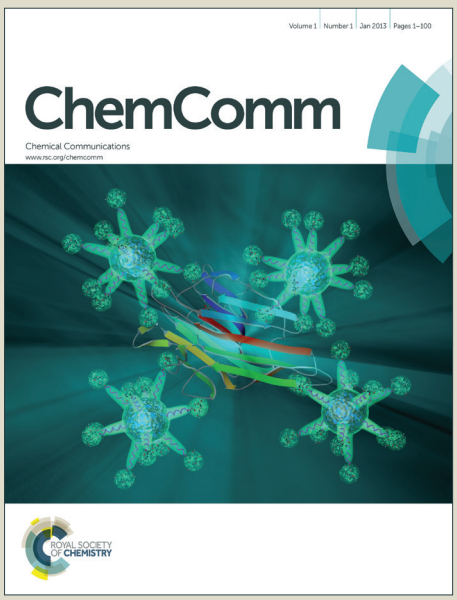
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Palladium-Catalyzed Selective Aminoamidation and Aminocyanation of Alkenes Using Isonitrile as Amide and Cyanide Sources

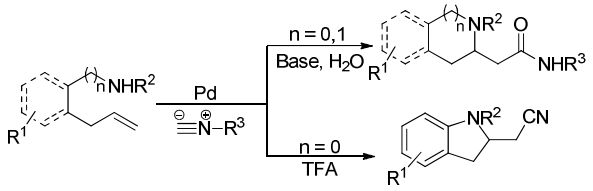
Hanling Gao, Bifu Liu, Wanqing Wu, Huanfeng Jiang*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A mild and efficient palladium-catalyzed intermolecular aminoamidation and aminocyanation of alkenes with a broad substrate scope has been developed. This cyclization process provides a valuable synthetic tool for substituted indolines, tetrahydroisoquinolines and pyrrolidines in good to excellent yields.

The pursuit of concise strategies for the construction of nitrogen-heterocyclic compounds continues to be a long sought after target due to their wide existence in biological and medicinal chemistry. It was an attractive and challenging area of research in organic synthesis to get direct access to a final molecule from readily available substrates. In addition, alkene difunctionalization reactions are an attractive alternative means with significant synthetic potential to rapidly increase molecular complexity.[1] These reactions are particularly appealing and of fundamental importance because they constituted a breakthrough in both organic synthesis and green chemistry.[2] Recently, our group has successfully developed a series of transition-metal-catalyzed alkene difunctionalization reactions, such as diacetoxylation of alkenes and dehydrogenative aminohalogenation of unactivated alkenes *etc*.[3] Meanwhile, alkene aminofunctionalization reactions represent a highly versatile synthetic methods for the synthesis of valuable nitrogen-containing heterocycles and they are studied extensively as well.[4]

In the past decade, prosperous development of transition metal-catalyzed aminofunctionalization reactions have emerged as a very attractive branch of modern organic synthesis.[4g, 4h] Besides palladium[5] catalysts, copper,[6] gold[7] and other metals[8] have also been employed successfully in this catalytic reactions.



Scheme 1 Aminoamidation and aminocyanation of alkenes with isocyanide.

