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Copper-Catalyst-Controlled Site-Selective Allenylation of Ketones and Aldehydes with Propargyl Boronates

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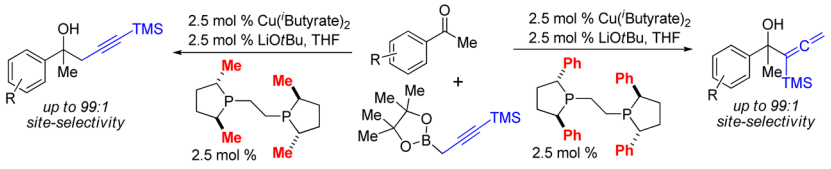
ABSTRACT



A practical and highly site-selective copper-PhBPE-catalyst-controlled allenylation with propargyl boronates has been developed. The methodology has shown to be tolerant of diverse ketones and aldehydes providing the allenyl adducts in high selectivity. The BPE ligand and boronate substituents were shown to direct the site selectivity for which either propargyl or allenyl adducts can be acquired in high selectivity. A model is proposed that explains the origin of the site selectivity.

The organometallic addition to carbonyl compounds has been a fundamental method for the construction of carbon−carbon bonds.[1] In this capacity, efforts have been afforded toward the alleneylation of ketones and aldehydes as the resulting allenyl carbinols are an effective handle for the synthesis of complex architectures.[2] The direct allenylation of carbonyls via a metallic propargyl intermediate has been shown with B,[3] Al,[4] Si,[5] Cr,[6] Zn,[7] and Lewis acid mediated processes.[8] The site selectivity of these methods is dictated by the selective formation of the propargyl intermediate. The metallic propargyl/allenyl intermediate is often in a state of equilibration in which the site selectivity is dictated by the relative stability of the respected allenyl or propargyl metallic species. In this capacity, Knochel[9] and others[10] have shown that the site selectivity can be directed by the substitution pattern on the propargyl/allenyl unit, whereas the more sterically demanding substituted propargyl reagents favor the metallic propargyl intermediates, thus providing the allenyl carbinols selectively. However, the site selectivity of these methodologies is limited to either selective formation of

(1) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Whiley-VCH: Weinheim, 2004.

(2) For selected examples, see: (a) Bonazzi, S.; Binaghi, M.; Fellay, C.; Wach, J.-Y.; Gademann, K. *Synthesis* **2010**, *4*, 631–642. (b) Yang, D.; Cwynar, V.; Donahue, M. G.; Hart, D. J.; Mbogo, G. *J. Org. Chem.* **2009**, *74*, 8726–8732. (c) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550–2551.

(3) For selected examples, see: (a) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130–8131. (b) Roy, C. D.; Soundararajan, R.; Brown, H. C. *Monatsh. Chem.* **2008**, *139*, 241–249. (c) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, 878–879. (d) Herandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5379–5400.

(4) For selected examples, see: (a) Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1990**, *397*, 127–137. (b) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579–1582.

(5) For selected examples, see: (a) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392–6393. (b) Shnneider, U.; Sugiura, M.; Kobayashi, S. *Tetrahedron* **2006**, *62*, 496–502.

(6) For selected examples, see: (a) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252–255. (b) Durán-Galván, M.; Connell, B. T. *Eur. J. Org. Chem.* **2010**, 2445–2448.

(7) 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*, 5616–5619.

(8) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208–5216.

(9) Guo, L.-N.; Gao, H.; Mayer, P.; Knochel, P. *Chem.—Eur. J.* **2010**, *16*, 9829–9834.

(10) For selected examples, see: (a) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042–13043. (b) Banerjee, M.; Roy, S. *Org. Lett.* **2004**, *6*, 2137–2140. (c) Yu, C.-M.; Yoon, S.-Y.; Baek, K.; Lee, J.-Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2392–2394.

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propargyl intermediates or by the inherent preference of the substituted allenyl subunit. To date, there has not been a system reported that can direct the site selectivity through the catalyst structure alone.

