chem. Sci.* **2013**, *4*, 3857. (e) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4149.

(11) (a) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414. (b) Gamez, P.; Arends, I. W. C. E.; Sheldon, R. A.; Reedijk, J. *Adv. Synth. Catal.* **2004**, *346*, 805. (c) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901. (d) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742. (e) Rahimi, A.; Ulbrich, A.; Coon, J. J.; Stahl, S. S. *Nature* **2014**, *515*, 249. (f) Ryland, B. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 8824.

(12) For selected examples of aerobic oxidative dehydrogenative coupling of aniline with nucleophiles, see: (a) Rousselet, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1995**, *36*, 4999. (b) Basle, O.; Li, C. *Green Chem.* **2007**, *9*, 1047. (c) Sureshkumar, D.; Sud, A.; Klussmann, M. *Synlett* **2009**, *2009*, 1558. (d) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C. *Chem. Commun.* **2009**, 953. (e) Basle, O.; Borduas, N.; Dubois, P.; Chapuzet, J. M.; Chan, T. H.; Lessard, J.; Li, C.-J. *Chem. - Eur. J.* **2010**, *16*, 8162. (f) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Fares, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (g) Yan, X.-M.; Chen, Z.-M.; Yang, F.; Huang, Z.-Z. *Synlett* **2011**, *2011*, 569.

(13) (a) Varala, R.; Nuvula, S.; Adapa, S. *J. Org. Chem.* **2006**, *71*, 8283. (b) Wu, Y. C.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 9522. (c) Sarkar, A.; Roy, S. R.; Parikh, N.; Chakraborti, A. K. J. *J. Org. Chem.* **2011**, *76*, 7132.