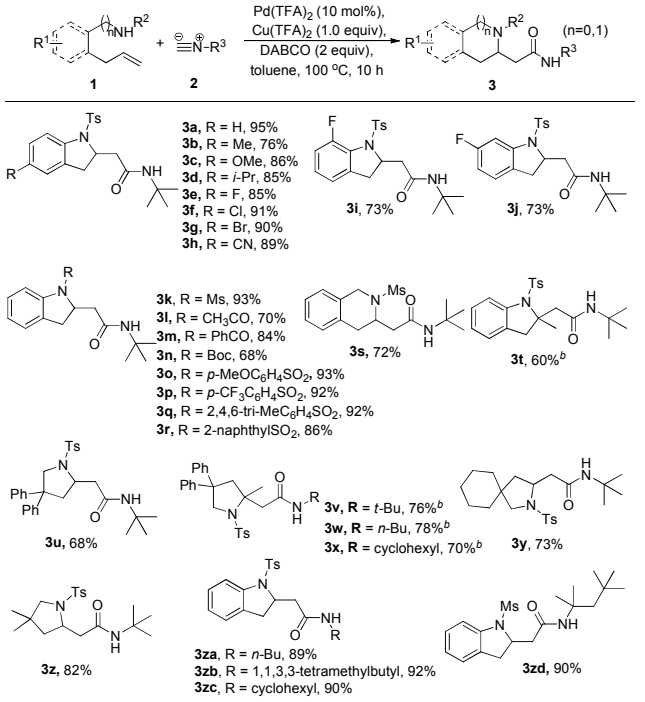
Isocyanides, a class of unsaturated molecules acting as isoelectronic species similar to carbon monoxide, which yet play an irreplaceable role over carbon monoxide for simple operation, an extra diversity point and possibilities for further elaboration using convertible isocyanide.[9] Therefore, it is not surprising that large numbers of reactions with the insertion of isocyanides into the C-Pd bond have sprung up.[10] Recently, we have developed various methods for Pd-catalyzed isocyanides insertion to the synthesis of diversified amides and nitrogen heterocyclic compounds.[11] To our knowledge, isocyanides can be utilized as a source of both carbonyl and amino group to the formation of synthetically useful amide and cyano compounds.[11a,12] Inspired by our previous work[11g] and the related report about alkene aminofunctionalization reaction,[6b] we herein report the first Pd-catalyzed aminoamidation and aminocyanation of alkenes with isocyanide insertion to directly give 2-substituted indolines and pyrrolidines or tetrahydroisoquinolines (Scheme 1), which function as versatile precursors of highly important building blocks such as *β*-amino acids. On the other hand, these class of scaffolds are embedded widely in natural products or designed compounds with a broad range of biological activities.[13]

We began our investigation of the aminoamidation reaction focused on *N*-sulfonyl-2-allylaniline (**1a**) with *tert*-butyl isocyanide (**2a**) as the substrates to screen the reaction conditions. When a solution of **1a** and **2a** in the presence of 10 mol % of different catalysts with $Cu(OAc)_2$ as oxidant and $NaHCO_3$ as the base in dichloroethane at 100 °C under air, the desired product **3a** could be achieved in 48% yield along with 10% of by-product (2-methyl-1-tosyl-1*H*-indole)[14] in the presence of $Pd(TFA)_2$ (Table S1, entry 4; see the Supporting Information), which was superior to any other catalysts. Then an extensive screening concerning copper salts, solvents, additives and temperature revealed that the use of $Cu(TFA)_2$ as oxidant in toluene at 100 °C for 10 h turned out to be the best choice and resulted in 95% yield.

With this optimized reaction conditions in hand, we then surveyed the generality of this aminoamidation reaction (Table 1). With a variety of *para*-substituted *N*-sulfonyl-2-allylanilines as the substrates, we were pleased to find that functional groups both electron-donating (Me, OMe, *i*-Pr) and electron-withdrawing groups (CN, F, Cl, Br) could react smoothly with *tert*-butyl isocyanide, and the corresponding 2-acetamidated indolines (**3a**-**3h**) were obtained in good to excellent yields. Furthermore, *ortho*- and *meta*-substituted of the aromatic ring could be also effectively generated in good yields (**3i** and **3j**). In addition, a

