

Monophasic Catalytic System for the Selective Semireduction of Alkynes

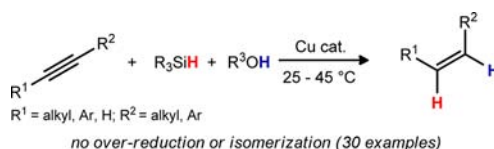
Aaron M Whittaker and Gojko Lalic*

Department of Chemistry, University of Washington, Seattle, Washington 98195, United States

lalic@chem.washington.edu

Received January 20, 2013

ABSTRACT



A highly efficient semireduction of alkynes has been developed. Using 0.5–2 mol % of a copper catalyst, semireduction can be accomplished with a wide range of substrates, including both internal and terminal alkynes without over-reduction. The new method has excellent chemoselectivity, and the semireduction can be accomplished even in the presence of nitro and aryl iodo groups. Finally, commercial availability of a catalyst precursor adds to the appeal of the new catalytic system.

One of the most important transformations of alkynes is their semireduction to alkenes, a transformation usually accomplished using Lindlar¹ or P2 nickel² catalysts. However, both catalysts have significant limitations. P2 nickel is not selective in reductions of terminal alkynes and has to be prepared fresh before each reaction.^{2b} Lindlar catalyst induces *E*–*Z* isomerization and further reduction of the alkene products, thus, strict monitoring of the reaction progress is necessary.³ Over-reduction is even more pronounced with terminal alkynes and alkynes that adsorb well to the catalyst surface, such as arylacetylenes, and alkynes containing polar functional groups.^{3b,4} Finally, the notorious batch variability further complicates the use of the Lindlar catalyst.^{4b}

To address these problems, numerous attempts have been made to control the reactivity of solid-state catalysts by modifications of the catalyst surface.⁵ Although significant progress has been made in the reduction of arylacetylenes with this approach,^{5r–t} few reports also describe selective reduction of terminal alkynes,^{5b,s} which

is still a major challenge.^{5m–o} Similarly, few catalysts have been used for the reduction of alkynes in the presence of nitro or aryl iodo groups.^{5b}

Considerable effort has also been devoted to the development of molecular catalysts of rhodium,⁶ chromium,⁷ palladium,^{4b,8} vanadium,⁹ and other metals.¹⁰ Although

(1) (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446. (b) Lindlar, H.; Dubuis, R. *Org. Synth. Coll.* **1973**, *5*, 880.

(2) (a) Brown, C. A. *Chem. Commun.* **1970**, 139. (b) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.

(3) (a) Molnár, A.; Sárkány, A.; Varga, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 185. (b) Ulan, J. G.; Maier, W. F.; Smith, D. A. *J. Org. Chem.* **1987**, *52*, 3132.

(4) (a) van Laren, M. W.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3715. (b) Kluwer, A. M.; Koblenz, T. S.; Jonischkeit, T.; Woelk, K.; Elsevier, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15470.

