Organic LETTERS

Letter

pubs.acs.org/OrgLett

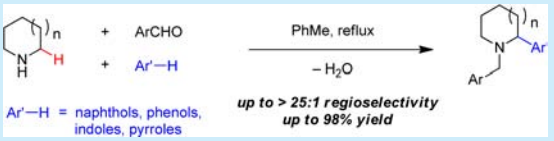
Redox-Neutral α-Arylation of Amines

Weijie Chen, Richard G. Wilde, and Daniel Seidel*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

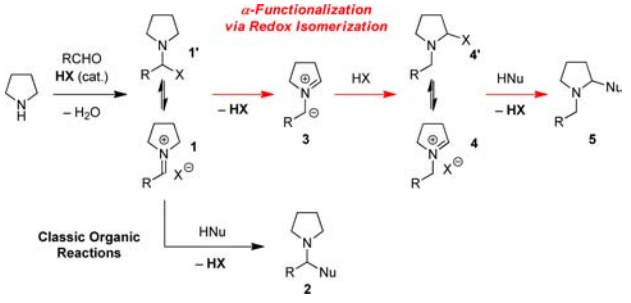
Supporting Information

ABSTRACT: The direct α-arylation/*N*-alkylation of cyclic amines was achieved in a redox-neutral fashion under mild conditions. Transformations occur in the absence of any additives or are promoted by simple carboxylic acids.



Redox-neutral[1] approaches to the α-functionalization of amines offer attractive alternatives to the more prevalent oxidative variants.[2] With regard to the mechanism of these reactions, the majority of redox-neutral amine α-functionalizations involve hydride shifts or sigmatropic H-transfer steps.[3] As part of a broader effort, our group has developed a number of reactions in which amine α-functionalization is accomplished via a different approach that features azomethine ylides as reactive intermediates (Scheme 1).[4−6] Here we report a strategy that enables the redox-neutral α-arylation of simple cyclic amines.

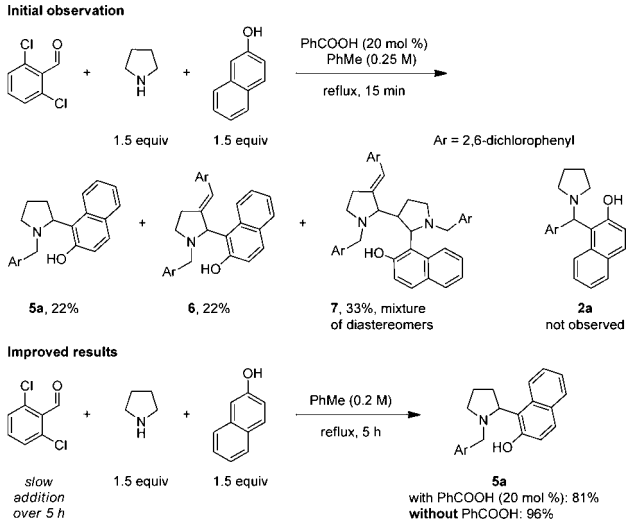
Scheme 1. Concept for Redox-Neutral Amine α-Functionalization



Our approach to the redox-neutral α-functionalization of amines involves the condensation of a secondary amine (e.g., pyrrolidine) with an aldehyde to give intermediates **1**/**1**′ (Scheme 1). These species undergo redox isomerization via azomethine ylide **3** to provide intermediates **4**/**4**′ which are ultimately captured with a nucleophile HNu to yield α-functionalized amine **5**. The difficulty in realizing such transformations lies in the well-established propensity of species **1**/**1**′ to undergo classic organic reactions (e.g., Strecker, Mannich, Kabachnik−Fields reaction, Friedel−Crafts alkylation, alkynylation, etc.). In previous work, we have successfully averted the classic reaction pathway by employing appropriate catalysts such as carboxylic acids or copper carboxylates in combination with sterically demanding aldehydes (e.g., 2,6-dichlorobenzaldehyde, mesitaldehyde). In favorable cases (α-cyanation[4f] and α-phosphine oxide formation[4j]) compounds **2** can undergo equilibration to the apparently thermodynamically more stable regioisomers **5**. This finding enabled the use of simple aromatic aldehydes as reaction partners.

