Organic LETTERS

Letter

pubs.acs.org/OrgLett

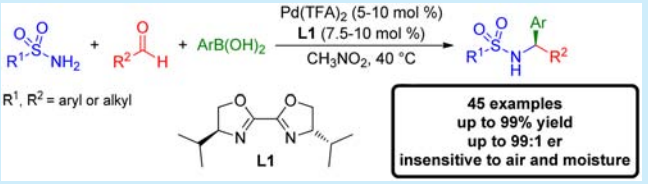
Palladium-Catalyzed Enantioselective Three-Component Synthesis of α-Substituted Amines

Tamara Beisel and Georg Manolikakes*

Department of Organic Chemistry and Chemical Biology, Goethe-University Frankfurt, Max-von-Laue-Strasse 7, 60438 Frankfurt am Main, Germany

Supporting Information

ABSTRACT: The first general palladium-catalyzed, enantioselective three-component synthesis of α-arylamines starting from sulfonamides, aldehydes, and arylboronic acids has been developed. These reactions generate a wide array of α-arylamines with high yields and enantioselectivities. Notably, this process is tolerant to air and moisture, providing an operationally simple approach for the synthesis of chiral α-arylamines.



Chiral α-arylamines are a prevalent structural motif in biologically active natural products and drugs,[1] such as levocetirizine[2] or repaglinide[3] (Figure 1).

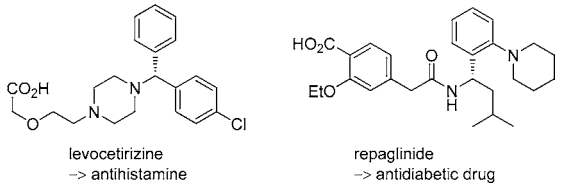
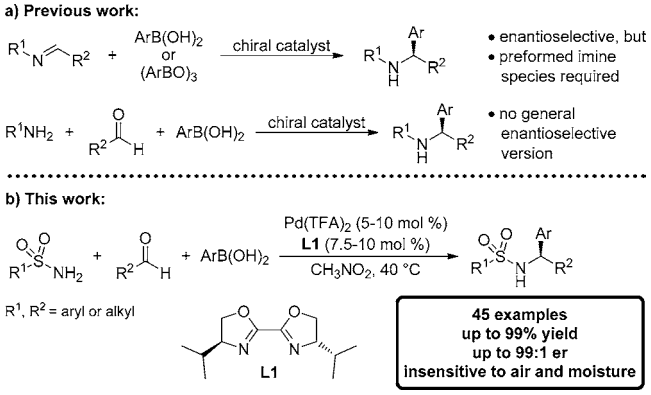


Figure 1. Representative examples of biologically active substances with a chiral α-arylamine motif.

One of the most useful methods for the construction of such molecules is the asymmetric addition of carbon nucleophiles to imines.[4] In past years, transition-metal-catalyzed enantioselective 1,2-additions of organoboron reagents to imines have emerged as a particularly versatile method for the preparation of chiral α-arylamines (Scheme 1a).[5−9] Although a powerful synthetic tool for the enantioselective construction of α-substituted amines, these methods suffer from one common drawback: the utilization of preformed imines. The synthesis of the imine starting materials requires additional resources, time, and energy. Despite the fact that in situ generation of the reactive imine is compatible with transition-metal catalysis, no general enantioselective three-component version has been reported so far.[10] To the best of our knowledge, there is only one report of a palladium-catalyzed enantioselective one-pot synthesis of arylglycine derivatives from ethyl glyoxylate, *p*-toluenesulfonyl isocyanate, and arylboronic acids.[11] In this sequential procedure, the two single steps, formation of the imino ester and addition of the boronic acid, were accomplished in one pot without isolation of the intermediate imine. However, this method is limited to reactive glyoxylates as the aldehyde component utilizes highly reactive and water-sensitive tosyl isocyanate and the sequential procedure hampers operational simplicity. The development of general, operationally simple asymmetric three-component synthesis of important chiral α-arylamines from simple starting materials would be highly desirable.[12,13] Herein, we report the first general palladium-catalyzed enantioselective three-component synthesis of α-branched amines starting from sulfonamides, aldehydes, and arylboronic acids.

