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Ring Lithiation and Functionalization of Imidazol-2-ylidene-boranes

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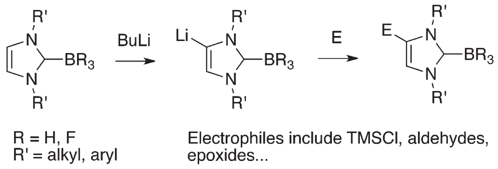
ABSTRACT



***N,N′*-Dialkyl and *N,N′*-diaryl imidazol-2-ylidene-boranes and trifluoroboranes are rapidly lithiated at C4 of the imidazole ring, and the resulting intermediates have been quenched with an assortment of electrophiles to provide ring-functionalized imidazol-2-ylidene-boranes. Further deprotonation and functionalization of C5 have been demonstrated. Deboronation of the products by treatment with triflic acid or iodine and then methanol opens a route to C4/C5 functionalized imidazolium salts and imidazol-2-ylidenes.**

N-Heterocyclic carbenes (NHC) and their metal and main group complexes are important reagents and catalysts for synthesis of molecules and materials alike.[1] Relatively stable imidazol-2-ylidenes **B** (Figure 1) are a popular class of NHC ligands for the preparation of catalytically active complexes **C** with transition metals[2] and for the stabilization of unusual states of main group elements.[3] Carbenes **B** and complexes **C** lacking substituents on the ring carbon atoms (R^4 = R^5 = H) are easily prepared from common imidazolium salts **A**.[4]

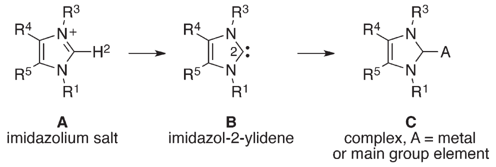


Figure 1. General structures of imidazolium salts, imidazol-2-ylidenes, and complexes thereof (formal +/− charges on **C** and related structures are omitted for simplicity).

Substitution at C4 and C5 in free imidazol-2-ylidene carbenes **B** or carbene complexes **C** (R^4, $R^5 \neq$ H) allows for tuning steric or electronic properties[5] or for attaching a handle for further functionalization, easier separation, or recycling. The main strategy to introduce such substituents is to make suitably substituted acyclic precursors first (e.g., 1,2-diimines) and then to form the imidazolium ring **A**.[4] Such processes can take several steps and may not be compatible with a broad range of R^4 and R^5 groups.

For many substituents R^4 and R^5, it would be convenient to make more substituted carbenes **B** or complexes **C** from less substituted ones, and ring metalation followed by electrophilic substitution is an appealing strategy.[6] However, the direct application of this strategy to imidazolium salts **A** is complicated because H^2 is much more acidic than H^4. Indeed, the acidity of H^2 is the basis of carbene formation.

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(1) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122–3172.

(2) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.

(3) (a) Wang, Y.; Robinson, G. H. *Inorg. Chem.* **2011**, DOI: 10.1021/ic200675u. (b) Carmalt, C. J.; Cowley, A. H. *Advances in Inorganic Chemistry*; Academic Press: 2000; Vol. 50, pp 1–32.

(4) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705–2733.

(5) Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940–6952.

(6) (a) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722. (b) Snieckus, V.; Macklin, T. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005, p 106–118.

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Bertrand has used strong bases to functionalize the C4 position of C2-substituted imidazolium salts via so-called abnormal carbenes,[7] and Robinson has deprotonated the C4 position of the free carbene *N*,*N*′-(2,6-diisopropylphenyl)imidazol-2-ylidene.[8] The resulting lithio-carbene was quenched with TMSCl and BH_3. Direct borylation of carbenes by very strong electrophiles is also possible.[9] Imidazol-2-ones[10] and -2-thiones[11] are also useful NHC precursors that can be functionalized by metalation. Metalated carbene-lanthanide[12] and carbene-phosphinidene[13] complexes have also been described.

