Cascade Copper-Catalyzed 1,2,3-Trifunctionalization of Terminal Allenes

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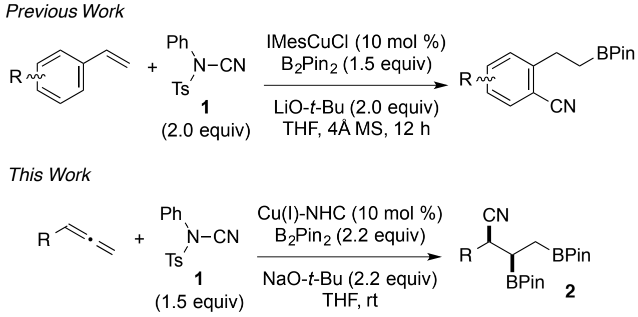
Supporting Information Placeholder

ABSTRACT: A cascade cyanation / diborylation of terminal allenes proceeds efficiently with copper catalysis using *bis*(pinacolato)diboron (B_2Pin_2) and *N*-cyano-*N*-phenyl-*p*-methyl benzenesulfonamide (NCTS) as reagents. Mechanistic studies suggest that the process proceeds through cyanoborylation of the substituted π-system of the allene followed by hydroboration of the remaining π-component. A wide array of product derivatives may be accessed through site-selective cross-couplings and *N*-bromosuccinimide-promoted heteroarylations as well as standard oxidative and reductive conversions of the initially obtained adducts.

Allenes present a versatile and highly-reactive substrate class for the development of catalytic functionalization processes.[1] Methods that involve a 1,2-addition process to one of the two contiguous, orthogonal π systems of an allene present considerable challenges in regioselectivity, since four possible regioisomers can result from a simple 1,2-addition process.[1,2] Additionally, over-addition processes can be difficult to suppress. Of the known regioselective allene 1,2-addition processes, hydrofunctionalizations that introduce a single non-hydrogen substituent to the allene core structure are most common.[1,3] Methods that introduce more complexity have also been developed, but most examples involve the incorporation of two identical groups (such as two BPin units from B_2Pin_2),[1,4] which reduces the number of possible regioisomers to two. Fewer methods involve incorporation of two different groups,[5] and only rarely have trifunctionalization processes of allenes been developed, typically involving an initial difunctionalization followed in sequence by a second difunctionalization.[6] The development of cascade trifunctionalizations of allenes with all of the reactive components simultaneously present introduces considerable challenges in regiocontrol and chemoselectivity that have not yet been effectively addressed.

Recent work from our laboratory described an efficient copper-catalyzed cascade functionalization process that allows the union of styrenes, diboranes, and *N*-cyano-*N*-phenyl-*p*-methyl benzenesulfonamide (**1**) (NCTS) to efficiently afford cyanoborylated products in high yield with excellent regioselectivity (Scheme 1).[7] These findings build upon important earlier studies from Buchwald and Liu and coworkers, who illustrated the utility of this reagent combination in the derivatization of vinyl naphthalenes and the underlying mechanistic features of the addition process.[8] Seeking to further advance copper-NHC catalysis with B_2Pin_2 and NCTS, we have now explored the corresponding additions to terminal allenes with this catalyst / reagent combination.[9] In contrast to additions of styrenes, where cyanation was accompanied by monoborylation, the introduction of simple allenes as substrates provided an unprecedented cyanation / diborylation cascade to provide 1,2,3-trifunctionalized products **2** with exceptional chemo-, regio-, and diastereoselectivity (Scheme 1). The discovery, exploration and mechanistic study of this highly selective multicomponent process are described herein.

Scheme 1. Copper-catalyzed cyanoborylation processes.