series of substituents on the nitrogen atom were found to be efficiently to give the desired products **3k-3r** in yields ranging from 68% to 93% under the standard conditions. Encouraged by the aforementioned aminoamidation reaction, we extented this catalytic system to the aminoamidation of *N*-(2-allylbenzyl)methanesulfonamide and 4-pentenylsulfonamides for the synthesis of corresponding substituted tetrahydroisoquinolin (**3s**) and pyrrolidines (**3u-3z**) in moderate to good yields. It was noteworthy that alkenes bearing methyl group at the allylic olefinic carbon atoms (**1t, 1v**) could not react with *tert*-butyl isocyanide (**2a**) to give the corresponding product unless employing 2 equivalents of **2a** and raising the temperature to 130 °C. Next, we turned our attention to test the reactivity of *N*-sulfonyl-2-allylaniline (**1a**) and 4-methyl-*N*-(4-methyl-2,2-diphenylpent-4-en-1-yl)benzenesulfonamide (**1v**) with different isocyanides. Alkyl isocyanides such as *n*-butyl isocyanide, 1,1,3,3-tetramethylbutylisocyanide, and cyclohexylisocyanide (**3v-3x**, **3za-3zc**) were found to effectively undergo insertion whereas aromatic isocyanide was unable to provide the desired product.

Table 1. Scope of the Aminoamidation of Alkenes and Isocyanide Insertion [a]

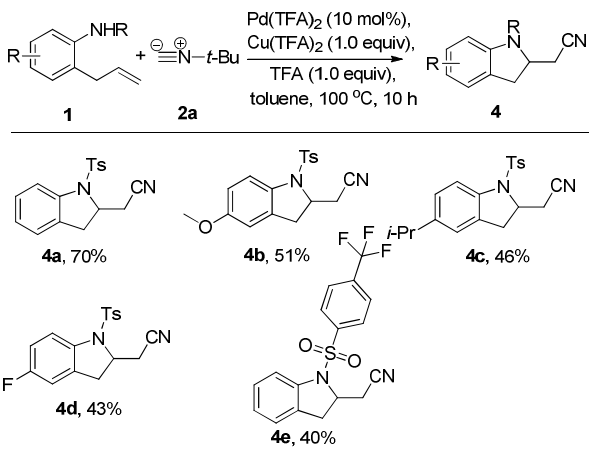


[a] Reaction conditions: all reactions were performed with **1** (0.3 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (10 mol %), DABCO (0.6 mmol), $Cu(OAc)_2$ (0.3 mmol), in toluene (2.0 mL) at 100 °C for 10 h unless otherwise noted. [b] Reactions were performed under 2 equivalents of **2** at 130 °C.

To our expectation, the reaction of *N*-(2-allylphenyl)methanesulfonamides with 1,1,3,3-tetramethylbutylisocyanide proceeded very well to afford the product (**3zd**) in 90% yield under the optimized conditions.

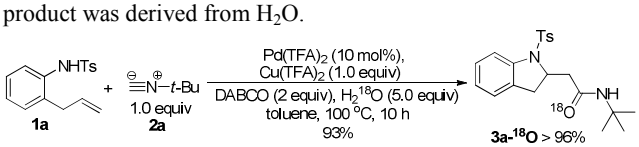
To expand the generality and scope of this tandem reaction, we were excited to detect the aminocyanation products (Table S1, entry 19; see the Supporting Information). Among our exploration of this aminocyanation reaction, electron-donating (**4b** and **4c**) and electron-withdrawing (**4d**) groups of the substrate could go smoothly in this reaction to give the corresponding products in moderate to good yields. Furthermore, different substituent on the nitrogen atom (**4e**) was also well tolerated and provide the desired product in moderate yield.