(5) Selected examples: (a) Campos, K. R.; Cai, D.; Journet, M.; Kowal, J. J.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 3634. (b) Yabe, Y.; Yamada, T.; Nagata, S.; Sawama, Y.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2012**, *354*, 1264. (c) Gruttadauria, M.; Noto, R.; Deganello, G.; Liotta, L. F. *Tetrahedron Lett.* **1999**, *40*, 2857. (d) Khan, N. A. *J. Am. Chem. Soc.* **1952**, *74*, 3018. (e) Nitta, Y.; Imanaka, T.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3579. (f) Brunet, J. J.; Gallois, P.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1937. (g) Gallois, P.; Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1946. (h) Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 4058. (i) Yoon, N. M.; Park, K. B.; Lee, H. J.; Choi, J. *Tetrahedron Lett.* **1996**, *37*, 8527. (j) Armbrüster, M.; Kovnir, K.; Behrens, M.; Teschner, D.; Grin, Y.; Schlögl, R. *J. Am. Chem. Soc.* **2010**, *132*, 14745. (k) Gruttadauria, M.; Liotta, L. F.; Noto, R.; Deganello, G. *Tetrahedron Lett.* **2001**, *42*, 2015. (l) Mastalir, Á.; Király, Z.; Szöllosi, G.; Bartók, M. *J. Catal.* **2000**, *194*, 146. (m) Nishio, R.; Sugiura, M.; Kobayashi, S. *Org. Biomol. Chem.* **2006**, *4*, 992. (n) Alonso, F.; Osante, I.; Yus, M. *Adv. Synth. Catal.* **2006**, *348*, 305. (o) Shao, Z.; Li, C.; Chen, X.; Pang, M.; Wang, X.; Liang, C. *ChemCatChem* **2010**, *2*, 1555. (p) Mastalir, Á.; Király, Z. *J. Catal.* **2003**, *220*, 372. (q) Panpranot, J.; Phandinthong, K.; Sirikajorn, T.; Arai, M.; Praserttham, P. *J. Mol. Catal. A: Chem.* **2007**, *261*, 29. (r) Weerachawanasak, P.; Mekasuwandumrong, O.; Arai, M.; Fujita, S.-I.; Praserttham, P.; Panpranot, J. *J. Catal.* **2009**, *262*, 199. (s) Hori, J.; Murata, K.; Sugai, T.; Shinohara, H.; Noyori, R.; Arai, N.; Kuroono, N.; Ohkuma, T. *Adv. Synth. Catal.* **2009**, *351*, 3143. (t) Dominguez-Dominguez, S.; Berenguer-Murcia, A.; Pradhan, B. K.; Linares-Solano, A.; Cazorla-Amoros, D. *J. Phys. Chem. C* **2008**, *112*, 3827.

(6) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143.

(7) Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1985**, *50*, 1147.

most homogeneous catalysts developed so far are inferior to Lindlar, some show remarkable selectivity such as those developed by Trost^{8b} and Shibaskaki.⁷ Unfortunately, low yields of the alkene^{8b} or high temperature and hydrogen pressure⁷ make these catalysts impractical. The most significant progress has been achieved using palladium^{4,8a} and copper^{10a} complexes in the semireduction of aryl- and diarylacetylenes.

Overall, while significant progress has been made in developing both homogeneous and heterogeneous catalysts for the semireduction of alkynes, none offer a practical alternative to Lindlar catalyst in terms of substrate scope, selectivity, and the ease of use. As a result, and despite the associated problems, Lindlar catalyst remains the reagent of choice for the semireduction of most alkynes.

Our approach to the development of a selective catalyst for semireduction of alkynes was inspired Sadighi's report describing transmetalation of copper alkoxide with silane, followed by hydrocupration of an alkyne.¹¹ Prompted by these stoichiometric reactions, we decided to explore an alkyne semireduction strategy using hydrometalation followed by protonation of the resulting alkenyl copper.

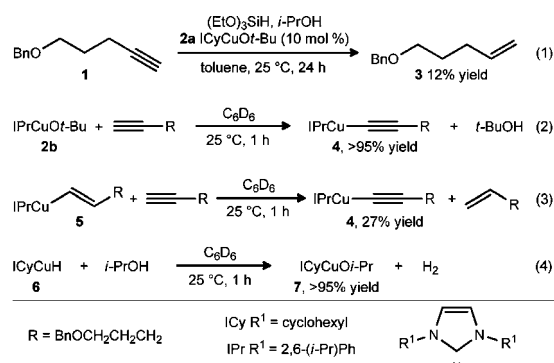
The most appealing aspect of this approach is that it is fundamentally different from the standard delivery of hydrogen through alkyne insertion then reductive elimination. Furthermore, hydrocupration has barely been explored in the context of the semireduction of alkynes. Stryker has reported a stoichiometric reduction of alkynes using 0.5 equiv of $(\text{PPh}_3)\text{CuH}$ and water.¹² However, over-reduction was a significant problem, while derivatives of propargylic alcohols primarily gave allene products. Recently, the first report of a catalytic semireduction of alkynes involving copper hydride was reported.¹³ Tsuji showed that a bisphosphine copper complex can be used as a catalyst in a selective semireduction of activated aryl and diaryl acetylenes. Unfortunately, this catalyst was ineffective in reductions of less reactive simple alkynes. For the six simple substrates examined, three catalysts and four sets of conditions were used, reflecting the difficulties associated with the development of a general catalytic system.