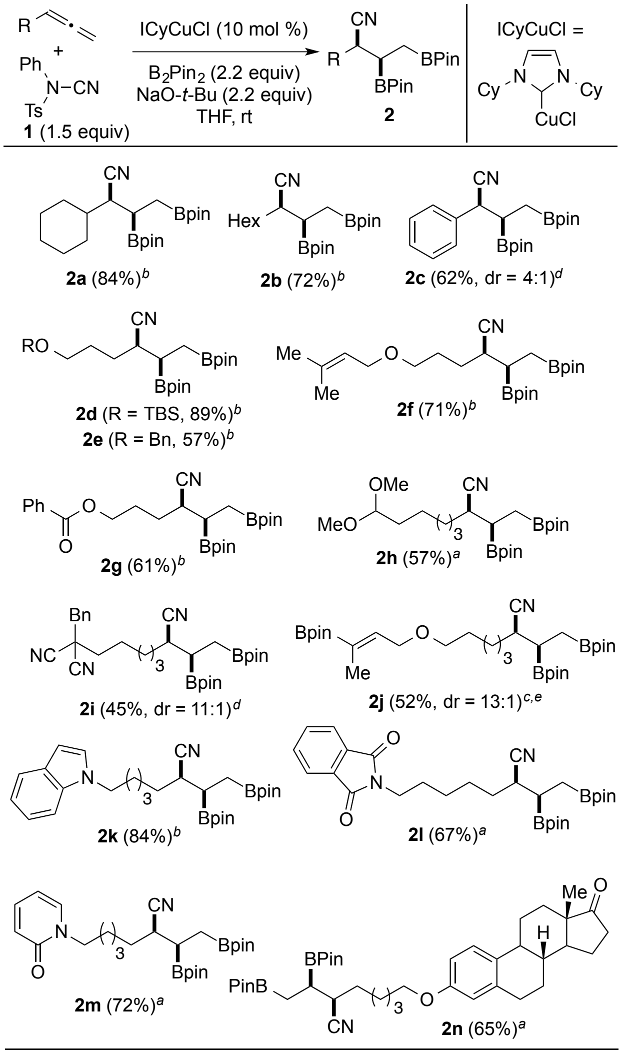


Initial evaluation of the catalytic union of cyclohexyl allene, B_2Pin_2, and NCTS (**1**) was conducted using a range of copper NHC catalysts at rt. Using IMes•CuCl as catalyst, THF and NaO-*t*-Bu were found to be the optimal solvent and base. A range of NHC ligands, including IMes, SIMes, IPr, and ICy all performed comparably, with ICy providing the best combination of yields and diastereoselectivities, generating product **2a** (Table 1) in 84% isolated yield and >20:1 dr (see supporting information for ligand studies and optimization details). Using these standard conditions, couplings of a range of terminal allenes were examined. In a few instances, as described below, addition of small quantities of methanol result in increased yield, albeit with a slight erosion in diastereoselectivity. Each entry provides optimized conditions for the product shown.

In addition to allenes bearing a secondary branched substituent (product **2a**), allenes bearing an unbranched aliphatic substituent (product **2b**) or an aromatic substituent (product **2c**) were tolerated. The standard procedure was low-yielding (30%, 8:1 dr) with phenyl allene, whereas the addition of 1.2 equiv of methanol improved the yield to 62%. Silyl, benzyl, and substituted allyl ethers were cleanly tolerated (products **2d**

– **2f**). Additionally, substitution with benzoate esters, dimethylacetals, and malonitriles was also allowed (products **2g** – **2i**). Alkynes, however, were not tolerated, as an acetylenic allene substrate underwent cyanodiboration of the allene and hydroboration of the alkyne under the reaction conditions (product **2j**).[10] A variety of heterocycles were also tolerated, as efficient cyanodiboration of the allene was observed using substrates that possessed indole, phthalimido, and pyridone ring systems (products **2k** – **2m**). The ketone functionality of a steroid framework was also unaffected in the process (product **2n**). While diastereoselectivities were generally excellent in this cascade process, attempts to utilize chiral NHC ligands that had been successful in other classes of copper-catalyzed asymmetric additions of B_2Pin_2[4e] unfortunately led to low ee's (see supporting information for details).

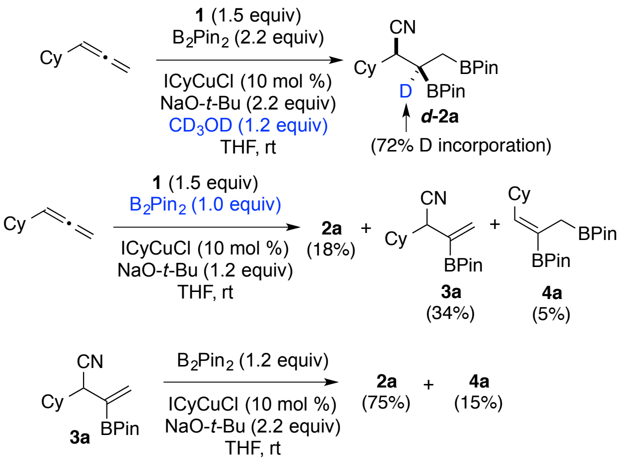
Table 1. Scope of copper-catalyzed allene cyanation-diborylations.