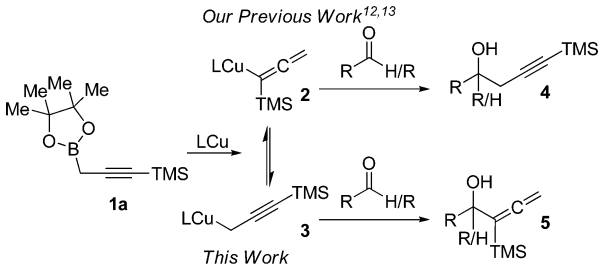
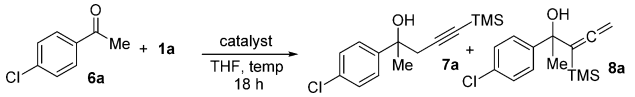


Figure 1. Site selective propargylations and allenylations.

Recently the Cu−B exchange has been shown to be an effective method for the catalytic propargylation of carbonyl compounds.[11] The site-selective propargylations of aldehydes[12] and ketones[13] have recently been shown with TMS-propargyl boronates mediated by copper−bisphosphine complexes. By inference, the active intermediate is the allenyl cuprate thus providing the propargyl adduct selectively (Figure 1). By destabilizing the allenyl cuprate **2** the equilibrium can shift to the propargyl cuprate **3**, thus providing the allenyl substrate **5** directly. Herein, we wish to report the site-selective allenylation of aldehyde and ketones catalyzed by Cu-PhBPE complexes.

Table 1. Initial Survey for the Site-Selective Allenylation[a]



entry	catalyst	temp (°C)	conversion[b]	(**7a:8a**)[b]
1	none	0	20%	99:1
2	2.5 mol % Cu(^{i}Butyrate)$_2$	0	68%	82:18
3	2.5 mol % LiOtBu	0	99%	99:1
4	2.5 mol % Cu(^{i}Butyrate)$_2$ and 2.5 mol % LiOtBu	0	99%	85:15

[a] Typical conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate in 3 mL of THF. [b] Molar conversion and site selectivity determined by HPLC analysis.

Initial surveys of the allenylation employed 4-chloroacetophenone **6a** as a model substrate and the readily prepared TMS-propargyl boronate **1a**.[14] A control experiment without a catalyst forms the propargyl adduct **7a** in high site selectivity and low conversion (entry 1, Table 1). Although the conversion can be improved by employing catalytic amounts of either Cu(iButyrate)$_2$, LiOtBu, or the combination of the two, the system forms the propargyl adduct selectively.

As previously shown[12,13] the presence of bisphosphine and monophosphine ligands in the reaction provides high site selectivity for the propargyl adduct (Figure 2). This effect appears to be general for a wide structural class of ligands. We felt that by selecting ligands that can more effectively encapsulate the Cu metal we could perturb the propargyl/allenyl Cu equilibrium to favor the propargyl intermediate. This effect was observed with PhBPE, whereas complete site selectivity was observed to favor the allenyl adduct **8a** (99:1 dr) with complete conversion and in moderate enantioselectivity (32% ee). This result appears to represent the first reported site-selective Cu-catalyzed allenylation of carbonyl compounds.

After establishing the Cu-PhBPE system for the site-selective allenylation of the model ketone **6a**, a survey of different ketones was conducted (Figure 3). The catalyst system has been shown to be tolerant of electronically diverse acetephenones (**6a**−**6c**, **6e**) as well as a cyclic ketone **6d** providing high selectivity for the allenyl adducts.

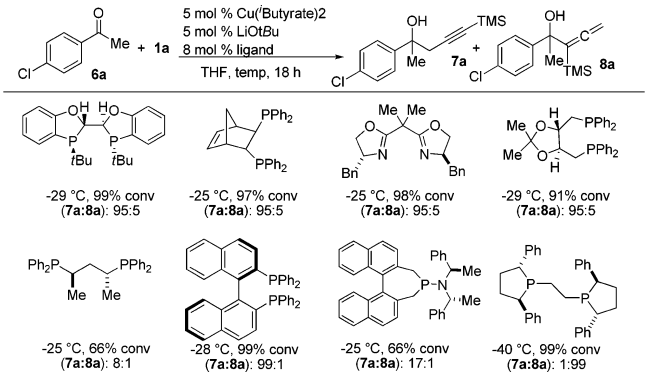


Figure 2. Ligand survey for the site-selective allenylation. Typical conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate in 3 mL of THF. Molar conversion and site selectivity determined by HPLC analysis.