Scheme 1. General View of Previous Work and This Report



Based on our previous research on acylimine-based three-component reactions for the preparation of α-substituted amides and amino acids,[14] we expected to perform the more challenging, asymmetric version by using an appropriate chiral catalyst. First, encouraging results were obtained with *p*-toluenesulfonamide as the amide component. After extensive screening (see Supporting Information), we were able to realize a highly enantioselective synthesis of α-substituted amides by using $Pd(TFA)_2$ as catalyst in combination with the easily

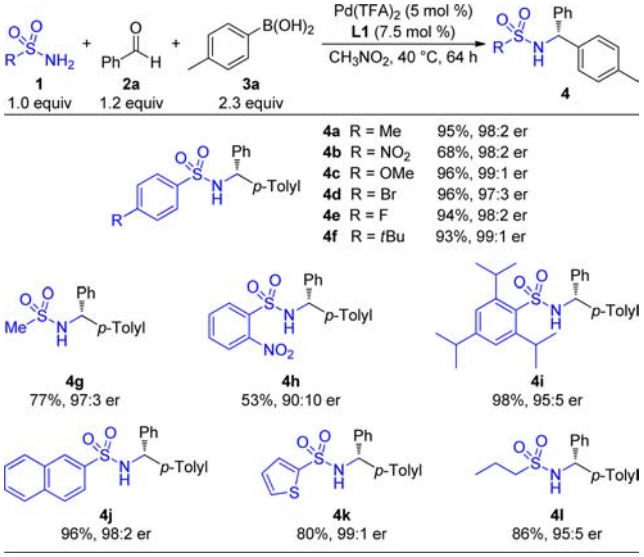
Received: May 22, 2015
Published: June 8, 2015

DOI: 10.1021/acs.orglett.5b01502
Org. Lett. 2015, 17, 3162–3165

accessible chiral bis(oxazoline) ligand **L1** (Scheme 1b). Notably, the reaction can be performed without the exclusion of air or moisture.

With the optimized conditions in hand, we explored the scope of this reaction. A broad range of aromatic and heteroaromatic as well as aliphatic sulfonamides are suitable substrates for the three-component reaction. High yields and enantioselectivities were obtained in all cases (Scheme 2).

Scheme 2. Variation of Sulfonamides[a]



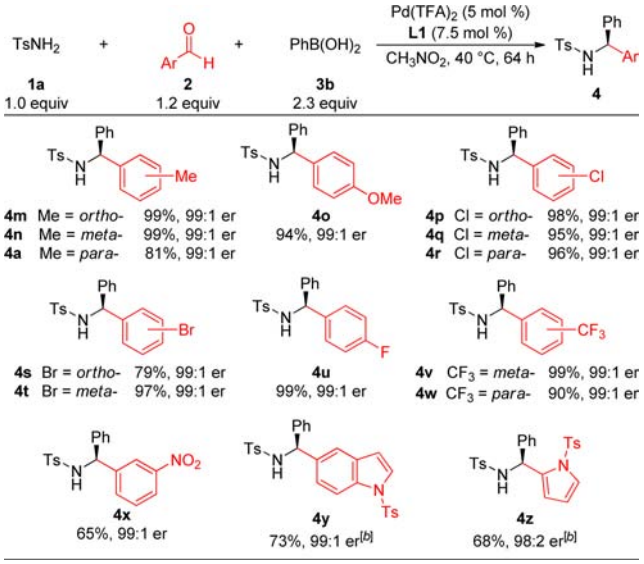
[a]Yield of isolated products. Enantiomeric ratios determined by chiral HPLC analysis.

Electron-donating (**4c**) or -withdrawing (**4b**) as well as halogen substituents for further derivatization (**4d**, **4e**) are well-tolerated. The only exception is 2-nitrobenzenesulfonamide, which furnished product **4h** in only 53% yield and 90:10 er. The reaction with the bulky 2,4,6-triisopropylbenzenesulfonamide afforded the desired amide **4i** in 98% yield and high enantioselectivity (95:5 er).

We further explored the scope in terms of the aldehyde component (Scheme 3). Various aryl aldehydes were found to be efficient starting materials, and the corresponding α-substituted amides were obtained in high yield and enantioselectivity. Aldehydes containing *ortho*-substituents (**4m**), halogens (**4p**–**4u**), or trifluoromethyl groups (**4v**, **4w**) were well-tolerated. Only in the case of strongly electron-poor substrates such as 3-nitrobenzaldehyde were lower yields obtained. To our delight, heteroaromatic aldehydes are suitable substrates for our multicomponent reaction, although a slightly higher catalyst loading is necessary for an efficient reaction. The corresponding heteroaromatic amines **4y** and **4z** could be isolated in good yields and high enantioselectivities.