a) Standard procedure: ICyCuCl (10 mmol%), B_2pin_2 (2.2 eq), NaO-*t*-Bu (2.2 eq), THF (1 mL), rt for 40 h. dr>20:1. b) Standard procedure, then NaOH (10.0 eq)/H_2O_2 (10.0 eq). The yield shown is overall yield for cyandiboration and oxidation to the diol. c) Standard procedure was followed using B_2pin_2 (3.2 eq), NaO-*t*-Bu (3.2 eq) and MeOH (2.2 eq). d) Standard procedure using MeOH (1.2 eq). e) This example utilizes 8-(but-2-yn-1-yloxy)octa-1,2-diene as starting material.

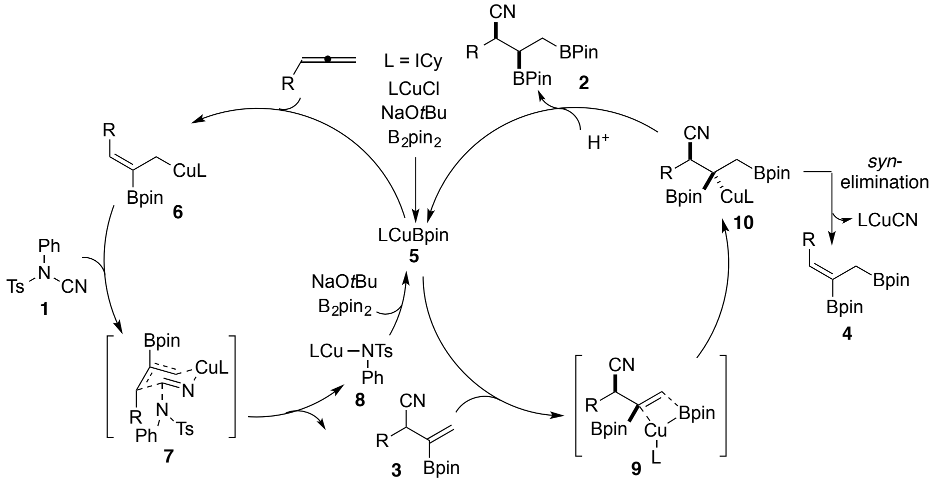
The catalytic process to generate product **2** involves cyanation of the substituted carbon of the allene, borylation of both the central and terminal carbons of the allene, and delivery of a hydrogen atom to the allene central carbon. A number of experiments using cyclohexylallene shed additional light on the reaction mechanism (Scheme 2). While the intentional addition of a proton source such as methanol is not strictly required in the catalytic process, the addition of 1.2 equiv of CD_3OD, followed by oxidation with H_2O_2, resulted in 72% deuterium incorporation at the allene central carbon in the resulting diol, suggesting that adventitious water plays a similar role in experiments that lack methanol as the additive. Reducing the stoichiometry of B_2Pin_2 to 1.0 equiv resulted in the production of product **2a** (18%), alkenylborane **3a** (34%), and alkenyldiborane **4a** (5%). While isolated **4a** was not converted to product **2a** when resubjected to the optimized coupling conditions (Table 1, standard procedure), the alkenylborane **3a** was converted to a mixture of product **2a** (75%) and product **4a** (15%) when subjected to the standard procedure.

Scheme 2. Deuterium labeling and evaluation of potential intermediates.