Furthermore, an aliphatic methyl ketone is also well tolerated providing for high site selectivity for **8g**.

The Cu-PhBPE catalyst was also shown to be effective in the site-selective allenylation of a wide variety of aldehydes (Figure 4). The methodology was applicable for a diverse array of electronically differentiated aldehydes providing for ~10:1 selectivity for the allenyl adducts (**11**). The corresponding naphthyl (**9g**) and alkene (**9h**) aldehydes were

(11) Shi, S.-L.; Zu, L.-W.; Oisaki, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639.

(12) 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*, 7600–7601.

(13) 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*, 10332–10335.

(14) Fandrick, D. R.; Roschangar, F.; Kim, C.; Hahm, B.; Cha, M. H.; Kim, H. Y.; Yoo, G.; Kim, T.; Reeves, J. T.; Song, J. J.; Tan, Z.; Qu, B.; Haddad, N.; Shen, S.; Grinberg, N.; Lee, H.; Yee, N.; Senanayake, C. H. *Org. Process Res. Dev.* **2012**, *16*, 1131–1140.

tolerant in the system providing for 7.3 to 20:1 selectivity for the allenyl products.

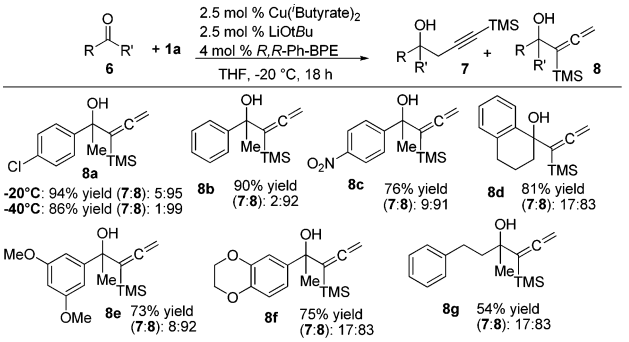


Figure 3. Site-selective allenylation of ketones catalyzed by Cu-PhBPE. Typical conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate in 3 mL of THF. Site selectivity determined by ^{1}H NMR analysis of the crude reaction mixture.

As mentioned previously, moderate enantioselectivity is obtained with the chiral PhBPE ligand. A Hammett plot[15] of the enantioselectivity (log(ratio of enantiomers)) of the allenylation of a series of aldehydes with respect to the σ-values shows a negative and near-linear relationship (Figure 5). Whereas, for electronically donating substituents an enantioselectivity of 82:18 (er, *p*-NMe_2 **9f**) can be obtained. However, for the *p*-NO_2 **9c** almost no enantiocontrol is observered (1.1:1 er).

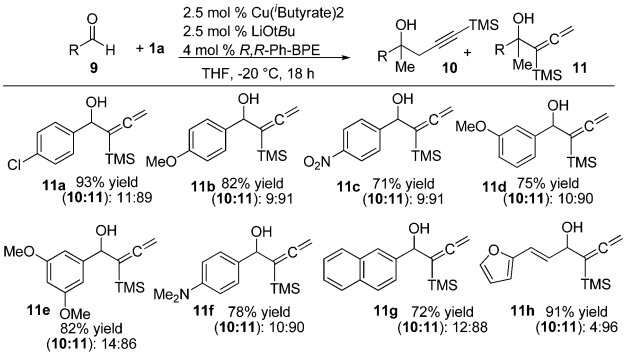


Figure 4. Site-selective allenylation of aldehydes catalyzed Cu-PhBPE. Typical conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate in 3 mL of THF. Site selectivity determined by ^{1}H NMR analysis of the crude reaction mixture.