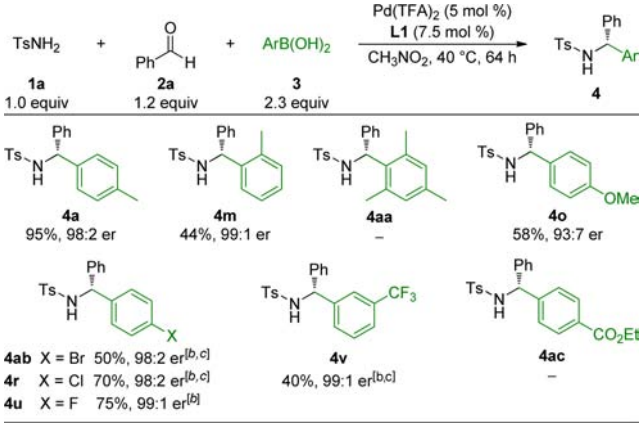
Moreover, various arylboronic acids can be used as a substrate in the three-component reaction (Scheme 4). Unfortunately, the substrate scope in terms of the boronic acid component is not as broad as that for the amide and the aldehyde component. Halogenated or electron-poor boronic acids required a higher catalyst loading to achieve good yields (**4ab**, **4r**–**4v**), and the sterically hindered *o*-tolylboronic acid afforded the desired product **4m** in only 44% yield. Introduction of more steric hindrance in the *ortho* positions (**4aa**) or stronger electron-withdrawing groups (**4ac**) shut

Scheme 3. Variation of Aryl Aldehydes[a]



[a]Yield of isolated products. Enantiomeric ratios determined by chiral HPLC analysis. [b]Reaction performed with 10 mol % of $Pd(TFA)_2$ and 15 mol % of **L1**.

Scheme 4. Variation of Arylboronic Acids[a]



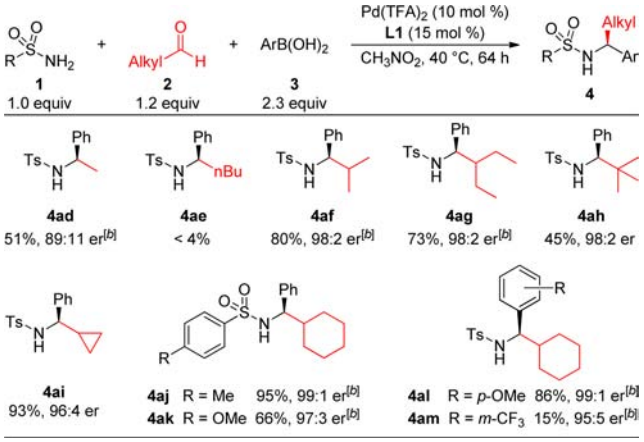
[a]Yield of isolated products. Enantiomeric ratios determined by chiral HPLC analysis. [b]Reaction performed with 10 mol % of $Pd(TFA)_2$ and 15 mol % of **L1**. [c]Reaction performed with 15 mol % of benzoquinone as additive.

down reactivity. In all successful examples, high enantioselectivities were achieved with the exception of the electron-rich *p*-methoxyphenylboronic acid (**4o**, 93:7 er).[15]

Despite the recent advances in enantioselective addition reactions of aryl boron reagents, most reported methods are limited to aromatic imines.[16] Therefore, we investigated reactions with alkyl aldehydes as the aldehyde component. To our delight, different alkyl aldehydes are suitable substrates for our three-component reactions (Scheme 5). Two modifications of our standard reaction conditions are crucial for obtaining high yields of the desired α-aryl alkyl amines. Both a higher catalyst loading of 10 mol % of $Pd(TFA)_2$ and the addition of phenol as an external proton source[17] can increase the yield considerably (see Supporting Information for further details). With these modified conditions, various alkyl aldehydes react with different sulfonamides and arylboronic acids to afford the corresponding aryl alkyl amines in high

DOI: 10.1021/acs.orglett.5b01502
Org. Lett. 2015, 17, 3162–3165

Scheme 5. Variation of Alkyl Aldehydes[a]