Carbene-boranes[14] are an increasingly valuable class of synthetic reagents[15] and polymerization co-initiators,[16] spurring demand for ring-functionalized variants. Such boranes are very stable, and their B−H protons are weakly basic, not acidic.[17] Cavel observed fluorine promoted H/D exchange on the imidazolylidene rings of an unusual bis-carbene trifluoroborane under forcing conditions (100 °C, 100 h).[18] Later, we described the first example of a ring-metalated carbene trihydridoborane (see below).[19] And recently Roesky reported the deprotonation of dipp-Imd-BH_3 (**1d**) by BuLi and solved the crystal structure of the lithiated intermediate (**2** with R = H, R′ = dipp).[20]

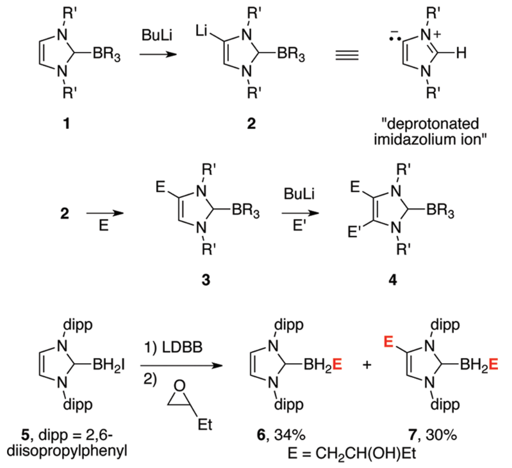

Figure 2. Proposed generation and trapping of lithiated carbene-boranes (top) and a clue that such reactions were possible (bottom).

Here we show that direct lithiation of *N*,*N*′-disubstituted imidazol-2-ylidene-boranes **1** is a general reaction that has significant preparative value. Onward reactions of the resulting lithiated intermediates **2** with electrophiles (E) to form diverse new ring-substituted carbene-boranes **3** are studied (Figure 2, top). Repeat metalation and functionalization of C5 to give **4** are also demonstrated. Sample deboronation reactions prove the principle that lithiated reagent **2** is the synthetic equivalent of the imaginary "deprotonated imidazolium ion" synthon.

We recently developed a procedure for reductive lithiation of boron−halide bonds of such complexes by reaction of boryl iodide **5** with lithium di-*tert*-butylbiphenylide (Figure 2, bottom).[19] Trapping of this intermediate with ethyloxirane provided the expected B-alkylated product **6** in 34% yield with substantial amounts (30%) of a bis-B/C-alkylated product **7**, evidently a secondary product derived from deprotonation of **6** at C4.

Preliminary experiments showed that BuLi was a convenient base for deprotonation. Table 1 shows the results of lithiation and silylation of a series of imidazolylidene complexes NHC-BH_3 (**1a**−**e**) bearing different *N*-substituents. The carbene-boranes are all known and readily available. In a typical experiment, 1 equiv of BuLi was added to a solution of diiPr-Imd-BH_3 **1a** in THF. After 5 min, the resulting anion was quenched by addition of 1.1 equiv of trimethylsilyl chloride. Standard workup and flash chromatography provided C4-silylated product **8a** in 93% isolated yield (entry 1).

Good yields of C4-silylated products were obtained with several *N*-alkyl (entries 1−3) and *N*-aryl (entries 4−5) substituted imidazol-2-ylidene-boranes. The products of the reactions **8a**−**e** are generally stable white solids that are

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(7) Mendoza-Espinosa, D.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2010**, *132*, 7264–7265.

(8) (a) Wang, Y.; Xie, Y.; Abraham, M. Y.; Wei, P.; Schaefer, H. F.; Schleyer, P. v. R.; Robinson, G. H. *J. Am. Chem. Soc.* **2010**, *132*, 14370–14372. (b) Wang, Y.; Xie, Y.; Abraham, M. Y.; Wei, P.; Schaefer, H. F.; Schleyer, P. v. R.; Robinson, G. H. *Organometallics* **2011**, *30*, 1303–1306.

(9) For a recent example, see: Kronig, S.; Theuergarten, E.; Holschumacher, D.; Bannenberg, T.; Daniliuc, C. G.; Jones, P. G.; Tamm, M. *Inorg. Chem.* **2011**, *50*, 7344–7359.

(10) Llopart, C. C.; Ferrer, C.; Joule, J. A. *Can. J. Chem.* **2004**, *82*, 1649–1661.

(11) Arduengo, A. J., III; Bannenberg, T. P.; Tapu, D.; Marshall, W. J. *Chem. Lett.* **2005**, *34*, 1010–1011.

(12) Arnold, P. L.; Liddle, S. T. *Organometallics* **2006**, *25*, 1485–1491.

(13) Wang, Y.; Xie, Y.; Abraham, M. Y.; Gilliard, R. J.; Wei, P.; Schaefer, H. F.; Schleyer, P. v. R.; Robinson, G. H. *Organometallics* **2010**, *29*, 4778–4780.

(14) Curran, D. P.; Solovyev, A.; Makhlouf Brahmi, M.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 10294−10317.