In this paper, we present the development of a copper catalyst that can serve as a practical alternative to Lindlar and P2 nickel catalysts in semireduction of both terminal and internal alkynes.

In initial experiments, we focused on the reduction of terminal alkynes and decided to explore the reduction of **1**

using conditions similar to the stoichiometric reactions by Sadighi.¹¹ Unfortunately, we observed only 12% of the desired alkene product **3**. Through a combination of stoichiometric and competition experiments, we identified three side reactions responsible for the low yield of the catalytic reaction (Scheme 1). The major problem was the formation of catalytically inactive copper acetylide **4** by deprotonation of the alkyne, by the copper alkoxide **2**, or by the alkenyl copper complex **5**. Another obstacle was the protonation of the copper hydride by *i*-PrOH. Although the copper isopropoxide **7** formed in this reaction is catalytically active, this side reaction consumes both the silane and the alcohol.

Scheme 1. Catalytic Reduction of Alkynes and Side Reactions



Through optimization of several components of the catalytic system we were able to suppress all three side reactions. The formation of hydrogen could be suppressed by the use of sterically demanding NHC ligands. For example, in stoichiometric reactions with silane, alcohol, and alkyne, the use of an ICyCuO-*t*-Bu complex resulted in silane consumption by the formation of hydrogen gas (Scheme 2, eq 5), while a complex supported by a sterically demanding IPr ligand suppressed hydrogen formation, and produced alkene as the major product (Scheme 2, eq 6). As shown in eqs 7 and 8 (Scheme 2), the choice of silane had a significant effect on the formation of the copper acetylide. With highly reactive PMHS (polymethylhydrosiloxane) the copper alkoxide is engaged in a fast transmetalation, and deprotonation of the alkyne is completely suppressed.

The results of the experiments shown in Scheme 2 guided our optimization of the catalyst and the silane and allowed us to achieve the complete conversion in the catalytic semireduction of alkyne **8** (Table 1, entries 1–6). Increasing the amount of *t*-BuOH to 10 equivalents resulted in an increase in the rate of the reduction (entry 7), but for the complete conversion, 2 mol % of the catalyst was still necessary. We suspected that the side reaction shown in eq 3, although slow, was responsible for removing the active catalyst from the reaction mixture. Indeed, we found that in the presence of a stronger acid (*i*-BuOH) that increases the rate of protonation of alkenyl copper intermediate, 0.5 mol % of the catalyst was sufficient for the complete reduction of the alkyne in less than 1 h (Table 1, entry 8).

(8) (a) Hauwert, P.; Maestri, G.; Sprengers, J. W.; Catellani, M.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3223. (b) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657. (c) Li, J.; Hua, R.; Liu, T. *J. Org. Chem.* **2010**, *75*, 2966.

(9) La Pierre, H. S.; Arnold, J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 3900.

(10) (a) Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542. (b) Belger, C.; Neisius, N. M.; Plietker, B. *Chem.—Eur. J.* **2010**, *16*, 12214.

(11) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

(12) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397.

(13) During our work on this project, Tsuji reported selective reduction of a wide range of mostly aryl and diaryl acetylenes using the same approach. See ref 10a.