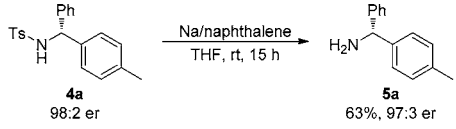


[a]Yield of isolated products. Enantiomeric ratios determined by chiral HPLC analysis. [b]Reaction performed with 3.0 equiv of phenol as additive.

yields and enantioselectivities. With electron-poor boronic acids, low yields are obtained, albeit with high enantioselectivities (**4am**). In general, our method is limited to α-branched alkyl aldehydes, such as isobutyraldehyde or cyclohexylcarbaldehyde (**4af**, **4aj**). Reaction with paraldehyde furnished amine **4ad** in only 51% yield and a lower enantioselectivity (89:11 er). In the case of longer, linear alkyl aldehydes, such as pentanal (**4ae**), no desired product could be isolated.

Removal of the tosyl (Ts) group can be achieved with Na/naphthalene.[18,19] As shown in Scheme 6, the deprotection of **4a** afforded free amine **5a** with complete retention of configuration.

Scheme 6. Removal of the Amine Ts Group[a]



[a]Yield of isolated product. Enantiomeric ratios determined by chiral HPLC analysis.

In summary, we have reported the first general palladium-catalyzed enantioselective three-component synthesis of α-substituted amines from sulfonamides, aldehydes, and arylboronic acids. A wide variety of commercially available starting materials function well in this transformation, delivering products with uniformly high yields and enantioselectivities. Furthermore, this method displays a remarkable tolerance toward air and moisture, and reactions are typically performed in screw-top vials under an atmosphere of air without prior purification of any commercially obtained materials. Finally, a single catalyst system utilizing easily accessible BOX-ligand **L1** provides excellent results, rendering this transformation a practical and operationally simple method for the enantioselective synthesis of α-arylamines. Studies to extend the scope of this method and to investigate the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01502.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: g.manolikakes@chemie.uni-frankfurt.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Fonds der Chemischen Industrie (Liebig Fellowship to G.M.) and the Stiftung Polytechnische Gesellschaft Frankfurt am Main (PhD Fellowship to T.B.). We would like to thank Prof. Michael Göbel (Goethe-University Frankfurt) for his support, and BASF SE, Evonik Industries AG, and Rockwood Lithium GmbH for the generous donation of chemicals.

■ REFERENCES

(1) (a) Ratti, S.; Quarato, P.; Casagrande, C.; Fumagalli, R.; Corsini, A. *Eur. J. Pharmacol.* **1998**, *355*, 77. (b) Plobeck, N.; Delorme, D.; Wei, Z.-Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Sue, S.-Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P.-E.; Projean, D. *J. Med. Chem.* **2000**, *43*, 3878. (c) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692. (d) Carson, J. R.; Coats, S. J.; Codd, E. E.; Dax, S. L.; Lee, J.; Martinez, R. P.; Neilson, L. A.; Pitis, P. M.; Zhang, S.-P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2109. (e) McIntyre, J. A.; Castaner, J. *Drugs Future* **2004**, *29*, 992. (f) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454. (g) Bräse, S.; Baumann, T.; Dahmen, S.; Vogt, H. *Chem. Commun.* **2007**, 1881. (h) French, K. J.; Zhuang, Y.; Maines, L. W.; Gao, P.; Wang, W.; Beljanski, V.; Upson, J. J.; Green, C. L.; Keller, S. N.; Smith, C. D. *J. Pharmacol. Exp. Ther.* **2010**, *133*, 129.

(2) (a) Bloebaum, R. M.; Grant, J. A. *Expert Opin. Pharmacother.* **2004**, *5*, 1581. (b) Chen, C. *Curr. Med. Chem.* **2008**, *15*, 2173.

(3) Massi-Benedetti, M.; Damsbo, P. *Expert Opin. Invest. Drugs* **2000**, *9*, 885.

(4) (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Petrini, M.; Torregiani, E. *Synthesis* **2007**, *2*, 159. (c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626 and references therein.