Attention then was turned to the effects of the substituent on the boronate (Table 2). As expected, the less sterically demanding boronates (both allenyl boronate **1b** and propargyl boronate **1c**[7]) provide the propargyl adduct exclusively (99:1 selectivity). Since both substrates converge to the same propargyl product, this would imply that the intermediate Cu-allenyl/propargyl species can readily interconvert. However, the placement of a terminal substituent on the propargyl boronate (Ph, **1d**; TMS **1a**) provides the corresponding allenyl adduct in high site selectivity (> 90:10). Identical results were obtained with aldehyde **9b** (Supporting Information).

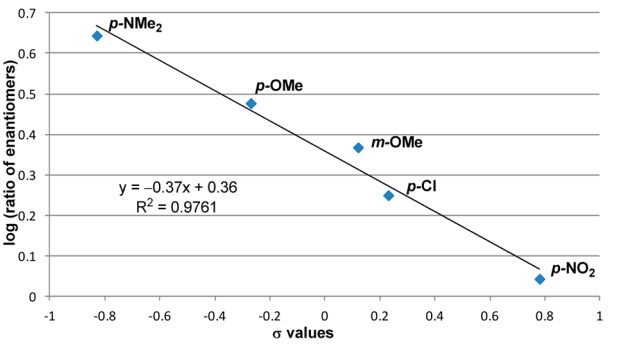
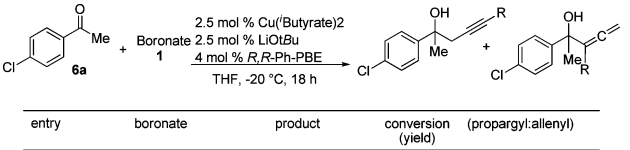
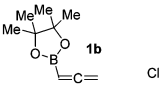
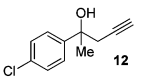
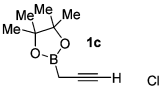
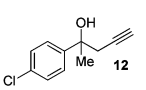
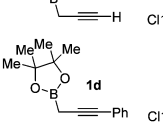
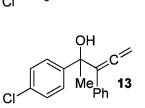
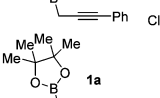
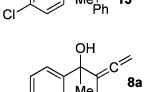


Figure 5. Hammett plot for the asymmetric allenylation of aldehydes catalyzed by Cu-PhBPE.

The substitution pattern on the BPE ligands was found to be vital for the site selectivity of the process (Table 3). Whereas, the MePBE and EtPBE ligands provide the corresponding propargyl adducts exclusively. However, the *i*PrPBE ligand shows a slightly lower preference for the propargyl product. Whereas the PhBPE ligand reverses the site selectivity preference and provides the allenyl adduct with good selectivity (20:1). These results would imply the substituent on the PBE ligand plays an intimate role in the site selectivity.

Table 2. Survey of Substituted Boronates **1** with Cu-Ph-PBe Catalyst[a]

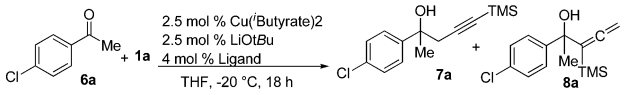


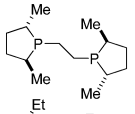
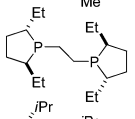
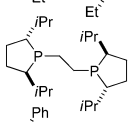
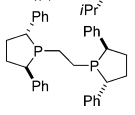
entry	boronate	product	conversion (yield)	(propargyl:allenyl)
1	 1b	 12	50%	99 : 1
2	 1c	 12	91% (88%)	99 : 1
3	 1d	 13	99% (97%)	1 : 99
4	 1a	 8a	99% (94%)	5 : 95

[a] Typical conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate in 3 mL of THF. Conversion and site selectivity determined by ^{1}H NMR analysis.

(15) (a) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96–103. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

Table 3. Effects of BPE Ligand Substitution on the Site Selectivity[a]



entry	ligand		conversion (yield)	(propargyl:allenyl)
1		***S,S*-Me-PBE**	99%	99 : 1
2		***S,S*-Et-PBE**	99%	99 : 1
3		***R,R*-*i*Pr-PBE**	99%	43 : 1
4		***R,R*-Ph-PBE**	99% (94%)	6 : 94

[a] Typical conditions: 1.2 mmol of ketone, 1.7 mmol of propargyl boronate in 3 mL of THF. Molar conversion and site selectivity determined by HPLC analysis.

