Organic LETTERS

Letter

pubs.acs.org/OrgLett

Reductive Hydrazination with Trichlorosilane: A Method for the Preparation of 1,1-Disubstituted Hydrazines

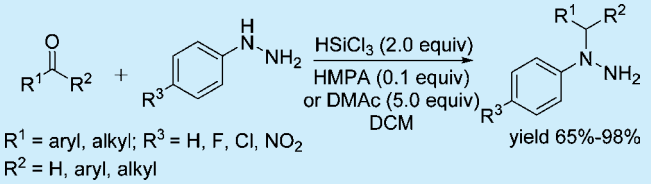
Tao Wang, Xiao Di, Chao Wang,* Li Zhou, and Jian Sun*

Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041 China

Graduate School of Chinese Academy of Sciences, Beijing, 10049, China

Supporting Information

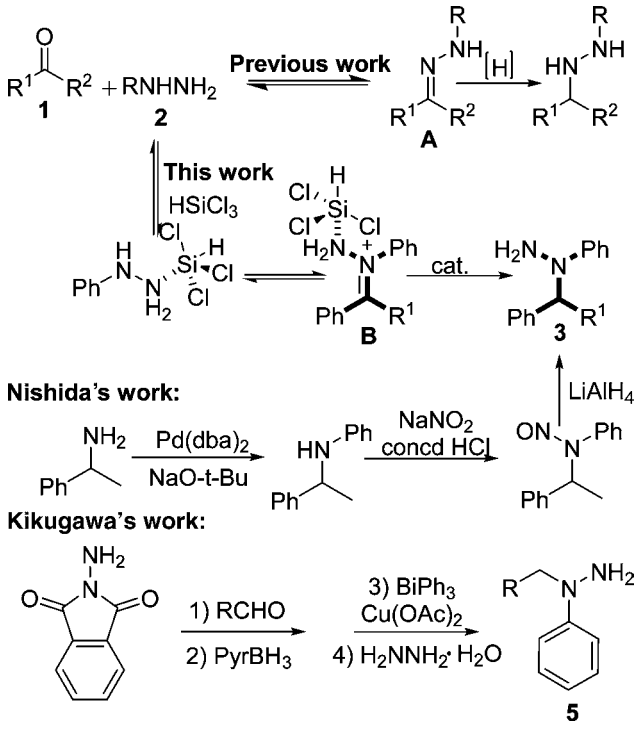
ABSTRACT: A straightforward and facile method has been developed to prepare 1,1-disubstituted hydrazines via Lewis base promoted direct reductive hydrazination. Under the catalysis of hexamethylphosphoramide (HMPA) and *N,N*-dimethylacetamide (DMAc), respectively, various ketones and aldehydes could react with phenylhdrazines to prepare 1,1-disubstituted hydrazines with good to high yields.



Direct reductive amination (DRA) represents a convenient and straightforward method for the synthesis of amines, which have seen wide applications in organic synthesis.[1−3] The amines that could be used as effective reactants for DRA include various primary and secondary alkyl amines,[4−6] aryl amines,[7−11] hydroxyl amines,[12] and alkoxyl amines.[13] As a special type of amines, hydrazines should in principle also be good reactants for DRA. To date, however, there have been no organocatalytic methods reported in the literature that could implement DRA using hydrazines as reactants, so-called direct reductive hydrazination (DRH).[14] Since hydrazines have two vicinal amino groups, conceivably, the difficulties confronted with DRH include the following: (1) the in situ formed hydrazone intermediate (A, Scheme 1) is normally much more stable and less reactive than the carbonyl substrates toward nucleophilic reduction; (2) the regioselectivity is hard to control if the two amino groups are both active and have different substitutions. The use of preformed hydrazones and thus indirect reductive hydrazination (IRH) method could address these difficulties to some degree, but it needs extra operations and is less convenient and economic.[15−18]

Hydrosilylation of unsaturated double bonds by trichlorosilane with Lewis base as an activator is a well-known reduction method.[19−22] Its strength has been well demonstrated by others and us in asymmetric catalysis.[23−34] We were interested in extending the application of this method to DRH. The chance is that trichlorosilane should preferentially react with the terminal amino group of hydrazine **2** and leave the middle amino group to interact with the carbonyl group of **1**. The resulting intermediate **B** should be highly active toward the hydrosilylation. Herein, we wish to communicate the results of our study and present a highly effective new method to implement DRH using organic Lewis base as promoter and trichlorosilane as reducing agent, which furnishes the condensation of various aldehydes and ketones with aryl hydrazines and reduction in one-pot under mild conditions to afford 1,1-disubstituted hydrazines as exclusive regioisomers with good to high yields.