(5) For Rh-catalyzed 1,2-additions, see: (a) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (c) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307. (d) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (e) Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 2567. (f) Marelli, C.; Monti, C.; Gennari, C.; Piarulli, U. *Synlett* **2007**, *14*, 2213. (g) Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623. (h) Shintani, R.; Narui, R.; Tsutsumi, Y.; Hayashi, S.; Hayashi, T. *Chem. Commun.* **2011**, *47*, 6123. (i) Cui, Z.; Yu, H.-J.; Yang, R.-F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 12394. (j) Brönnimann, R.; Chun, S.; Marti, R.; Abele, S. *Helv. Chim. Acta* **2012**, *95*, 1809. (k) Hirner, S.; Kolb, A.; Westmeier, J.; Gebhardt, S.; Middel, S.; Harms, K.; von Zezschwitz, P. *Org. Lett.* **2014**, *16*, 3162. (l) Ye, J.; Limouni, A.; Zaichuk, S.; Lautens, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 3116.

DOI: 10.1021/acs.orglett.5b01502
Org. Lett. 2015, 17, 3162–3165

(6) For Pd-catalyzed 1,2-additions, see: (a) Ma, G.-N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875. (b) Chen, J.; Lu, X.; Lou, W.; Ye, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2012**, *77*, 8541. (c) Yang, G.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540. (d) Johnson, T.; Lautens, M. *Org. Lett.* **2013**, *15*, 4043.
(7) For Ru-catalyzed 1,2-additions, see: Marques, C. S.; Burke, A. J. *Eur. J. Org. Chem.* **2012**, 4232.
(8) For an achiral Cu-catalyzed variation, see: Liao, Y.-X.; Hu, Q.-S. *J. Org. Chem.* **2011**, *76*, 7602.
(9) For a transition-metal-free variation, see: Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337.
(10) For recent developments of achiral three-component reactions, see: (a) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723. (b) Yu, A.; Wu, Y.; Cheng, B.; Wei, K.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 767. (c) Morin, M. S. T.; Lu, Y.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2012**, *77*, 2013. (d) Frauenlob, R.; García, C.; Bradshaw, G. A.; Burke, H. M.; Bergin, E. *J. Org. Chem.* **2012**, *77*, 4445.
(11) Yu, A.; Wu, Y.; Cheng, B.; Wei, K.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 767.
(12) (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (b) Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371. (c) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (d) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712. (e) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237.
(13) The corresponding Petasis reaction and its asymmetric version are limited to specific substrates: (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169. (c) Ramadhar, T. R.; Batey, R. A. Recent Advances in Nucleophilic Addition Reactions of Organoboronic Acids and Their Derivatives to Unsaturated C−N Functionalities. In *Boronic Acids—Preparation and Applications in Organic Synthesis, Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Vol. *2*, pp 427−477. (d) Koolmeister, T.; Södergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5969. (e) Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017. (f) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922. (g) Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 976.
(14) (a) Beisel, T.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 6046. (b) Halli, J.; Manolikakes, G. *Eur. J. Org. Chem.* **2013**, 7471. (c) Schneider, A. E.; Manolikakes, G. *Synlett* **2013**, *24*, 2057. (d) Schneider, A. E.; Beisel, T.; Shemet, A.; Manolikakes, G. *Org. Biomol. Chem.* **2014**, *12*, 2356.
(15) Reactions with electron-rich heteroaromatic or alkenylboronic acids were unsuccessful. In the case of more reactive boronic acids, we observe only direct addition to the aldehyde and decomposition products. Also, reactions with other arylboron derivatives, such as pinacol boronates, trifluoroboronates, or MIDA-boronates, were unsuccessful.
(16) There are only three reports of Rh-catalyzed enantioselective addition reactions of arylboron reagents to alkyl aldimines; see refs 5g, 5h, and 5i.
(17) (a) Miyamura, S.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 2255. (b) Yu, A.; Wu, Y.; Cheng, B.; Wei, K.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 767.
(18) (a) Niu, F.-L.; Xin, Y.-C.; Wang, R.-L.; Jiang, F.; Xu, P.-F.; Hui, X.-P. *Synlett* **2010**, *5*, 765. (b) Chen, C.-C.; Gopula, B.; Syu, J.-F.; Pan, J.-H.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *J. Org. Chem.* **2014**, *79*, 8077.
(19) The *N*-tosyl group can be easily removed reductively, even in the synthesis of complex molecules. For some recent examples, see: (a) Smith, A. B.; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247. (b) Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969.

DOI: 10.1021/acs.orglett.5b01502
Org. Lett. 2015, 17, 3162−3165