(15) (a) Ueng, S.-H.; Makhlouf Brahmi, M.; Derat, E.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *J. Am. Chem. Soc.* **2008**, *130*, 10082–10083. (b) Chu, Q.; Makhlouf Brahmi, M.; Solovyev, A.; Ueng, S.-H.; Curran, D.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem.—Eur. J.* **2009**, *15*, 12937–12940. (c) Monot, J.; Makhlouf Brahmi, M.; Ueng, S.-H.; Robert, C.; Desage-El Murr, M.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Org. Lett.* **2009**, *11*, 4914–4917. (d) Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Biomol. Chem.* **2011**, *9*, 3415–3420. (e) Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Lett.* **2010**, *12*, 3002–3005.

(16) (a) Tehfe, M.-A.; Makhlouf Brahmi, M.; Fouassier, J.-P.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E.; Lalevée, J. *Macromolecules* **2010**, *43*, 2261–2267. (b) Tehfe, M.-A.; Monot, J.; Makhlouf Brahmi, M.; Bonin-Dubarle, H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E.; Lalevée, J.; Fouassier, J.-P. *Polym. Chem.* **2011**, *2*, 625–631.

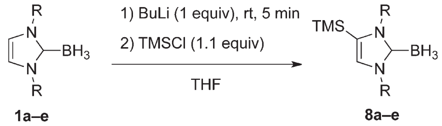
(17) (a) Nielsen, D. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2003**, *352*, 143–150. (b) Clyburne observed a close contact in the crystal structure of 1,3-dimesitylimidazol-2-ylidene-borane between the B−H bond of one complex and the C4−H bond of another, implying that the latter bond might be acidic. Ramnial, T.; Jong, H.; McKenzie, I. D.; Jennings, M.; Clyburne, J. A. C. *Chem. Commun.* **2003**, 1722–1723.

(18) Solovyev, A.; Chu, Q.; Geib, S. J.; Fensterbank, L.; Malacria, M.; Lacôte, E.; Curran, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 15072–15080.

(19) Monot, J.; Solovyev, A.; Bonin-Dubarle, H.; Derat, É.; Curran, D. P.; Robert, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 9166–9169.

(20) Jana, A.; Azhakar, R.; Tavčar, G.; Roesky, H. W.; Objartel, I.; Stalke, D. *Eur. J. Inorg. Chem.* **2011**, 3686–3689.

Table 1. Reactions of Deprotonated NHC-BH$_3$ Complexes with TMSCl



entry	precursor	R	prod	yield[a]
1	diiPr-Imd-BH$_3$ **1a**	*i*-Pr	**8a**	93%
2	diCy-Imd-BH$_3$ **1b**	cyclohexyl	**8b**	92%
3	diMe-Imd-BH$_3$ **1c**	Me	**8c**	85%
4	dipp-Imd-BH$_3$ **1d**	2,6-diisopropylphenyl	**8d**	89%[b]
5	diMes-Imd-BH$_3$ **1e**	mesityl	**8e**	52%

[a] After purification by flash chromatography. [b] Residual **1d** (about 10%) was not separable in this case.

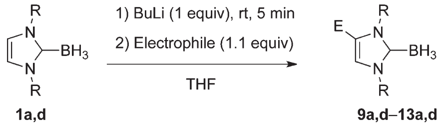
readily handled in ambient lab conditions. Unlike the corresponding imidazolium salts or free carbenes, they can conveniently be purified by flash chromatography. The only significant side product in these reactions was recovered starting material, which was typically present at the level of 10% or less. This could be separated from the silylated products by chromatography in most cases, but not in the case of **1d**/**8d**, whose diisopropylphenyl substituents make both compounds very nonpolar.

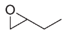
Table 2 summarizes the results of a series of experiments with diiPr-Imd-BH$_3$ **1a** and dipp-Imd-BH$_3$ **1d** that begin to outline the scope of the electrophilic trapping reaction. The isolated yields after purification by flash chromatography are reported. Like TMSCl, benzaldehyde is an excellent trapping reagent to give **9a**,**d** (entry 1, 88% and 82%). And ethyloxirane can also be used to form **10a**,**d** (entry 2, 40% and 60%), as anticipated by the results in Figure 2.

Primary alkyl bromides give alkylation products **11a**,**d** and **12a** in variable yields (entries 3, 4), although even these yields are perhaps surprising given that no transmetalation was attempted. An azide substituent, potentially useful for downstream click chemistry, survives the reaction and purification (entry 3). Furthermore, the products **11a**,**d** are stable, so evidently carbene-boranes do not directly reduce alkyl azides. Reactions with diphenylphosphinyl chloride gave expected phosphorylated products **13a** (33%) and **13d** (75%) (entry 5).

