Sigmatropic Rearrangement

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Regio- and Stereospecific 1,3-Allyl Group Transfer Triggered by a Copper-Catalyzed Borylation/*ortho*-Cyanation Cascade

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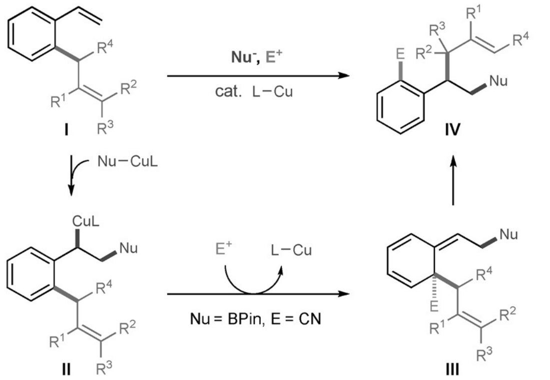
Abstract: *A copper-catalyzed borylation/ortho-cyanation/allyl group transfer cascade was developed. Initiated by an unconventional copper-catalyzed electrophilic dearomatization, this process features regio- and stereospecific 1,3-transposition of the allyl fragment enabled by an aromatization-driven Cope rearrangement. This method provides an effective means for the construction of adjacent tertiary and quaternary stereocenters with excellent diastereocontrol.*

Since its discovery in 1940,[1] the Cope rearrangement has been widely utilized as a powerful method for the construction of complex molecular architectures.[2] By using the chair-like six-membered transition state as the dominant stereocontrol element, this venerable transformation enables the efficient creation of well-defined stereochemical arrays in a predictable fashion. Owing to the reversible nature of this sigmatropic rearrangement, the use of substrates featuring ring strain or possessing specialized substitution patterns (e.g., oxy-Cope)[2] represents the most commonly employed tactic to drive the reaction towards the desired rearranged products. In this context, the development of alternative strategies to facilitate Cope rearrangement is pivotal for its further advancement as a synthetically useful transformation.

We previously reported that the capture of a vinylarene-derived benzylcopper species with an electrophilic cyanating reagent leads to the highly selective formation of a dearomatized intermediate.[3,4] Very recently, the elegant work of Montgomery and Zhao has expanded the scope of this transformation to simple styrenes.[5] A related borylative bromine recycling strategy was pioneered by Schomaker and co-workers,[6] and has been shown to proceed through a similar mechanism.[6d] Based on these precedents, we envisioned that the catalytic generation of a semibenzene intermediate (**III**) could serve as a generic platform for the development of a broad spectrum of novel rearrangement reactions, including Cope rearrangement (Scheme 1). In contrast to conventionally applied strategies, this process utilizes aromatization as the crucial driving force for the rearrangement of these previously difficult-to-access dearomatized intermediates. As detailed in Scheme 1, interception of the transient benzylcopper intermediate **II**, which is generated from 2-allylstyrene **I** with an electrophile, would provide the dearomatized intermediate **III**. Enabled by the rearomatizing Cope rearrangement, the subsequent 1,3-transposition of the allyl unit would be expected to proceed in a completely regio- and stereospecific fashion, thereby affording densely functionalized products bearing two adjacent stereocenters. Notably, the selective cleavage of the allyl fragment from an aromatic moiety and the subsequent allyl-group shuttling achieved in this cascade remained unexplored in the context of bond activation chemistry.[7] It was recognized that the realization of this proposed transformation would be nontrivial. The electrophilic cyanation of benzylcopper **II** would give rise to an unstable dearomatized intermediate **III** possessesing an all-carbon quaternary center, and could thus be both thermodynamically and kinetically unfavorable. In addition, the catalyst would need to effectively distinguish between the two similar olefins present in substrate **I** for the initial borocupration. Herein, we report the successful implementation of our proposed strategy. The key to our success lay in the use of a copper catalyst supported by a bulky, electron-rich monodentate biarylphosphine ligand (CyJohnPhos, **L1**) developed in the Buchwald lab.[8]



■ two contiguous stereocenters ■ formal regio- and stereospecific allyl migration
■ simultaneous olefin and arene functionalization

Scheme 1. Copper-catalyzed borylation/cyanation/cope rearrangement: A strategy for regio- and stereospecific 1,3-allyl transposition.