Scheme 1. Strategies for the Synthesis of 1,1-Disubstituted Hydrazines



1,1-Disubstituted hydrazines **3** are important organic synthons used in a various of reactions such as Fisher indolization for the synthesis of indole and its derivatives. Kikugawa and co-workers[35] reported a four-step method to

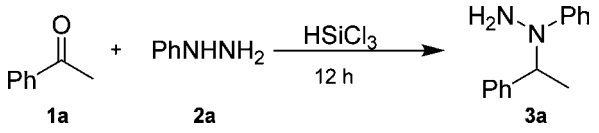
Received: March 9, 2016
Published: April 6, 2016

DOI: 10.1021/acs.orglett.6b00675
Org. Lett. 2016, 18, 1900−1903

prepare hydrazines **5**. Nishida[36] and Garg[37] reported a three-step method for the preparation of hydrazines **3**, respectively (Scheme 1). Although various 1,1-disubstituted hydrazines could be obtained by these methods, the atom economy of these methods is very low since multiple synthesis processes are required. The method we presented in this study should offer a straightforward new approach to the synthesis of this type of hydrazines.

Initially, we used the DRH of acetophenone **1a** with phenylhydrazine **2a** as the model reaction to test the catalytic ability of the Lewis bases. Interestingly, the desired product **3a** could be obtained with moderate to good yields in DCM at 0 °C under the catalysis of 1 equiv of the easily available Lewis bases (Table 1, entries 1−13). A 98% yield could be achieved

Table 1. Exploration of Reaction Conditions for the Direct Reductive Hydrazination[a]



1a **2a** **3a**

entry	solvent	LB (equiv)	temp (°C)	yield[b] (%)
1	DCM	TMEDA (1.0)	0	57
2	DCM	2,6-lutidine (1.0)	0	36
3	DCM	pyridine (1.0)	0	76
4	DCM	TEA (1.0)	0	26
5	DCM	DIPEA (1.0)	0	47
6	DCM	DMAP (1.0)	0	60
7	DCM	Ph_3PO (1.0)	0	64
8	DCM	HMPA (1.0)	0	98
9	DCM	DMF (1.0)	0	60
10	DCM	DMAc (1.0)	0	60
11	DCM	imidazole (1.0)	0	38
12	DCM	HMDS (1.0)	0	62
13	DCM	PPh_3 (1.0)	0	47
14	$CHCl_3$	HMPA (1.0)	0	38
15	CCl_4	HMPA (1.0)	0	60
16	DCE	HMPA (1.0)	0	60
17	toluene	HMPA (1.0)	0	26
18	MeCN	HMPA (1.0)	0	71
19	THF	HMPA (1.0)	0	57
20	DCM	HMPA (0.5)	0	81
21	DCM	HMPA (0.2)	0	81
22	DCM	HMPA (0.1)	0	78
23	DCM	HMPA (0.1)	25	93
24	DCM	HMPA (1.0)	−20	38
25	DCM	HMPA (1.0)	−40	24

[a]Unless noted otherwise, reactions were carried out with ketone (0.20 mmol), hydrazine (0.20 mmol), and $HSiCl_3$ (2.0 equiv) in 1.0 mL of solvent for 12 h. [b]Isolated yield. Tetramethylethylenediamine (TMEDA), triethylamine (TEA), *N*,*N*-diisopropylethylamine (DIPEA), 4-dimethylaminopyridine (DMAP), hexamethylphosphoramide (HMPA), dimethylacetamide (DMAc), bis(trimethylsilyl)amine (HMDS).

when 1 equiv of hexamethylphosphoramide (HMPA) was added as catalyst. Dichloromethane was found to be the best solvent for the reaction. The solvent was changed to $CHCl_3$, CCl_4, DCE, toluene, MeCN, and THF, and all of them caused a lower yield of the desired product **3a** (Table 1, entries 14−19). When the amount of HMPA was reduced to 10 mol %, the yield of the product **3a** dropped to 78%. However, the yield could be increased to 93% when the reaction temperature was increased to 25 °C. After careful investigation, we identified the best reaction conditions in which the reduction hydrazination of acetophenone and phenylhydrazine were performed using 10 mol % of HMPA and trichlorosilane (2.0 equiv) in DCM at 25 °C for 12 h.