Table 2. Scope of the Aminocyanation of Alkenes and Isocyanide Insertion [a]



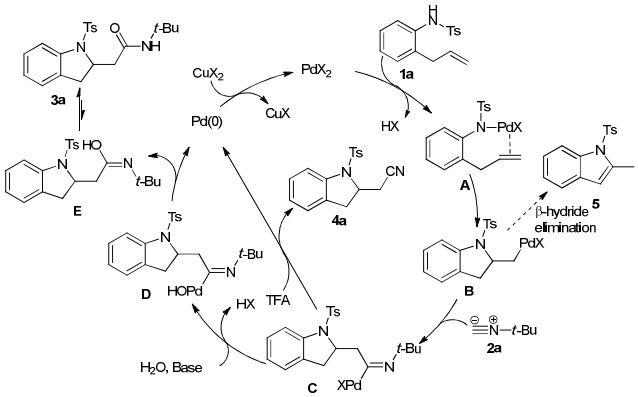
Reaction conditions: all reactions were performed with **1** (0.3 mmol), **2a** (0.36 mmol), $Pd(OAc)_2$ (10 mol %), TFA (0.3 mmol), $Cu(OAc)_2$ (0.3 mmol), anhydrous toluene (2.0 mL) at 100 °C for 10 h

To gain insight into the reaction mechanism, a control experiment was performed as shown in Scheme 2[15]. When *N*-sulfonyl-2-allylaniline (**1a**) and *tert*-butyl isocyanide (**2a**) were treated in anhydrous toluene in the presence of external $H_2{}^{18}O$ (5.0 equiv), **3a-^{18}O** was was obtained nearly as the sole product. This result indicated that the oxygen atom of the amide in the product was derived from H_2O.



Scheme 2. Mechanistic Studies.

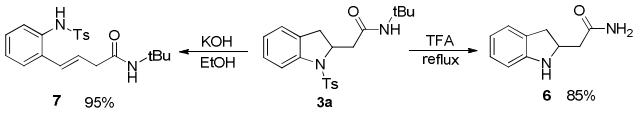
Based on the above results and previous work[16], a possible process of this reaction was proposed in Scheme 3. The reaction was initiated by the reaction of Pd^{II} with **1a** to form the organometallic intermediate **A**. Followed by aminopalladation of intermediate **A** generates the alkylpalladium species **B**, which may undergo β-hydride elimination to give the by-product **5** (2-methyl-1-tosyl-1*H*-indole). Subsequent migratory insertion of **2a**



Scheme 3. Proposed mechanism.

into the alkylpalladium intermediate **B** to generate intermediate **C**. The intermediate **C** might go through two pathways: a) β-tert-butyl elimination of intermediate **C** provides the product **4a** together with concomitant removal of isobutene[17] and the formation of Pd(0); b) with the assistance of the base and H_2O presented in the reaction, intermediate **D** was formed.

In view of the prevalence of primary amide motifs in the natural world, we tested the possibility of forming such amides from our initial products. According to the method reported in the literature,[12e] for example, when *N*-(*tert*-butyl)-2-(1-tosylindolin-2-yl)acetamide (**3aa**) was heated to reflux in trifluoroacetic acid for 24 h, the desired 2-(indolin-2-yl)acetamide (**6**) was obtained in more than 85% yield (Scheme 4). Surprisingly, during our deprotection work, we found an approach to obtain product **7** when **3a** was added KOH in EtOH reflux for 4 h.[18]



Scheme 4. Transformation of *N*-tert-butyl amides **3a**.

In summary, we have demonstrated an efficient and rapid method to the preparation of three important classes of nitrogen heterocycles, 2-substituted indolines, tetrahydroisoquinolins and pyrrolidines from the intermolecular aminoamidation and aminocyanation of alkenes with isocyanide insertion. This protocol proved to be effective for a broad substrate scope in good to excellent yields with operational convenience.

We are grateful to the National Natural Science Foundation of China (21172076), the National Basic Research Program of China (973 Program) (2011CB808600), the Guangdong Natural Science Foundation (10351064101000000), and the Fundamental Research Funds for the Central Universities (2014ZP0004 and 2014ZZ0046).

