Organic LETTERS

Letter

pubs.acs.org/OrgLett

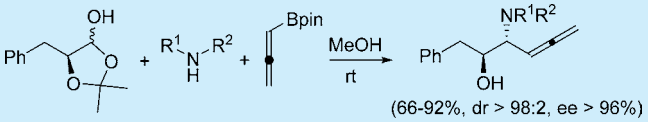
Regioselective and Diastereoselective Borono-Mannich Reactions with Pinacol Allenylboronate

Thanaphat Thaima and Stephen G. Pyne*

School of Chemistry, University of Wollongong, Wollongong, New South Wales 2522, Australia

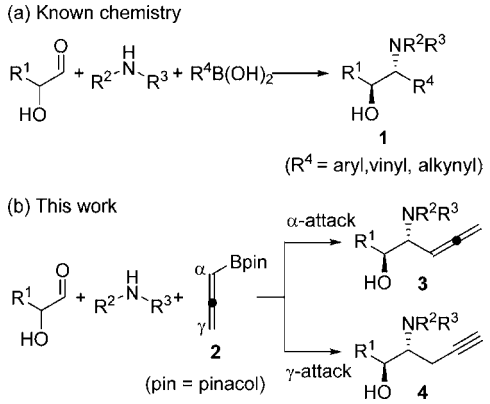
Supporting Information

ABSTRACT: The first documented study of the borono-Mannich (Petasis) reactions of pinacol allenylboronate is described. The reactions of salicylaldehyde and primary and secondary amines are highly regioselective and give homopropargylamine and α-allenylamine products, respectively. In contrast, glycoaldehyde and chiral α-hydroxyaldehydes give exclusively *anti*-β-amino-β-allenyl alcohol products, irrespective of the nature of the amine component. These reactions are highly regio- and diastereoselective and can be employed using an enantiomerically enriched α-hydroxyaldehyde without detectable racemization.



The boronic acid or borono-Mannich reaction (Petasis reaction)[1] is an important, three-component reaction, generally performed between a carbonyl component (usually an aldehyde), a primary (1°) or secondary (2°) amine, and an organoboronic acid or related derivative (boronate or potassium trifluoroborate).[2] These reactions work most efficiently when the carbonyl substrate is an α-hydroxyaldehyde,[2−4] a glyoxylic acid,[2] or a salicylaldehyde.[2,5] Reactions involving α-hydroxyaldehydes and aryl or vinyl boronic acids or boronates reliably produce *anti*-1,2-amino alcohol products **1** in a highly diastereoselective manner (Scheme 1a).[2−4] Asymmetric versions of these reactions using either a chiral Lewis acid or Bronsted acid catalyst are more recent developments.[6] These reactions are well documented for aryl, heteroaryl, vinyl, allyl, and alkynyl boronic acids, boronates, and potassium trifluoroboronates.[2] Related reactions using allenyl boronic acid or boronates, however, have been less widely communicated.[7] Such reactions can potentially provide ready access to β-amino-β-allenyl alcohols **3** or isomeric 2-amino-4-alkynyl alcohols **4**, depending on the regiochemistry of nucleophilic attack (α versus γ) by the allenyl boronic acid or boronate (e.g., pinacol allenylboronate **2**) (Scheme 1b).[8−13] The former allenic compounds **3** are not readily synthetically accessible[14] but are potentially valuable substrates for the synthesis of important heterocycles, including 1,5-dihydropyrrolidines, pyrans, and oxazolidinones, through metal-catalyzed intramolecular cyclization reactions.[15] Further, these heterocyclic derivatives would be valuable intermediates in bioactive alkaloid synthesis.

Scheme 1. Known and Proposed Chemistry



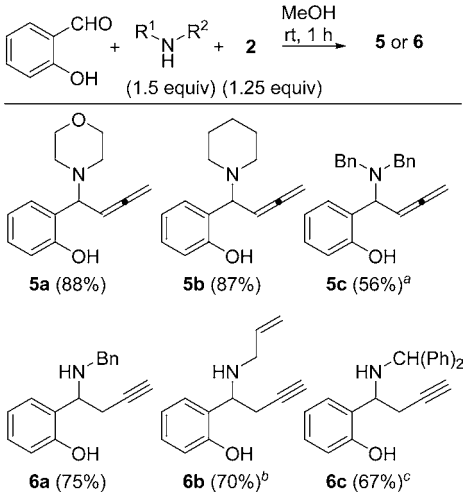
We report here on our study of the borono-Mannich reaction of salicylaldehyde, glycoaldehyde, and chiral α-hydroxyaldehydes with 1° and 2° amines and commercially available pinacol allenylboronate **2**.