With the optimized reaction conditions in hand, the scope and limitations for the substrates of the DRH were investigated (Figure 1). Both electron-donating and -withdrawing substitutions at the *para* position of the phenyl ring of acetophenone were tolerated (Figure 1, **3a**−**h**). A 84%−96% yield could be obtained when the *para* position of the phenyl ring of acetophenone was substituted with F, Cl, Br, CF_3, NO_2, Me, and MeO, respectively. Yields of 92% and 94% could be

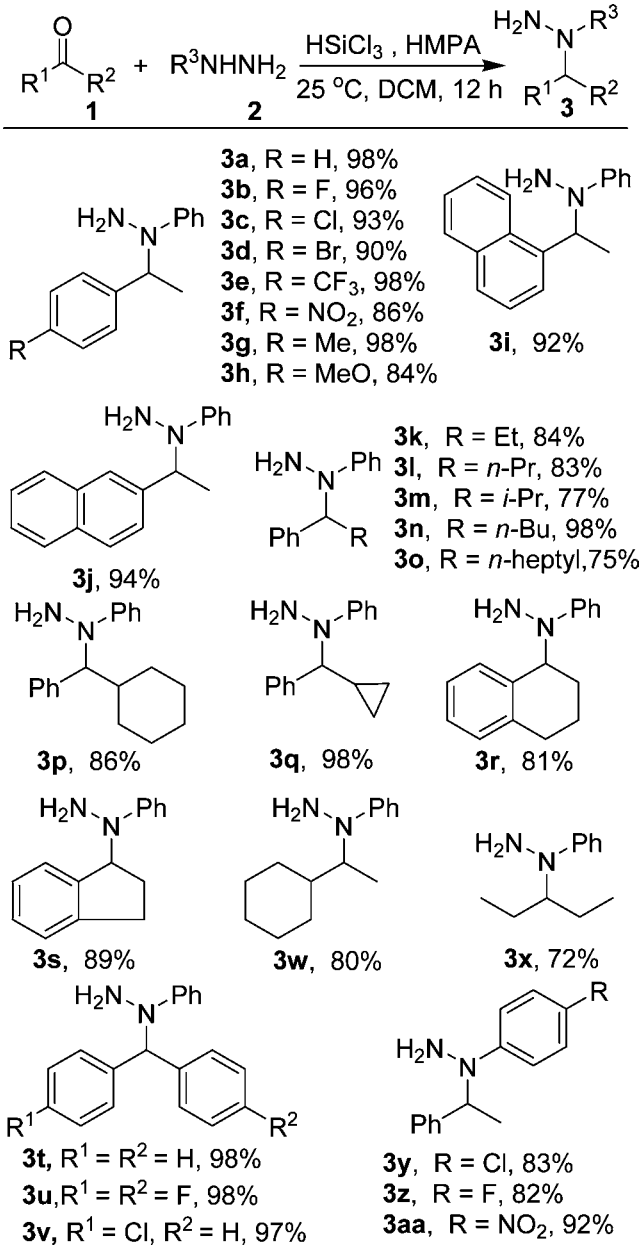


Figure 1. Direct reductive hydrazination of ketone. Unless noted otherwise, reactions were carried out with ketone (0.20 mmol), hydrazine (0.22 mmol), HMPA (0.02 mmol), and $HSiCl_3$ (2.00 equiv) in 1.0 mL of solvent at 25 °C for 12 h. Isolated yield based on ketone.

DOI: 10.1021/acs.orglett.6b00675
Org. Lett. 2016, 18, 1900−1903

obtained also, respectively, when 1-acetylnaphthalene and 2-acetylnaphthalene were used as the substrate in the reaction.

Moreover, the methyl group of the acetophenone could also be replaced with other groups such as Et, *n*-Pr, *i*-Pr, *n*-Bu, and *n*-heptyl. The desired product **3k−o** could be obtained with 74%−98% yields when these substrates were used in the reaction. Yields of 86% and 98% could be obtained when the methyl group of the acetophenone was replaced with cyclohexyl and cyclopropyl, respectively. 1-Tetralone and 1-indanone could also be used in the reaction to prepare the corresponding product **3r** and **3s** with 81% and 89% yield.