Notes and references

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China. Fax: +86 20-87112906; Tel: +86 20-87112906; E-mail: jianghf@scut.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

1. (a) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981; (b) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462; (c) K. H. Jensen, J. D. Webb, M. S. Sigman, *J. Am. Chem. Soc.*, 2010, **132**, 17471; (d) L. Liao, R. Jana, K. B. Urkalan, M. S. Sigman, *J. Am. Chem. Soc.*, 2011, **133**, 5784. (e) M. F. Semmelhack, C. Bodurow, *J. Am. Chem. Soc.,* 1984, **106**, 1496; (f) Y. Xia, A. J. Boydston, R. H. Grubbs, Angew. Chem. Int. Ed., 2011, **50**, 5882; (g) D. C. Koester, M. Kobayashi, D. B. Werz, Y. Nakao, *J. Am. Chem. Soc.,* 2012, **134**, 6544; (h) D. M. Schultz, J. P. Wolfe, *Synthesis.,* 2012, **44**, 351; (i) H. Harayama, A. Abe, T. Sakado, M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.,* 1997, **62**, 2113; (j) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.,* 2009, **131**, 9488.

2. M. Hojo, C. Murakami, K. Ohno, J. Kuboyama, S.-y. Nakamura, H. Ito, A. Hosomi, *Heterocycles.* 1998, 47, 97.

3. (a) A. Wang, H. Jiang, H. Chen, *J. Am. Chem. Soc.*, 2009, **131**, 3846; (b) X. Ji, H. Huang, W. Wu, H. Jiang, *J. Am. Chem. Soc.*, 2013, **135**, 5286; (c) L. Huang, H. Jiang, C. Qi, X. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 17652; (d) A. W, H. Jiang, *J. Org. Chem.*, 2010, **75**, 2321.

4. (a) J. P. Wolfe, *Eur. J. Org. Chem.,* 2007, **571**; (b) A. Minatti, K. Muñiz, *Chem. Soc. Rev.,* 2007, **36**, 1142, (c) P. S. Hanley, J. F. Hartwig, *Angew. Chem. Int. Ed.,* 2013, **52**, 8510; (d) G. Liu, X. Lu, *Org. Lett.,* 2001, **3,** 3879; (e) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.,* 2007, **129**, 6328 (f) Z. Pan, S. M. Pound, N. R. Rondla, C. J. Douglas, *Angew. Chem. Int. Ed.*, 2014, **53**, 5170; (g) Y. Miyazaki, N. Ohta, K. Semba, Y. Nakao, *J. Am. Chem. Soc.,* 2014, **136**, 3732; (h) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu, Q. Zhang, *Angew. Chem. Int. Ed.,* 2013, **52**, 2529; (i) K. Muñiz, C. Martínez, *J. Org. Chem.,* 2013, **78**, 2168; (j) F. Cardona, A. Goti, *Nat. Chem.,* 2009, **1**, 269.

5. (a) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.*, 2005, **127**, 7690; (b) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.*, 2006, **128**, 7179.

6. (a) T. W. Liwosz, S. R. Chemler, *J. Am. Chem. Soc.*, 2012, **134**, 2020; (b) F. C. Sequeira, B. W. Turnpenny, S. R. Chemler, *Angew. Chem. Int. Ed.*, 2010, **49**, 6365; (c) T. P. Zabawa, S. R. Chemler, *Org. Lett.*, 2007, **9**, 2035; (d) Y. Luo, K. Ji, Y. Li, L. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 17412; (e) J.-S. Lin, Y.-P. Xiong, C.-L. Ma, L.-J. Zhao, B. Tan, X.-Y. Liu, *Chem. Eur. J.*, 2014, **20**, 1332.

7. (a) W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard, III, F. D. Toste, *Angew.Chem. Int. Ed.*, 2010, **49**, 5519; (b) X.-Y. Liu, C.-H. Li, C.-M. Che, *Org. Lett.*, 2006, **8**, 2707; (c) S. Zhu, L. Ye, W. Wu, H. Jiang, *Tetrahedron.* 2013, **69**, 10375.