Molecular modeling[16] based on the Cu-*R*-BINAP crystal structure of Anslyn[17] of the proposed cyclic intermediates[12,13] for the CuPhPBE and CuMePBE complexes shows marked differences in the available space for the TMS group (Figure 6). With the Cu-MePBE system there is available space for the TMS fragment in the Cu-allenyl complex thus allowing the system to provide the preferred propargyl adducts. However, for the Cu-PhPBE system this space is limited by the appended Ph-rings thus destabilizing the seemingly preferred allenyl-Cu complex and favoring the Cu-propargyl complex, which in turn provides the allenyl product. This model would also explain the reversed site selectivity for the unsubsituted boronates **1b** and **1c** (Table 2).

In conclusion, the Cu-PBE catalyst has been shown to be an effective complex which can undergo either a propargylation or an allenylation of carbonyl compounds with a common TMS-propargyl boronate reagent depending on the PBE substitution. A model was proposed that supports the observed site-selectivity preferences for the PBE ligand and boronate substitution. This system represents the first catalyst-controlled site-selective allenylation and propargylation of carbonyl compounds.

(16) The molecular model was generated by replacing the appended couterions on the Cu-BINAP crystal structure with the aldehyde followed by the TMS-allene or TMS-propargyl unit. The BINAP ligand was then replaced with the BPE ligand. The distance between the terminus of the allene/propargyl carbon and the carbonyl carbon was constrained to 2.9 Å, after which a single-point energy minimization was performed using Spartan '08 (version 1.1.1).

(17) Nieto, S.; Lynch, V. M.; Anslyn, E. V.; Kim, H.; Chin, J. *Org. Lett.* **2008**, *10*, 5167–5170.

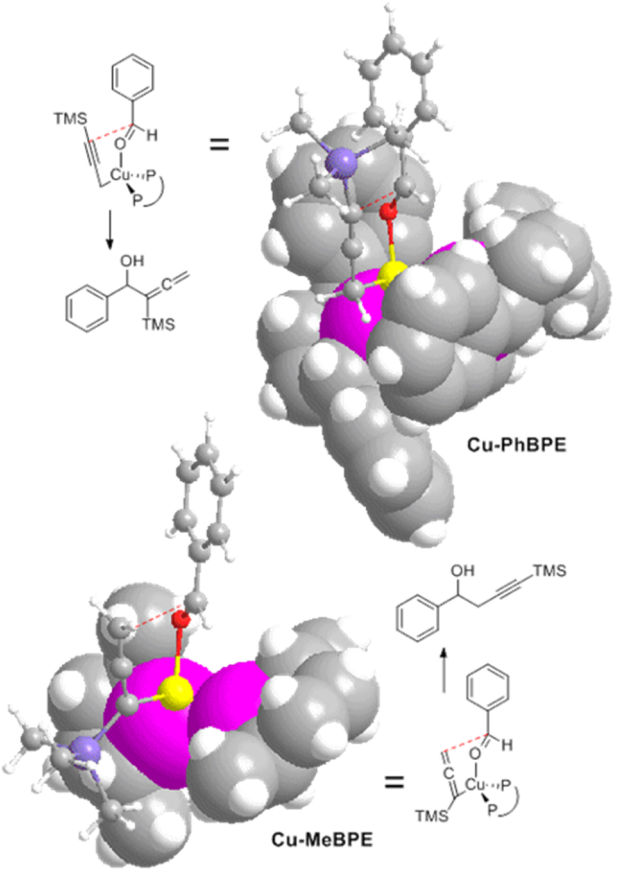


Figure 6. Molecular models for the Cu-PhBPE allenylation and Cu-MeBPE propargylation.

Supporting Information Available. Optimization studies, additional experiments employing aldehyde **9a** and **9b**, experimental procedures, ee for all substrates, and characterization data (^{1}H and ^{13}C NMR spectra for all products, and chiral HPLC data and copies of chromatograms). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.