Benzophenone, 4,4′-difluorobenzophenone, and 4-chlorobenzophenone are all good substrates for the reaction. The desired product could be obtained with 97%−98% yields when these substrates were used in the reaction. Aliphatic ketones such as acetylcyclohexane and pentan-3-one could also be used as substrates for the reaction, and yields of 80% and 72% were obtained, respectively, when they were used in the reaction. Furthermore, substituted phenylhydrazines such as (4-chlorophenyl)hydrazine, (4-fluorophenyl)hydrazine, and (4-nitrophenyl)hydrazine could also be used in the reaction. The desired products **3y**, **3z**, and **3aa** could be obtained with 83%, 82%, and 92% yields, respectively.

We next tested whether aldehyde could be used as good substrate in the DRH reaction to prepare the corresponding product under the existing reaction conditions. However, no desired product **5a** could be detected when phenylaldehyde was used in the reaction under the existing reaction conditions. Most of the phenylaldehydes were reduced to phenylmethanol or converted to the hydrazone intermediate, which could not be reduced by trichlorosilane. We found the reduction of aldehyde by trichlorosilane could be reduced by decreasing the reaction temperature, and the formation of hydrazone could be efficiently inhibited by premixing phenylhydrazine with trichlorosilane. Thus, in order to get a higher yield of the desired product, we tried to add phenyl aldehyde to the mixture of trichlorosilane and phenylhydryzine at lower temperature. Gratifyingly, the desired product **5a** could be isolated with 13% yield under the catalysis of 1 equiv of HMPA at −40 °C, and 58% yield could be obtained when the amount of HMPA was increased to 5 equiv. The yield of product **5a** could be further increased to 87% when 5 equiv of DMAc was used to replace HMPA (Figure 2).

With the reaction conditions in hand, the substrate scope of the aldehyde was investigated (Figure 2). Both electron-donating and -withdrawing substitution at the *meta* and *para* positions of the phenyl ring of phenylaldehyde were tolerated. The desired products could be obtained with 72%−84% yields when the *meta* and *para* positions of the phenyl ring were substituted with electron-withdrawing groups such F, Cl, CF_3, and NO_2, respectively (**5b−d,f−j**). Yields of 80% and 71% could be obtained, respectively, when the *meta* and *para* positions of the phenyl ring were substituted with MeO. The desired products could be obtained with 82% and 65% yields when *α*- and *β*-naphthaldehyde were used, respectively. Aliphatic aldehydes such as 3-phenylpropanal, cyclohexanecarboxaldehyde, and heptanal could also be used as good substrates for the reaction, and the desired products could be obtained with good yields (**5p−r**).

In order to develop the chiral version of the DRH reaction, chiral Lewis bases, which have been proven to be very useful catalysts in asymmetric hydrosilylation of imine and enamine in our previous work, were tested. We found the tested catalysts