We commenced our efforts toward the development of a redox-neutral amine α-arylation[7−11] by exposing a mixture of pyrrolidine, 2,6-dichlorobenzaldehyde, β-naphthol, and benzoic acid (20 mol %) to reflux in toluene (Scheme 2). Remarkably,

Scheme 2. Initial Results and Optimized Conditions for the α-Arylation of Pyrrolidine with β-Naphthol



the reaction was extremely facile and complete consumption of the aldehyde was noted after 15 min. However, the desired product **5a** was obtained in only 22% yield. In addition, products **6** and **7** were isolated in 22% and 33% yield, respectively. The formation of both **6** and **7** is consistent with the intermediacy of enamines and other species that would be expected along the path to 1,3-dibenzyl pyrroles.[5a] Notably, the "classic" Friedel−Crafts product **2a** was not observed under these conditions. We hypothesized that a consistently low

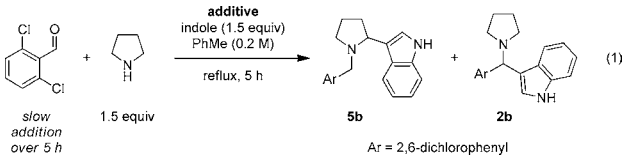
Received: November 26, 2013
Published: December 13, 2013

   dx.doi.org/10.1021/ol403431u | *Org. Lett.* 2014, 16, 730−732

concentration of aldehyde might prevent the formation of undesired byproducts. Consequently, a number of experiments were performed in which the aldehyde was added slowly via syringe pump.[11c] Indeed, with an aldehyde addition time of 5 h, **5a** was isolated in 81% yield. Interestingly, an otherwise identical experiment conducted in the absence of benzoic acid resulted in an improved yield of 96%. Apparently, β-naphthol is sufficiently acidic to promote the required redox isomerization.

A number of experiments were performed in an effort to extend the α-arylation procedure to indole as the nucleophile (Table 1). In the absence of any additive, the reaction provided

Table 1. Evaluation of Reaction Conditions for the α-Arylation of Pyrrolidine with Indole[a]



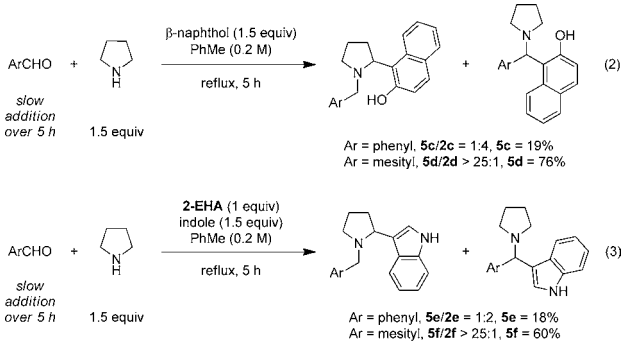
(1)

entry	additive (mol %)	ratio **5b**:**2b**	yield **5b** + **2b** (%)
1	–	1:1.8	76
2	PhCOOH (20)	9.5:1	79
3	4-dimethylamino benzoic acid (20)	11.3:1	81
4	2-ethylhexanoic acid (20)	11.6:1	80
5	2-ethylhexanoic acid (50)	21:1	85
6	2-ethylhexanoic acid (100)	>25:1	86
7[b]	2-ethylhexanoic acid (100)	>25:1	71

[a]Reactions were performed on a 0.5 mmol scale. [b]All reagents were mixed directly and heated in toluene (0.25 M) under reflux for 15 min.

the undesired regioisomer **2b** as the major product (entry 1). The situation improved dramatically upon addition of 20 mol % of benzoic acid (entry 2). In the event, **5b** and **2b** were isolated in a 9.5:1 ratio and 79% combined yield. Carboxylic acids with slightly reduced acidities such as (4-dimethylamino)benzoic acid and 2-ethylhexanoic acid (2-EHA) provided slightly improved results (entries 3–4). Increasing the amount of 2-EHA to 1 equiv led to an almost complete suppression of the undesired regioisomer and a further increase in the yield of **5b** (entry 6). Direct mixing of all components also resulted in an excellent product ratio but lower overall yield compared to the slow addition approach (entry 7).

In order to establish the impact of the aldehyde on product ratios, the reactions of pyrrolidine with either β-naphthol or indole were evaluated with two representative aldehydes, benzaldehyde and mesitaldehyde (eqs 2–3). Consistent with