Boron trifluoride (BF$_3$) complexes can also be metalated and functionalized, as shown by the two reactions with dipp-Imd-BF$_3$ **14** in Scheme 1. Metalation of **14** was again conducted with BuLi for 5 min and then the electrophile (TMSCl or ethyloxirane) was added, followed by workup and flash chromatography. Silylated product **15** was isolated in 85% yield, though it again could not be separated from some unreacted **14** because both are so nonpolar. The product of reaction with ethyl oxirane **16** was readily isolated in pure form in 66% yield. These results with the BF$_3$ complexes are comparable to the BH$_3$ analogs (**8d**, Table 1, entry 4; **10d**, Table 2, entry 2).

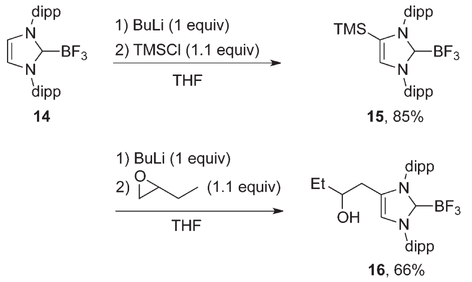
Table 2. Reactions of Deprotonated NHC-BH$_3$ Complexes **1a**,**d** with Electrophiles



entry	electrophile	E	R = iPr	yield[a]	R = dipp	yield[a]
1	PhCHO	PhCH(OH)–[b]	**9a**	88%	**9d**	82%
2		EtCH(OH)CH$_2$–[b]	**10a**	40%	**10d**	62%
3	N$_3$(CH$_2$)$_6$Br[c]	N$_3$(CH$_2$)$_6$–	**11a**	9%	**11d**	61%
4	C$_5$H$_9$Br	CH$_2$=CH(CH$_2$)$_3$–	**12a**	69%	**12d**	37%[d]
5	Ph$_2$P(O)Cl	Ph$_2$P(=O)–	**13a**	33%	**13d**	75%

[a] After purification by flash chromatography. [b] The reaction was quenched with methanol. [c] 5 equiv. [d] NMR yield: the product and residual starting material were inseparable.

Scheme 1. Lithiation and Electrophilic Trapping of Carbene Complex **14** with Boron Trifluoride



Scheme 2 shows selected results for the double functionalization at both C4 and C5, which could be accomplished in either one or two steps. The first one-step transformation came as a surprise. Metalation of **1a** as usual followed by addition of 4-toluenesulfonyl chloride (TsCl) provided the dichloride **17** in 45% yield based on **1a**. Evidently, the lithiated carbene-borane sees TsCl as a chlorinating agent,[21] not a sulfonylating agent. Further, the initially formed monochlorinated product is presumably deprotonated by the remaining lithiated carbene-borane to lead to the dichlorinated product **17**. Thus, the yield of **17** based on BuLi is 90%.

Carbene-boranes can also be treated with excess BuLi followed by addition of bis-electrophiles. For example, treatment of **1d** with 3 equiv of BuLi followed by addition of bromide **18** provided the interesting tetracycle **20** in 67% isolated yield. A similar reaction of **1d** with homologue **19** provided the corresponding eight-membered ring analog **21**, though only in 8% yield.

Finally, the monofunctionalized products can also be deprotonated and functionalized a second time. For example, metalation of **12a** (the product of Table 2, entry 4) followed by addition of benzaldehyde gave **22** in 61% isolated yield. Broad signals in the ^{1}H NMR spectrum of **22** that sharpen on heating show evidence of dynamic

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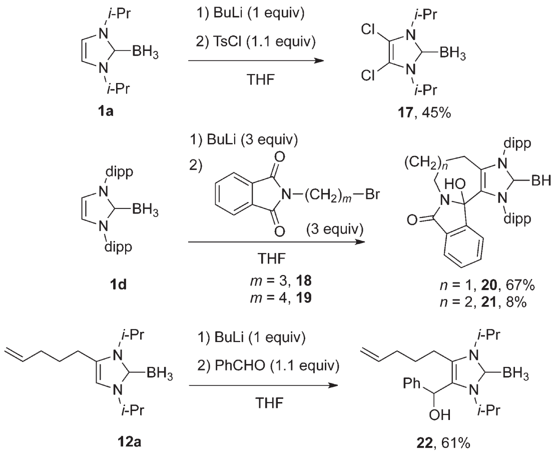
[21] (a) Slocum, D. W.; Gierer, P. L. *J. Org. Chem.* **1976**, *41*, 3668–3673. (b) Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. J.; Gribble, G. W. *J. Org. Chem.* **1989**, *54*, 4350–4356. (c) Brummond, K. M.; Gesenberg, K. D. *Tetrahedron Lett.* **1999**, *40*, 2231–2234. (d) Voinov, M. A.; Grigor'ev, I. A. *Tetrahedron Lett.* **2002**, *43*, 2445–2447.