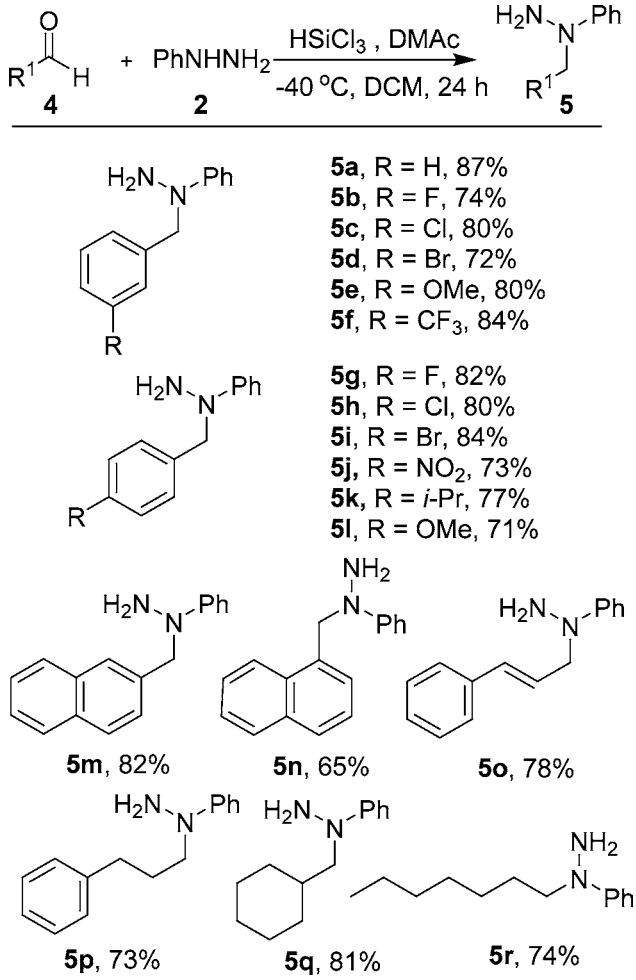
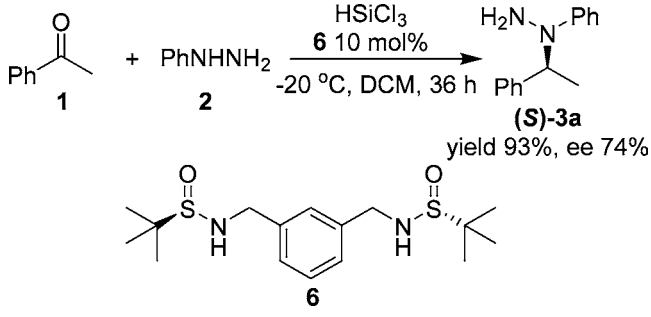


Figure 2. Direct reductive hydrazination of aldehyde. Aldehyde (0.20 mmol) was added to the solution of hydrazine (0.22 mmol), DMAc (1.00 mmol), and $HSiCl_3$ (2.00 equiv) in 1.0 mL of solvent at −40 °C for 24 h. Isolated yield based on aldehyde.

have moderate to high activity. The desired product **3a** could be obtained with 93% yield and 74% ee when the bis-sulfinamide catalyst **6**[38] was used.



In conclusion, an efficient method to prepare 1,1-disubstituted phenylhydrazine by Lewis base catalyzed direct reductive hydrazination has been reported. Under the catalytic effects of Lewis bases, trichlorosilane could be used as a powerful reducing agent to furnish the DRH reaction between a wide range of aryl/alkyl ketones/aldehyde and phenylhydrazines to obtain the desired products with good to high yields. On the basis of the results of the existing method and the literature data, we hypothesize the terminal NH_2 of the

DOI: 10.1021/acs.orglett.6b00675
Org. Lett. 2016, 18, 1900−1903

phenylhydrazines was blocked under the reaction conditions by trichlorosilane. The mechanistic aspects and the asymmetric catalytic system of this reaction are under exploration and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00675.

Experimental details, analytical data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wangchao@cib.ac.cn.
*E-mail: sunjian@cib.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the Western Light Talents Training Program of Chinese Academy of Sciences, the National Natural Science Foundation of China (Project Nos. 21272227 and 21402185).