Based on the above findings, the following mechanism can be formulated to explain the process (Scheme 3). In analogy to other processes involving copper-catalyzed borylation,[3a-c] the active catalyst is likely Cu(I)-BPin species **5**, which is generated by addition of B_2Pin_2 to LCuO-*t*-Bu. The borocupration of the unsubstituted allene π-system would initially produce allylcuprate **6**.[3a-c,11] Cyanation of the allyl cuprate using reagent **1** with allylic transposition via transition state **7** would afford the observed intermediate **3** along with copper intermediate **8**, which would generate the active Cu(I)-BPin species **5**. The cyanation with allylic transposition using reagent **1** is in direct analogy to the *ortho*-cyanation observed in catalytic additions to styrenes.[7-8] In a second cycle, copper species **5** then undergoes borocupration of **3** through transition state **9** to generate alkyl copper intermediate **10**. Protonation of the Cu-C bond with retention of configuration would afford the observed major product **2**,[12] whereas competitive *syn*-elimination of a Cu-CN species would afford byproduct **4**, which was identified as a minor component in experiments described above (Scheme 2). The origin of diastereoselectivity in the conversion of **3** to **2** is unclear, although diastereoselective catalytic alkene hydroborations originating from allylic stereocenters have previously been described.[13]

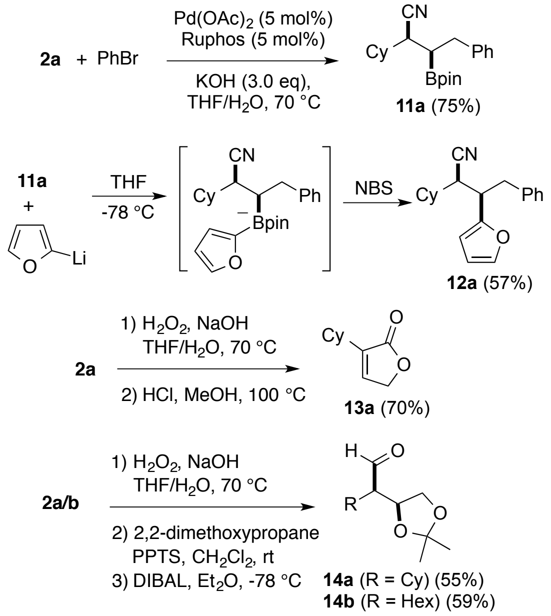
Scheme 3. Proposed mechanism of copper-catalyzed allene cyanation-diborylations.



The efficient and stereoselective cyanation / diborylation of allenes enables a variety of post-coupling manipulations to provide access to various structural motifs. For example, using product **2a**, palladium-catalyzed cross-coupling with phenyl bromide occurs selectively on the primary alkylborane to provide product **11a** in 75% isolated yield (Scheme 4).[14] Product **11a** was then further derivatized via the secondary alkylborane to provide product **12a** utilizing a recently developed procedure from Aggarwal for heteroarylation under electrophilic bromine-mediated migration of a pinacolate intermediate.[15] Alternatively, alkylborane oxidation followed by acid-catalyzed condensation provides lactone **13a**, whereas oxidation followed by acetonide formation and nitrile reduction affords aldehyde **14a** as a single diastereomer. Furthermore, the synthesis of the corresponding acetonide **14b** from compound **2b** allowed confirmation of stereochemistry through correlation with a previously reported compound.[16] Thus, numerous structural motifs may be easily accessed from the initially produced adducts from allene cyanation / diborylation.

In summary, the cascade trifunctionalization of terminal allenes is enabled by the copper-catalyzed addition of *bis*(pinacolato)diboron (B_2Pin_2) and *N*-cyano-*N*-phenyl-*p*-methyl benzenesulfonamide (NCTS). The process is highly diastereoselective and involves cyanation of the substituted allene carbon and borylation of the allene central and terminal carbons. Following this highly regioselective and stereoselective cyanation / diborylation process, the adducts obtained may be derivatized through a variety of sequences including sequential cross couplings or oxidation / reduction processes. Evidence for a mechanism involving initial cyanoborylation of the internal π-system followed by formal hydroboration of the terminal π-system is provided. The work provides a rare example of the selective trifunctionalization of terminal allenes.

Scheme 4. Synthetic manipulations of products from allene cyanation-diborylation.



ASSOCIATED CONTENT

Supporting Information. Experimental details and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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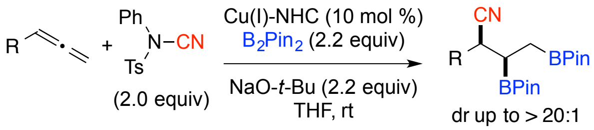
R
Ph
N–CN
Ts
(2.0 equiv)
Cu(I)-NHC (10 mol %)
B2Pin2 (2.2 equiv)
NaO-t-Bu (2.2 equiv)
THF, rt
CN
R
BPin
BPin
dr up to > 20:1