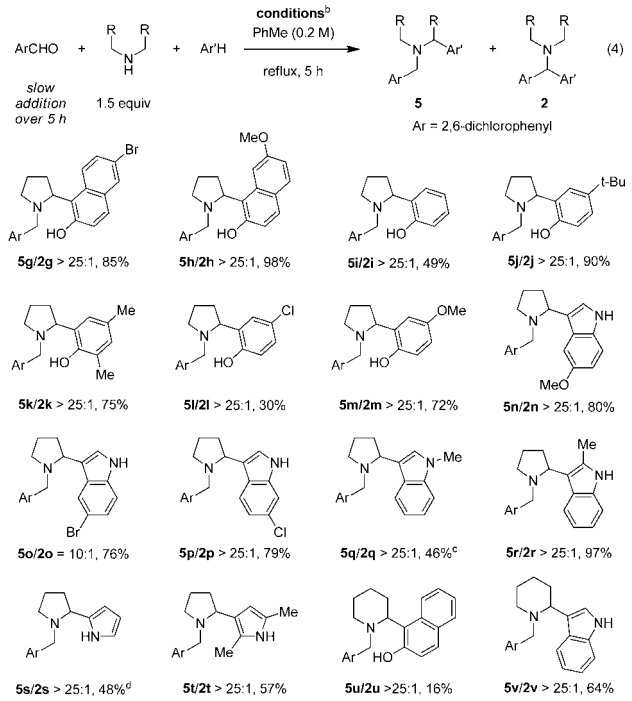
(2)

(3)

our observations in the α-alkynylation,[4g] benzaldehyde gave relatively poor product ratios while mesitaldehyde provided the desired regioisomers with excellent selectivities.

The α-arylation procedure was applicable to various naphthols, phenols, indoles, and pyrroles (Scheme 3). Excellent

Scheme 3. Substrate Scope for the α-Arylation[a]



(4)

[a]Reactions were performed on a 1 mmol scale. Yields correspond to the desired regioisomers. [b] Reactions with β-naphthols and indoles: Ar′H (1.5 equiv); reactions with phenols or pyrroles: Ar′H (5 equiv); reactions with indoles and pyrroles: 2-EHA (1 equiv). [c] 2.5 equiv of 2-EHA were used. [d] A 2,5-disubstituted pyrrole product was isolated as a byproduct in 19% yield (dr = 3:1).

product ratios were obtained in most instances, including with phenols and pyrroles. Notably, these substrates provided poor results in the corresponding decarboxylative three-component reaction that was developed previously by our group.[11c] Piperidine also furnished the corresponding products with excellent regioselectivities, albeit in reduced yields.

In summary, we have developed unprecedented redox-neutral α-arylations of simple cyclic amines that are applicable to a range of naphthols, phenols, indoles, and pyrroles. Further applications of our concept for redox-neutral amine α-functionalization are under development.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seidel@rutchem.rutgers.edu.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ol403431u | *Org. Lett.* 2014, 16, 730–732

■ ACKNOWLEDGMENTS

Financial support from the NIH−NIGMS (Grant R01GM101389-01) is gratefully acknowledged.

■ REFERENCES

(1) Reviews on redox economy and redox-neutral amine α-functionalization: (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (c) Peng, B.; Maulide, N. *Chem.—Eur. J.* **2013**, *19*, 13274.

(2) Selected reviews on amine α-functionalization: (a) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443. (b) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625. (c) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (d) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (e) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (f) Yoo, W. J.; Li, C. J. *Top. Curr. Chem.* **2010**, *292*, 281. (g) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (h) Liu, C.; Zhang, H.; Shi, W.; Lei, A. W. *Chem. Rev.* **2011**, *111*, 1780. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (j) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (k) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (l) Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159. (m) Zhang, C.; Tang, C. H.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (n) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10092. (o) Pan, S. C. *Beilstein J. Org. Chem.* **2012**, *8*, 1374. (p) Platonova, A. Y.; Glukhareva, T. V.; Zimovets, O. A.; Morzherin, Y. Y. *Chem. Heterocycl. Compd.* **2013**, *49*, 357.

(3) Selected recent examples of amine α-functionalization via H-shifts: (a) Barluenga, J.; Fananas-Mastral, M.; Aznar, F.; Valdes, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594. (b) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (c) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (d) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524. (e) Ruble, J. C.; Hurd, A. R.; Johnson, T. A.; Sherry, D. A.; Barbachyn, M. R.; Toogood, P. L.; Bundy, G. L.; Graber, D. R.; Kamilar, G. M. *J. Am. Chem. Soc.* **2009**, *131*, 3991. (f) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (g) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (h) Dunkel, P.; Turos, G.; Benyei, A.; Ludanyi, K.; Matyus, P. *Tetrahedron* **2010**, *66*, 2331. (i) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593. (j) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (k) Cao, W. D.; Liu, X. H.; Wang, W. T.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2011**, *13*, 600. (l) Haibach, M. C.; Deb, I.; De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100. (m) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. (n) Zhou, G. H.; Liu, F.; Zhang, J. L. *Chem.—Eur. J.* **2011**, *17*, 3101. (o) He, Y. P.; Du, Y. L.; Luo, S. W.; Gong, L. Z. *Tetrahedron Lett.* **2011**, *52*, 7064. (p) Jurberg, I. D.; Peng, B.; Woestefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 1950. (q) Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, *134*, 2504. (r) Wang, Y.; Chi, Y.; Zhang, W. X.; Xi, Z. F. *J. Am. Chem. Soc.* **2012**, *134*, 2926. (s) Han, Y. Y.; Han, W. Y.; Hou, X.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2012**, *14*, 4054. (t) Chen, L. J.; Zhang, L.; Lv, J.; Cheng, J. P.; Luo, S. Z. *Chem.—Eur. J.* **2012**, *18*, 8891. (u) He, Y. P.; Wu, H.; Chen, D. F.; Yu, J.; Gong, L. Z. *Chem.—Eur. J.* **2013**, *19*, 5232.