■ REFERENCES

(1) Tripathi, R. P.; Verma, S. S.; Pandey, J.; Tiwari, V. K. *Curr. Org. Chem.* **2008**, *12*, 1093−1115.
(2) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753−819.
(3) Wang, C.; Xiao, J., Asymmetric Reductive Amination. In *Stereoselective Formation of Amines*; Li, W., Zhang, X., Eds.; Topics in Current Chemistry 343;Springer-Verlag: Berlin, 2014; pp 261−282.
(4) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227−4230.
(5) Lee, O. Y.; Law, K. L.; Ho, C. Y.; Yang, D. *J. Org. Chem.* **2008**, *73*, 8829−8837.
(6) Wang, C.; Pettman, A.; Basca, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7548−7552.
(7) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074−13075.
(8) Rubio-Perez, L.; Perez-Flores, F. J.; Sharma, P.; Velasco, L.; Cabrera, A. *Org. Lett.* **2009**, *11*, 265−268.
(9) Wakchaure, V. N.; Zhou, J.; Hoffmann, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 4612−4614.
(10) Werkmeister, S.; Junge, K.; Beller, M. *Green Chem.* **2012**, *14*, 2371−2374.
(11) Lei, Q.; Wei, Y.; Talwar, D.; Wang, C.; Xue, D.; Xiao, J. *Chem. - Eur. J.* **2013**, *19*, 4021−4029.
(12) Malik, G.; Guinchard, X.; Crich, D. *Org. Lett.* **2012**, *14*, 596−9.
(13) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *Nat. Chem.* **2016**, *8*, 144−150.
(14) Chang, M.; Liu, S.; Huang, K.; Zhang, X. *Org. Lett.* **2013**, *15*, 4354−4357.
(15) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266−6267.
(16) Li, W.; Zhang, X., Asymmetric Hydrogenation of Imines. In *Stereoselective Formation of Amines*, Li, W., Zhang, X., Eds.; Topics in Current Chemistry 343;Springer-Verlag: Berlin, 2014; pp 103−144.
(17) Yoshikawa, N.; Tan, L.; McWilliams, J. C.; Ramasamy, D.; Sheppard, R. *Org. Lett.* **2010**, *12*, 276−279.
(18) Xu, H.; Yang, P.; Chuanprasit, P.; Hirao, H.; Zhou, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5112−5116.
(19) Malkov, A. V.; Vrankova, K.; Stoncius, S.; Kocovsky, P. *J. Org. Chem.* **2009**, *74*, 5839−5849.
(20) Guizzetti, S.; Benaglia, M. *Eur. J. Org. Chem.* **2010**, *2010*, 5529−5541.
(21) Jones, S.; Warner, C. J. A. *Org. Biomol. Chem.* **2012**, *10*, 2189−2200.
(22) Orlandi, M.; Tosi, F.; Bonsignore, M.; Benaglia, M. *Org. Lett.* **2015**, *17*, 3941−3943.
(23) Liu, X. W.; Yan, Y.; Wang, Y. Q.; Wang, C.; Sun, J. *Chem. - Eur. J.* **2012**, *18*, 9204−9207.
(24) Wang, Z. Y.; Wang, C.; Zhou, L.; Sun, J. *Org. Biomol. Chem.* **2013**, *11*, 787−797.
(25) Liu, X. W.; Wang, C.; Yan, Y.; Wang, Y. Q.; Sun, J. *J. Org. Chem.* **2013**, *78*, 6276−6280.
(26) Wang, C.; Wu, X. J.; Zhou, L.; Sun, J. *Org. Biomol. Chem.* **2015**, *13*, 577−582.
(27) Ye, J.; Wang, C.; Chen, L.; Wu, X.; Zhou, L.; Sun, J. *Adv. Synth. Catal.* **2016**, *358*, 1042.
(28) Jiang, Y.; Chen, X.; Hu, X. Y.; Shu, C.; Zhang, Y. H.; Zheng, Y. S.; Lian, C. X.; Yuan, W. C.; Zhang, X. M. *Adv. Synth. Catal.* **2013**, *355*, 1931−1936.
(29) Zheng, Y. S.; Xue, Z. Y.; Liu, L. X.; Shu, C.; Yuan, W. C.; Zhang, X. M. *Org. Biomol. Chem.* **2013**, *11*, 412−415.
(30) Hu, X. Y.; Zhang, M. M.; Shu, C.; Zhang, Y. H.; Liao, L. H.; Yuan, W. C.; Zhang, X. M. *Adv. Synth. Catal.* **2014**, *356*, 3539−3544.
(31) Pan, W.; Deng, Y.; He, J. B.; Bai, B.; Zhu, H. J. *Tetrahedron* **2013**, *69*, 7253−7257.
(32) Barrulas, P. C.; Genoni, A.; Benaglia, M.; Burke, A. J. *Eur. J. Org. Chem.* **2014**, *2014*, 7339−7342.
(33) Jones, S.; Zhao, P. C. *Tetrahedron: Asymmetry* **2014**, *25*, 238−244.
(34) Warner, C. J. A.; Reeder, A. T.; Jones, S. *Tetrahedron: Asymmetry* **2016**, *27*, 136−141.
(35) Nara, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Synth. Commun.* **2003**, *33*, 87−98.
(36) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181.
(37) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687−4695.
(38) Pei, D.; Zhang, Y.; Wei, S. Y.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, *350*, 619−623.

DOI: 10.1021/acs.orglett.6b00675
Org. Lett. 2016, 18, 1900−1903