The three-component, one-pot reactions of salicylaldehyde, morpholine, and pinacol allenylboronate **2** (1:1:1, molar ratio) were first performed in NMR tubes and were monitored by ^{1}H NMR spectroscopy. The reaction in MeOH-d_4 was complete in 1 h, while a separate reaction in $CDCl_3$ was complete in 20 h. These reactions were completely regioselective for the allene product **5a**, which could be isolated after purification by column chromatography in yields of 52% and 65%, respectively. Small amounts (<10%) of the homopropargyl alcohol product from addition of **2** to salicylaldehyde were also formed. Further optimization studies were performed in MeOH because of the more favorable rate of reaction. Higher yields of **5a** were realized by systematically increasing the molar amounts (1.0, 1.25, or 1.5 equiv) of the amine and/or the boronate components, with the isolated yield rising to 88% when 1.5 equiv of morpholine and 1.25 equiv of **2** were employed (Table 1). Under these reaction conditions, piperidine gave the corresponding allene **5b** in 87% yield. However, the analogous reaction of dibenzylamine required 20 h to achieve a more modest yield of 56% for the allene **5c**. In all cases, the corresponding regioisomeric alkyne product was not observed in the ^{1}H NMR spectrum of the crude reaction product.

Received: November 25, 2014
Published: February 5, 2015

DOI: 10.1021/ol503424k
Org. Lett. 2015, 17, 778−781

Table 1. Products from Salicylaldehyde



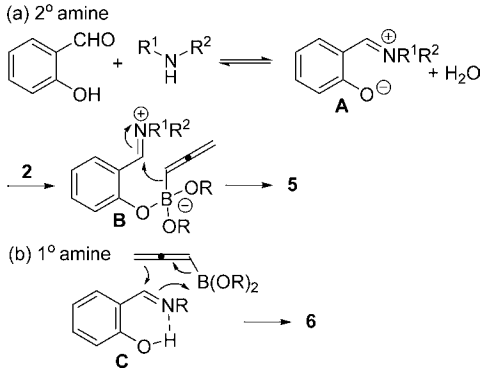
[a]Reaction time 20 h. [b]Reaction time 3 h. [c]Reaction time 9 d, MeOH-d^4/$CDCl_3$ (1:4).

In stark contrast, the reactions of salicylaldehyde, 1° amines (benzylamine, allylamine, and diphenylmethylamine), and **2** were completely regioselective for the alkyne products **6a**–**c** (Table 1). The reaction involving diphenylmethylamine in MeOH took 6 d (55% isolated yield of **6c**) due to the poor solubility of the intermediate imine in MeOH, which precipitated almost immediately upon mixing. This yield was increased to 67% in MeOH-d_4/$CDCl_3$ (1:4).

The analogous reactions of 2-methoxybenzaldehyde, 4-hydroxybenzaldehyde, or benzaldehyde with benzylamine or morpholine and **2** in MeOH (rt, 1–2 d) gave only low yields of the corresponding aldehyde addition products.[16] While the reaction of the preformed *N*-benzylimine of salicylaldehyde and **2** gave **6a** in 87% isolated yield after 24 h at rt, the reaction of the corresponding *N*-benzylimine of 2-methoxybenzaldehyde (rt, 48 h) resulted in mainly recovered unreacted imine. Interestingly, the reactions of salicylaldehyde and 2-methoxybenzaldehyde with **2**, in the absence of the amine component, were highly regioselective and high yielding for the homopropargylic alcohol products (85% and 79%, respectively). Monitoring these reactions by ^{1}H NMR spectroscopy (MeOH-d_4) indicated that they occurred at essentially the same reaction rates, with no evidence for rate acceleration by the 2-hydroxy group of salicylaldehyde. The rates of these reactions (100% conversion after 6 h), however, were considerably slower than those of the three-component reactions of salicylaldehyde, **2**, and benzylamine or morpholine (100% conversion after 1 h, see the Supporting Information).