Scheme 2. Optimization of the Catalytic System

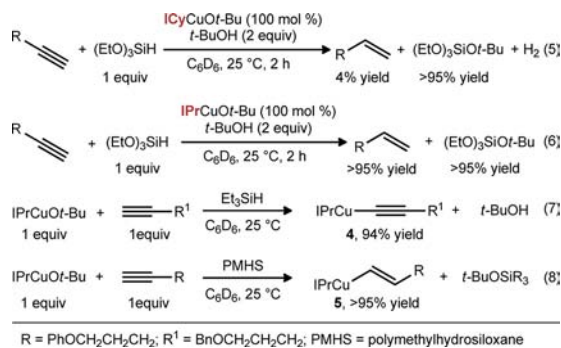


Table 1. Reaction Optimization

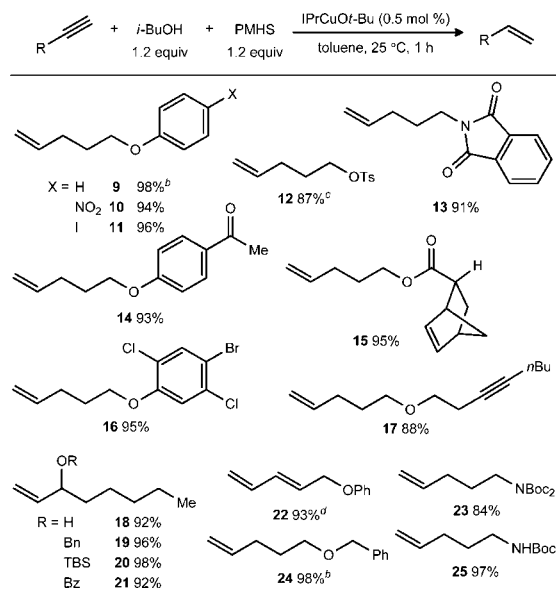
entry ^a	L	catalyst (mol %)	silane	ROH	time (h)	yield ^b (%)
1	ICy	2.0	(EtO) ₃ Si	<i>t</i> -BuOH	8	19
2	IMes	2.0	(EtO) ₃ Si	<i>t</i> -BuOH	8	69
3	SiPr	2.0	(EtO) ₃ Si	<i>t</i> -BuOH	8	61
4	<i>i</i> -Pr	2.0	(EtO) ₃ Si	<i>t</i> -BuOH	8	90
5	<i>i</i> -Pr	2.0	Et ₃ Si	<i>t</i> -BuOH	8	<5
6	<i>i</i> -Pr	2.0	PMHS	<i>t</i> -BuOH	8	>98
7 ^c	<i>i</i> -Pr	2.0	PMHS	<i>t</i> -BuOH	1	>98
8 ^c	<i>i</i> -Pr	0.5	PMHS	<i>t</i> -BuOH	1	65
9 ^d	<i>i</i> -Pr	0.5	PMHS	<i>i</i> -BuOH	1	>98

^a ROH (2.0 equiv), R₃SiH (2.0 equiv), 25 °C, toluene. ^b Determined by GC. ^c 10 equiv of *t*-BuOH used. ^d *i*-BuOH (1.2 equiv), PMHS (1.2 equiv), 25 °C, toluene.

Optimal results are obtained using just 0.5 mol % of the catalyst and a slight excess (1.2 equiv)¹⁴ of PMHS and isobutyl alcohol, which facilitates product isolation. It is worth noting that PMHS is readily available, air stable, cost-effective, and nontoxic and has a minimal environmental impact.¹⁵ Under optimized reaction conditions, selective semireduction of a wide range of terminal alkynes is accomplished within one hour at room temperature (Scheme 3). The semireduction can be achieved in the presence of nitroarenes, aryl halides, esters, sulfonates, carbamates, imides, alcohols, and ethers.