(4) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (b) Deb, I.; Seidel, D. *Tetrahedron Lett.* **2010**, *51*, 2945. (c) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, 233. (d) Deb, I.; Das, D.; Seidel, D. *Org. Lett.* **2011**, *13*, 812. (e) Zhang, C.; De, C. K.; Seidel, D. *Org. Synth.* **2012**, *89*, 274. (f) Ma, L.; Chen, W.; Seidel, D. *J. Am. Chem. Soc.* **2012**, *134*, 15305. (g) Das, D.; Sun, A. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3765. (h) Dieckmann, A.; Richers, M. T.; Platonova, A. Y.; Zhang, C.; Seidel, D.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 4132. (i) Richers, M. T.; Deb, I.; Platonova, A. Y.; Zhang, C.; Seidel, D. *Synthesis* **2013**, *45*, 1730. (j) Das, D.; Seidel, D. *Org. Lett.* **2013**, *15*, 4358.

(5) Examples of related amine redox transformations: (a) Oda, M.; Fukuchi, Y.; Ito, S.; Thanh, N. C.; Kuroda, S. *Tetrahedron Lett.* **2007**, *48*, 9159. (b) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889. (c) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16626. (d) Mao, H.; Xu, R.; Wan, J.; Jiang, Z.; Sun, C.; Pan, Y. *Chem.—Eur. J.* **2010**, *16*, 13352. (e) Ghavtadze, N.; Narayan, R.; Wibbeling, B.; Wuerthwein, E. U. *J. Org. Chem.* **2011**, *76*, 5185. (f) Xue, X. S.; Yu, A.; Cai, Y.; Cheng, J. P. *Org. Lett.* **2011**, *13*, 6054. (g) Zheng, Q.-H.; Meng, W.; Jiang, G.-J.; Yu, Z.-X. *Org. Lett.* **2013**, *15*, 5928. (h) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2013**, *52*, DOI: 10.1002/ange.201308699.

(6) Selected reviews on azomethine ylides: (a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, U.K., 2002; Vol. 59. (b) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (d) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (e) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873. (f) Najera, C.; Sansano, J. M. *Top. Heterocycl. Chem.* **2008**, *12*, 117. (g) Nyerges, M.; Toth, J.; Groundwater, P. W. *Synlett* **2008**, 1269. (h) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

(7) Examples of oxidative amine α-arylation: (a) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (b) Li, Z. P.; Bohle, D. S.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (c) Basle, O.; Li, C. J. *Org. Lett.* **2008**, *10*, 3661. (d) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wunsch, B.; Itami, K. *Chem.—Asian J.* **2009**, *4*, 1416. (e) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnurch, M. *Chem. Commun.* **2010**, *46*, 8836. (f) Jones, K. M.; Karier, P.; Klussmann, M. *ChemCatChem* **2012**, *4*, 51. (g) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (h) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092. (i) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Lett.* **2013**, *15*, 3650. (j) Ratnikov, M. O.; Xu, X. F.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 9475.

(8) Examples of metal catalyzed α-arylations of directing-group bearing amines: (a) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (b) Dastbaravardeh, N.; Schnurch, M.; Mihovilovic, M. D. *Org. Lett.* **2012**, *14*, 1930. (c) Peschiulli, A.; Smout, V.; Storr, T. E.; Mitchell, E. A.; Elias, Z.; Herrebout, W.; Berthelot, D.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2013**, *19*, 10378.

(9) For a radical based approach to amine α-arylation, see: Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568.

(10) Examples of photoredox approaches to amine α-arylation: (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (b) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94. (c) Zhong, J. J.; Meng, Q. Y.; Wang, G. X.; Liu, Q.; Chen, B.; Feng, K.; Tung, C. H.; Wu, L. Z. *Chem.—Eur. J.* **2013**, *19*, 6443.

(11) Related decarboxylative α-arylations of amino acids: (a) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (b) Bi, H.-P.; Chen, W.-W.; Liang, Y.-M.; Li, C.-J. *Org. Lett.* **2009**, *11*, 3246. (c) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798.