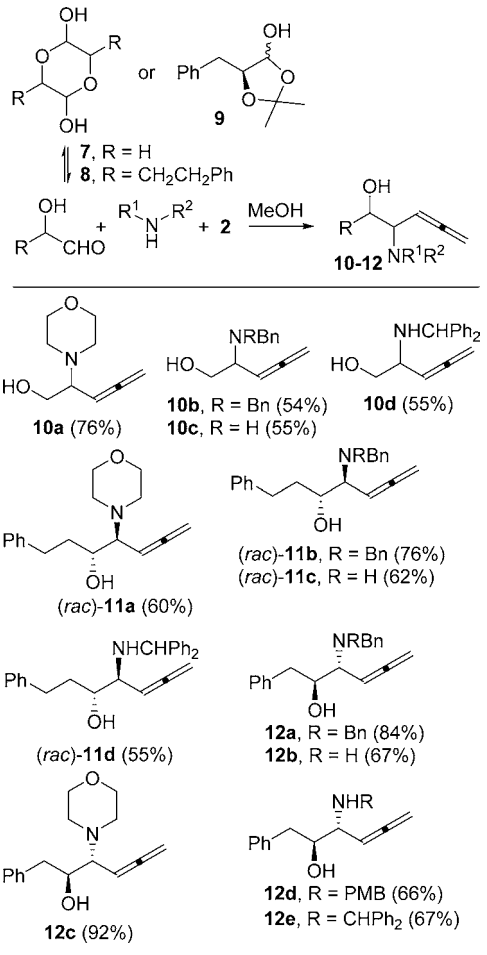
The different regiochemical outcomes between 2° (α-attack of **2**) and 1° (γ-attack of **2**) amines and the activating effect of the 2-hydroxy group can be explained by the intermediates shown in Scheme 2. For 2° amines, the initially formed zwitterion intermediate A can react with **2** to form the boronate intermediate B, which is set up to transfer the allenyl substituent through α-attack via a six-membered transition state, resulting in allenyl product **5** (Scheme 2a). For 1° amines, the reaction may occur through the six-membered transition state C in which the 2-hydroxy group may activate the imine intermediate to γ-attack by allenyl boronate **2** through internal H-bonding (Scheme 2b). However, this is unlikely to be a concerted process as indicated here.

Scheme 2. Possible Reactive Intermediates



The results of our study of the borono-Mannich reactions of glycoaldehyde **7** and the chiral α-hydroxy aldehydes *rac*-**8** and **9** with 1° and 2° amines and **2** are summarized in Table 2. In contrast to the reactions with salicylaldehyde, those using glycoaldehyde (**7**) occurred at a much slower rate. For example, the reaction of glycoaldehyde, morpholine, and **2** (1:1:1, molar ratio) using MeOH as the solvent gave a 42% yield of the β-

Table 2. Products from α-Hydroxyaldehydes



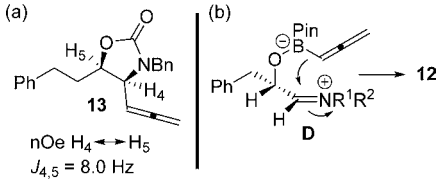
[a]**10a**–**d**: MW 120 °C, 10 min, RCHO/amine/**2** was 1:1:1 (except for **10c**, RCHO/amine/**2** was 1:1.5:1.5). [b]**11a**–**d**: RCHO and amine stirred rt 1 h then **2** added, (RCHO/amine/**2** was 1:1:1), rt, 18 h. [c]**12a**–**e**: rt, 6–24 h, RCHO/amine/**2** was 1:1:1.25 (except for **12a** and **12c**, RCHO/amine/**2** was 1:2:2).

DOI: 10.1021/ol503424k
Org. Lett. 2015, 17, 778–781

amino-β-allenyl alcohol **10a** after 2 d at rt and 70% yield after heating at 50 °C for 8 h. However, heating this mixture in a microwave reactor at 120 °C for 10 min provided **10a** in 76% yield (Table 2). Under similar reaction conditions, the β-amino-β-allenyl alcohols **10b−d** (Table 2) were prepared in more modest yields. In the reactions with benzylamine, the use of a slight excess amount of glycoaldehyde (1.25 equiv) resulted in a lower yield (41%) (perhaps due to further reactions with **10c** or an enhanced yield of aldehyde addition product(s)), whereas increasing the molar equivalents of the other components increased the yields only slightly. The best yield of **10c** (55%) was obtained when glycoaldehyde, benzylamine, and **2** were heated in a 1:1.5:1.5 molar ratio, respectively. In further contrast to the reactions of salicylaldehyde, both 1° and 2° amines gave exclusively allene products. No regioisomeric alkyne products could be detected in the ^{1}H NMR spectra of the crude reaction product mixtures.