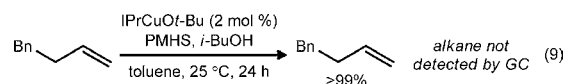
Although very similar conditions have been used for the reduction of ketones,¹⁶ they are also well tolerated in this reaction (14). Terminal alkynes are selectively reduced in the presence of both strained alkenes and internal alkynes (15 and 17). These two transformations are particularly difficult to accomplish using the currently available

Scheme 3. Catalytic Semireduction of Terminal Alkynes^a



^a Reactions were performed on 1 mmol scale. Yields of isolated products are reported, unless otherwise noted. ^b Determined by GC analysis. ^c IPrCuOt-Bu (2 mol %). ^d From 5-phenoxy-pent-3-ene-1-yne.

reagents. A propargylic alcohol and a variety of its derivatives, were reduced to the corresponding allylic derivatives (18–21) without any overreduction, a common problem with most catalysts.^{4,5a,5b,5n,5s} The formation of the corresponding allene product was not observed either, although similar conditions have been used in transformations of propargylic carbonates to allenes.¹⁷ Finally, terminal 1,3-enynes are selectively reduced to 1,3-dienes (22). Overall, the remarkable chemoselectivity of our catalytic system is complementary to the chemoselectivity of catalysts currently used for the semireduction of alkynes. It is important to note that we did not observe the formation of alkane products in any of the reactions shown in Scheme 3. Even with prolonged exposure of 1-phenyl-1-butene to the standard reaction conditions no over-reduction occurred (eq 9).



We also found that by using a closely related set of reaction conditions we could accomplish a stereoselective semireduction of internal alkynes. The major difference is that *t*-BuOH was the preferred proton source and that the reduction had to be performed at the slightly elevated temperature (45 °C). Under the optimal conditions internal alkynes could be reduced in the presence of benzyl ethers, nitro arenes, nitriles, aryl bromides, alkyl chlorides, imides, esters, alkenes, and alcohols (Scheme 4). Again, the derivatives of propargylic alcohols could be reduced to

(14) Equivalents of PMHS refer to the equivalents of Si-H units present in the amount of PMHS used in the experiment.

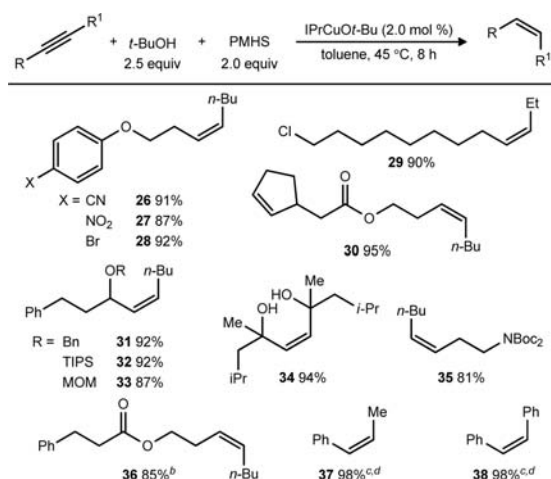
(15) (a) Klyaschitskaya, A. L.; Krasovskii, G. N.; Fridlyand, S. A. *Gig. Sanit.* **1970**, 35, 28. (b) J. Lawrence, N.; D. Drew, M.; M. Bushell, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381. (c) Jacquet, O.; Das Neves Gomes, C.; Ephritikhine, M.; Cantat, T. *J. Am. Chem. Soc.* **2012**, 134, 2934.

(16) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, 70, 4784.

(17) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett.* **2009**, 11, 5010.

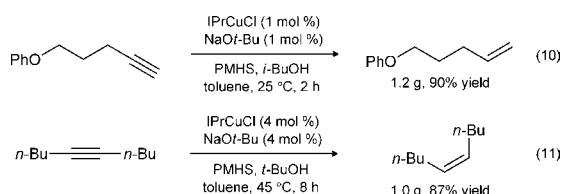
allylic alcohol derivatives. With all substrates, we observed the exclusive formation of the *Z* alkene, and we did not observe further reduction of the alkene products. It is important to note that at elevated temperatures aryl acetylenes are the only substrates with which we observed the formation of the alkane product. However, at 25 °C the *Z* alkene was the only product observed.