8. H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.*, 2007, **46**, 409.

9. A. V. Lygin, A. de Meijere, *Angew. Chem., Int. Ed.*, 2010, **49**, 9094.

10. (a) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.*, 2010, **110**, 5235; (b) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (c) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.*, 2003, **36**, 899.

11. (a) H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang, *Org. Lett.*, 2011, **13**, 1028; (b) Y. Li, J. Zhao, H. Chen, B. Liu, H. Jiang, *Chem. Commun.*, 2012, **48**, 3545; (c) B. Liu, Y. Li, H. Jiang, M. Yin, H. Huang, *Adv. Synth. Catal.*, 2012, **354**, 2288; (d) B. Liu, Y. Li, M. Yin, W. Wu, H. Jiang, *Chem. Commun.*, 2012, **48**, 11446; (e) B. Liu, M. Yin, H. Gao, W. Wu, H. Jiang, *J. Org. Chem.*, 2013, **78**, 3009; (f) B. Liu, H. Gao, Y. Yu, W. Wu, H. Jiang, *J. Org. Chem.*, 2013, **78**, 10319; (g) H. Jiang, H. Gao, B. Liu, W. Wu, *RSC Adv.*, 2014, **4**,17222; (h) H. Jiang, M. Yin, Y. Li, B. Liu, J. Zhao, W. Wu, *Chem. Commun.*, 2014, **50**, 2037.

12. (a) P. Wang, S. J. Danishefsky, *J. Am. Chem. Soc.*, 2010, **132**, 17045; (b) Y. Rao, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.*, 2009, **131**, 12924; (c) C. G. Saluste, R. J. Whitby, M. Furber, *Angew. Chem., Int. Ed.*, 2000, **39**, 4156; (d) S. Xu, X. Huang, X. Hong, B. Xu, *Org. Lett.*, 2012, **14**, 4614; (e) F. Zhou, K. Ding, Q. Cai, *Chem. Eur. J.,* 2011, **17**, 12268.

13. (a) P.-L. Wu, Y.-L. Hsu, C.-W. Jao, *J. Nat. Prod.*, 2006, **69**, 1467; (b) J. B. Bremner, W. Sengpracha, *Tetrahedron.* 2005, **61**, 941; (c) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.*, 1996, **25**, 117; (d) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656.

14. (a) R. C. Larock, T. R. Hightower, L. A. Hasvold, K. P. Peterson, *J. Org. Chem.*, 1996, **61**, 3584; (b) S. R. Fix, J. L. Brice, S. S. Stahl, *Angew. Chem. Int. Ed.*, 2002, **41**, 164. (c) Y. Yin, G. Zhao, *Heterocycles.* 2006, **68**, 23.

15. For details, see supporting information.

16. (a) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics.* 2004, **23**, 5618; (b) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.*, 2005, **127**, 7690; (c) L. S. Hegedus, G. F. Allen, D. J. Olsen, *J. Am. Chem. Soc.*, 1980, **102**, 3583; (d) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.,* 2005, **127**, 7690; (e) P. A. Sibbald, C. F. Rosewall, R. D. Swartz, F. E. Michael, *J. Am. Chem. Soc.,* 2009, **131**, 15945; (f) E. L. Ingalls, P. A. Sibbald, W. Kaminsky, F. E. Michael, *J. Am. Chem. Soc.,* 2013, **135**, 8854; (g) K.-T. Yip, N.-Y. Zhu, D. Yang, *Org. Lett.,* 2009, **11**, 1911; (h) K. Muñiz, C. H. Hövelmann, J. Streuff, J. Am. Chem.

Soc. 2008, **130**, 763; (i) K. Muñiz, J. Streuff, C. H. Hövelmann, A. Núñez, *Angew. Chem.,* 2007, **119**, 7255; (j) K. Muñiz, J. Streuff, C. H. Hövelmann, A. Núñez, *Angew. Chem.,* 2007, **46**, 7125.
17. N. Guimond, K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 12050.
18. See the Suporting Information for details.