In contrast, the reaction of *rac*-**8** with 1° and 2° amines and **2** (1:1:1 molar ratio) proceeded more efficiently at rt. It was found that pretreating the aldehyde dimer with the amine component first for 1−2 h prior to addition of **2** gave better yields of the β-amino-β-allenyl alcohol products **11a−d** (Table 2). In each case, only a single regioisomer and a single diastereomer of each product was observed from analysis of the ^{1}H NMR spectrum of the crude reaction product mixture. Diol products arising from the direct reaction of **2** with **8** could not be isolated, although ^{1}H NMR analysis of the crude reaction mixtures indicated that small amounts of these compounds (5−10%) could have been formed. The *anti*-relative configuration assigned to **11a−d** was based on ^{1}H NMR analysis of the oxazolidinone derivative **13** of **11c** (Scheme 3a). The NOESY spectrum of **13** showed correlations between H-4 and H-5 indicating their *syn*-stereochemical relationship. The magnitude of $J_{4,5}$ (8.0 Hz) was also consistent with this assignment.[17] The *anti*-relative configuration of **11c** is consistent with that found for the products arising from the borono-Mannich reactions of α-hydroxyaldehydes and aryl and vinyl boronic acids[2] and further supports the currently accepted mechanism involving a reactive boronate intermediate, analogous to intermediate **D** in Scheme 3 (b). This would also explain the regioselectivity of these reactions, involving α-attack by the allenyl boronate reagent[2,4c,17]

Scheme 3. (a) Oxazolidinone 13 and (b) Possible Boronate Intermediate D



The reactions of **9** with 1° and 2° amines and **2** (1:1:1.25 molar ratio, respectively) also proceeded in MeOH at rt to produce exclusively the β-amino-β-allenyl alcohol products **12a−e** (Table 2). In the case of **12a**, the yield was 61% due to formation of the ketone, $PhCH_2COCH_2NBn_2$ (17% isolated yield), from the prototropic rearrangement of the initially formed iminium ion. We speculated that the use of an excess amount of **2** would allow more efficient trapping of this intermediate and enhance the yield of **12a** relative to that of the undesired ketone. Thus, repeating this reaction using 2 molar equiv of both Bn_2NH and **2** gave **12a** in 84% yield. Under these same conditions, but using morpholine, the yield of **12c** was also significantly improved from 52% to 92%. The enantiomeric purities (ee's) of **12a** and **12c** were determined to be >96%, nearly the same as that of the chiral α-hydroxyacid precursor of **9** (ee >99%), as determined from ^{19}F and ^{1}H NMR analysis of their *R*- and *S*-Mosher ester derivatives. These derivatives were diastereomerically pure (dr >98:2) by ^{19}F and ^{1}H NMR analysis with each diastereomeric pair showing distinctly different resonances allowing an accurate analysis to be made (see the Supporting Information). The borono-Mannich reactions of other chiral α-hydroxyaldehydes, secondary amines, and vinyl or aryl boronic acids are known to provide 1,2-amino alcohol products in high enantiomeric purities.[3,17,18]

In summary, the borono-Mannich reaction of pinacol allenylboronate **2** with salicylaldehyde and 1° and 2° amines is highly regioselective and gives homopropargyl amine and α-allenyl amine products, respectively. In contrast, glycoaldehyde and chiral α-hydroxyaldehydes give exclusively *anti*-β-amino-β-allenyl alcohol products, irrespective of the nature of the amine component. These reactions are highly regio- and diastereoselective and can be employed using an enantiomerically enriched α-hydroxyaldehyde without detectable racemization. The high product purities, ease of synthesis and purification, and the economically efficient reagent stoichiometries, combined with the highly useful functionality of these products, make this method, and the resulting products, attractive for natural product targeted synthesis and diversity-oriented synthesis programs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C or ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: spyne@uow.edu.au.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the Australian Research Council.