Scheme 4. Catalytic Semireduction of Internal Alkynes^a



^a Reactions were performed on a 1 mmol scale. Yields of isolated products are reported, unless otherwise stated. ^b *t*-BuOH (3.5 equiv), PMHS (3 equiv), α , β -unsaturated ester also reduced in the process. ^c GC yield. ^d Reaction performed at 25 °C.

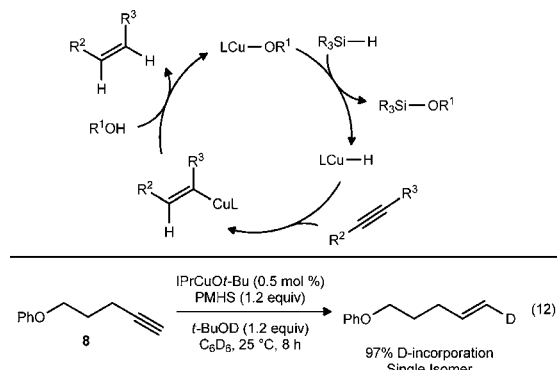
To demonstrate the synthetic utility of the new method, we have performed gram-scale reactions using commercially available and air stable IPrCuCl as a catalyst precursor. As shown in eqs 10 and 11, both terminal and internal alkynes can be reduced to the corresponding alkenes using this procedure.



We propose that the mechanism of the semireduction involves copper hydride formation, hydrocupration of the alkyne, then protonation of the alkenyl copper intermediate by the alcohol to form the copper alkoxide and the desired product (Scheme 5). Stoichiometric reactions performed by Sadighi,¹¹ Tsuji,^{10a} and us¹⁸ support each of these elementary steps. We have also shown that any of the three proposed intermediates can be used as catalysts in the reaction. Furthermore, a deuterium labeling experiment resulted in high deuterium incorporation (>97%) and regioselectivity (Scheme 5, eq 12). This observation contrasts lower deuterium incorporation observed in

experiments by Tsuji^{10a} and Lipshutz¹⁹ and suggests that there is no exchange between copper hydride and *t*-BuOH.

Scheme 5. Proposed Mechanism



We have also explored the difference in the reactivity of terminal and internal alkynes. In a reduction of terminal alkyne **8** performed in the presence of 10 mol % of IPrCuO-*t*-Bu and *t*-BuOH monitored by in situ ¹H NMR, only alkenyl copper was observed throughout the course of the reaction,¹⁸ indicating an alkenyl copper catalyst resting state. In a similar experiment performed with 6-dodecyne, we only observed copper hydride as the catalyst resting state.¹⁸

Overall, the difference in the rate of hydrocupration of terminal and internal alkynes allows us to understand the use of two different alcohols. With terminal alkynes, a less acidic proton source results in rate-limiting protonation of the alkenyl copper intermediate and can lead to the catalyst deactivation according to eq 3 (Scheme 1). In reactions of internal alkynes, hydrocupration is rate-limiting, and faster protonation of the alkenyl copper intermediate is unimportant. Instead, protonation of the copper hydride intermediate is a major concern, and the less acidic *t*-BuOH is the optimal proton source.

In conclusion, we have developed a highly efficient catalytic method for the selective semireduction of alkynes. Essential for the reaction development was an understanding of the mechanism and the competing processes. The new method can be used with a wide range of substrates, including both internal and terminal alkynes. Furthermore, the new method has excellent chemoselectivity, complementary to Lindlar and P2 nickel catalysts. Finally, practical reaction conditions (25 or 45 °C, low catalyst loading, monophasic mixture), together with the commercial availability of a catalyst precursor add to the systems appeal.

Acknowledgment. We thank the University of Washington and NSF (CAREER Award 1254636) for financial support.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

(18) See the Supporting Information for details.

(19) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352.