Scheme 2. Examples of One-Pot and Stepwise Double Functionalization Reactions



processes, which we attribute to slow rotation of either the C5−CH(OH)Ph bond or the N1−*i*-Pr bond.

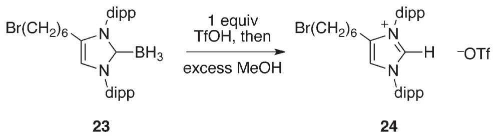
Our principal interest is in the actual carbene-borane products of these reactions. However, such products could also be convenient precursors of imidazolium salts and, in turn, carbenes and carbene complexes. The use of boranes as protecting/activating groups for carbenes is analogous with some uses of phosphine-boranes.[22] In both cases, the last step is a deboronation. We previously observed that treatment of dipp-Imd-BH_3 **1d** with I_2 or TfOH produced NHC-BH_2I or NHC-BH_2OTf complexes.[17] In the presence of water (or methanol), these compounds were observed by NMR spectroscopy to undergo fast hydrolysis (or methanolysis) to the corresponding imidazolium salts.

To follow up on these leads, we first prepared bromoalkyl-substituted NHC-borane **23** by the usual alkylation reaction with 1,6-dibromohexane (64% yield, see Table 2 for conditions). Reaction of **23** with 1 equiv of triflic acid followed by addition of excess methanol and workup provided hygroscopic imidazolium salt **24** in essentially quantitative yield (Scheme 3).

We then looked at combining deboronation and click chemistry with azide **11d** (Scheme 4). Here we also initially evaluated whether iodine could be used in place of triflic acid. In a first approach, treatment of **11d** with 0.6 equiv of iodine followed by methanolysis did not give the target azide, but instead provided amino-substituted imidazolium salt **25** in 81% yield. Apparently, the boryl iodide (NHC-BH_2I) or some other in situ generated borane[23] reduced the azide during the deboronation.

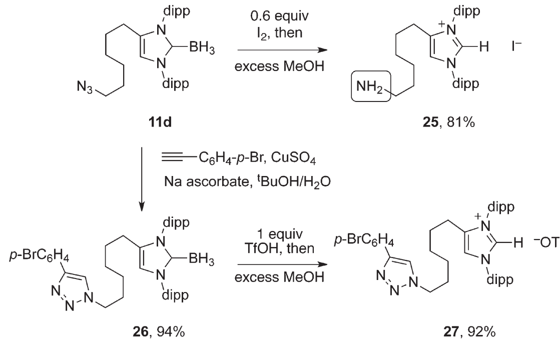
Reversing the order of the steps, we reacted azide **11d** with *p*-bromophenylethyne under Cu-catalyzed click conditions ($CuSO_4$, sodium ascorbate, *tert*-butanol/water)[24] to provide triazole-substituted NHC-borane **26**. Treatment of **26** with triflic acid and methanol gave salt **27** in 92% yield.

Scheme 3. Deboronation of a Functionalized Carbene-Borane **23** with Triflic Acid and Methanol



These preliminary results suggest that alkylation and deboronation of NHC-boranes will provide an attractive alternative to traditional routes to functionalized imidazolium salts.

Scheme 4. Deboronations Functionalized Carbene-Boranes **11d** and **26**



In summary, we developed a simple procedure for the C4 or C4,5 functionalization of imidazol-2-ylidene-borane complexes by lithiation (5 min, rt) and electrophile trapping. Handling and purification are facilitated because the reaction products are generally stable to air, water, and chromatography. This opens the way for the preparation of carbene-borane reagents possessing improved reactivity, solubility, separation, or other properties. Moreover, the functionalized products are precursors for the synthesis of C4 or C4,5 substituted imidazolium salts, free carbenes, and their complexes that are otherwise challenging to prepare.

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Supporting Information Available. Procedures, characterization of new compounds, and the reactions with other electrophiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023–4078.

(23) Lindsay, D. M.; McArthur, D. *Chem. Commun.* **2010**, *46*, 2474–2476.

(24) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.