■ REFERENCES

(1) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583.
(2) For reviews see: (a) Pyne, S. G.; Tang, M. *Org. React.* **2014**, *83*, 211. (b) Ramadhar, T. R.; Batey, R. A., In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Wienheim, 2011; pp 427−477. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169.
(3) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
(4) For recent examples, see: (a) Mandai, H.; Yamada, H.; Shimowaki, K.; Mitsudo, K.; Suga, S. *Synthesis* **2014**, *46*, 2672. (b) Bouillon, M. E.; Pyne, S. G. *Tetrahedron Lett.* **2014**, *55*, 475. (c) Jiangseubchatveera, N.; Bouillon, M. E.; Liawruangrath, B.; Liawruangrath, S.; Nash, R. J.; Pyne, S. G. *Org. Biomol. Chem.* **2013**, *11*, 3826. (d) Ghosal, P.; Shaw, A. K. *J. Org. Chem.* **2012**, *77*, 7627. (e) Ascic, E.; Le Quement, S. T.; Ishoey, M.; Daugaard, M.; Nielsen, T. E. *ACS Comb. Sci.* **2012**, *14*, 253. (f) Norsikian, S.; Soule, J.-F.;

DOI: 10.1021/ol503424k
Org. Lett. 2015, 17, 778−781

Cannillo, A.; Guillot, R.; Tran, H. D. M.-E.; Beau, J.-M. *Org. Lett.* **2012**, *14*, 544.
(5) For pioneering work see: (a) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063. (b) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023. (c) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539.
(6) (a) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922. (b) Inokuma, T.; Suzuki, Y.; Sakaeda, T.; Takemoto, Y. *Chem.—Asian J.* **2011**, *6*, 2902. (c) Muncipinto, G.; Moquist, P. N.; Schreiber, S. L.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8172. (d) Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 976. (e) Han, W.-Y.; Zuo, J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2013**, *69*, 537. (f) Shi, X.; Kiesman, W. F.; Levina, A.; Xin, Z. *J. Org. Chem.* **2013**, *78*, 9415.
(7) (a) Petasis, N. A.; Liepouri, F. *Abstracts of Papers*, 232nd National Meeting of the American Chemical Society, San Francisco, CA, Sep 10−14, 2006, American Chemical Society: Washington, DC, 2006; ORGN-482. (b) Petasis, N. A.; Liepouri, F. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, CA, Mar 13−17, 2005, American Chemical Society: Washington, DC, 2005; ORGN-483.
(8) For a review of the reactions of ketones and imines with allenyl and propargyl boronates see: Wisniewska, H. M.; Jarvo, E. R. *J. Org. Chem.* **2013**, *78*, 11629.
(9) For the enantioselective synthesis of α-allenyl alcohols from the reactions of aldehydes or ketones and allenylboronates, see: (a) Kohn, B. L.; Ichiishi, N.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 4414. (b) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 10947. (c) Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616.
(10) For the enantioselective synthesis of homopropargyl alcohols from the reactions of aldehydes or ketones and allenylboronates, see: (a) Reference 9a. (b) Tsai, A. S.; Chen, M.; Roush, W. R. *Org. Lett.* **2013**, *15*, 1568. (c) Reddy, L. R. *Org. Lett.* **2012**, *14*, 1142. (d) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391. (e) Barnett, D. S.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4020.
(11) For the enantioselective synthesis of α-allenyl alcohols from propargylboronates, see: Reddy, L. R. *Chem. Commun.* **2012**, *48*, 9189.
(12) For the enantioselective synthesis of homopropargyl alcohols from propargylboronates, see: (a) Fandrick, K. R.; Ogikubo, J.; Fandrick, D. R.; Patel, N. D.; Saha, J.; Lee, H.; Ma, S.; Grinberg, N.; Busacca, C. A.; Senanayake, C. H. *Org. Lett.* **2013**, *15*, 1214. (b) Fandrick, K. R.; Fandrick, D. R.; Reeves, J. T.; Gao, J.; Ma, S.; Li, W.; Lee, H.; Grinberg, N.; Lu, B.; Senanayake, C. H. *J. Am. Chem. Soc.* **2011**, *133*, 10332. (c) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600.
(13) For the synthesis of α-allenyl amines from the reactions of activated imines with propargyl boronates, see: (a) Mszar, N. W.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3362. For the synthesis of homopropargylamines, see: (b) Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 748.
(14) (a) Badanyan, Sh. O.; Agababyan, R. G.; Asratyan, G. V.; Voskanyan, M. G.; Vartanyan, S. A. *Army. Khim. Zhur.* **1972**, *25*, 133 (CAN 77:19106). (b) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121.
(15) For a review, see: Alcaide, B.; Almendros, P. *Adv. Synth. Catal.* **2011**, *353*, 2561.
(16) Monitoring these reactions involving benzylamine by ^{1}H NMR spectroscopy indicated that the corresponding imines formed rapidly and nearly quantitatively after 10 min in each case.
(17) Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097.
(18) (a) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718. (b) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830.

DOI: 10.1021/ol503424k
Org. Lett. 2015, 17, 778−781