Using NCTS (**2**) as the electrophilic cyanating reagent,[9] the proposed tandem borylation/cyanation/allyl transfer was examined by evaluating a series of copper catalysts that were previously used to promote styrene borocupration.[10] We found that the catalyst derived from CyJohnPhos (**L1**) facilitated the desired transformation, providing the cyanation/allyl migration product **3a** in 62% yield (Table 1, entry 1). The structure of **3a** was further confirmed by 2D NMR spectroscopy (^{1}H-^{1}H COSY). Hydroboration product **3b** lacking cyano group represented the only other product

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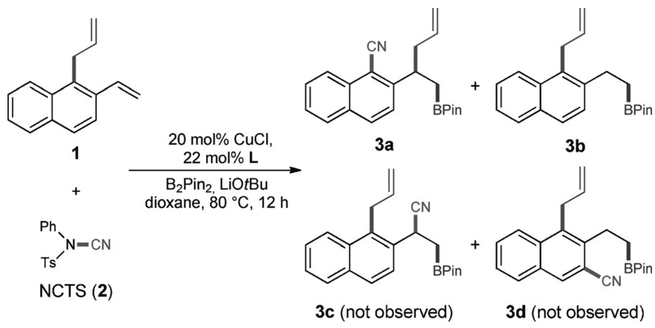
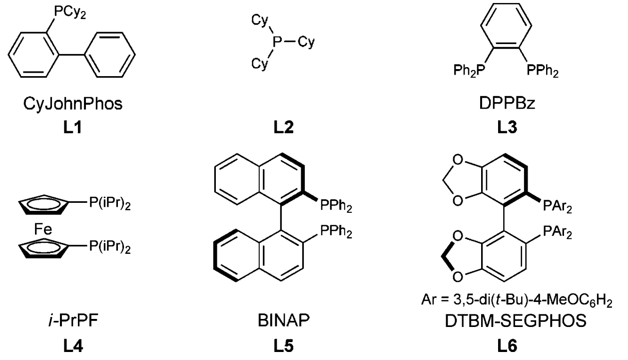
Table 1: Optimization of reaction conditions.[a]



Entry	L	Yield of **3a**	Yield of **3b**
1	**L1**	62%	16%
2[b]	**L2**	$<5\%$	66%
3	**L3**	$<5\%$	$<5\%$
4	**L4**	$<5\%$	51%
5	**L5**	18%	10%
6	**L6**	6%	19%
7[c]	**L1**	74%	13%

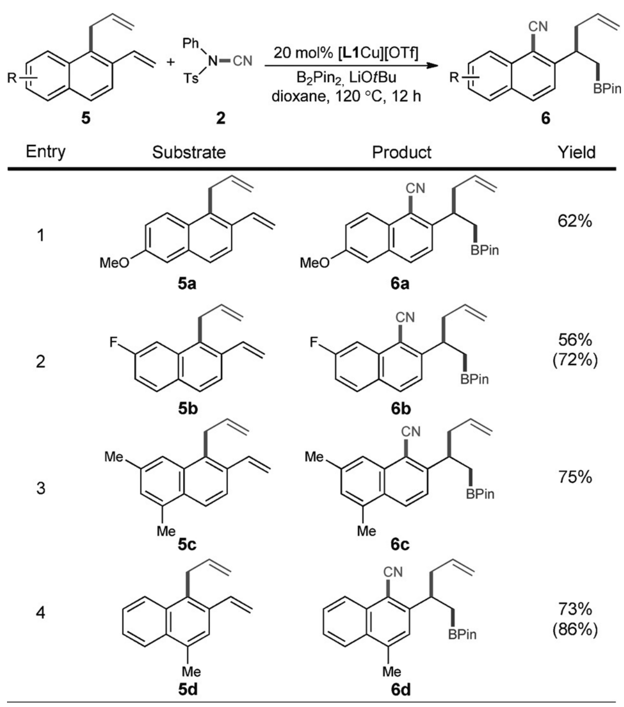
[a] Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), CuCl (0.020 mmol), **L** (0.022 mmol), B_2Pin_2 (0.11 mmol), LiO*t*Bu (0.12 mmol), dioxane (0.25 mL), 80 °C, 12 h. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with 1,1,2,2-tetrachloroethane as an internal standard. [b] 40 mol% **L**. [c] [(**L1**)Cu][OTf] (**4**; 20 mol%) was used in lieu of CuCl and **L1**, 120 °C. OTf = triflate.



observed. Notably, neither the benzylic cyanation product **3c** nor the C−H cyanation product **3d** was formed, as indicated by ^{1}H NMR spectroscopic analysis. Interestingly, replacement of **L1** with tricyclohexylphosphine (**L2**) resulted in a catalyst that was only capable of promoting the undesired hydroboration (Table 1, entry 2). Further evaluation of ligand effects revealed that commonly used bidentate phosphine ligands were much less effective (Table 1, entry 3–6). Finally, a preformed cationic copper(I)-phosphine complex[11] [(**L1**)Cu][OTf] (**4**) was identified as an excellent precatalyst for facilitating this reaction (Table 1, entry 7).

The substrate scope of this borylation/cyanation/allyl migration reaction (Schemes 2 and 3) was next explored. A variety of substituted 1-allyl-2-vinylnaphthalenes bearing electron-donating or electron-withdrawing functional groups were found to be excellent substrates (Scheme 2, **6a**–**6d**).

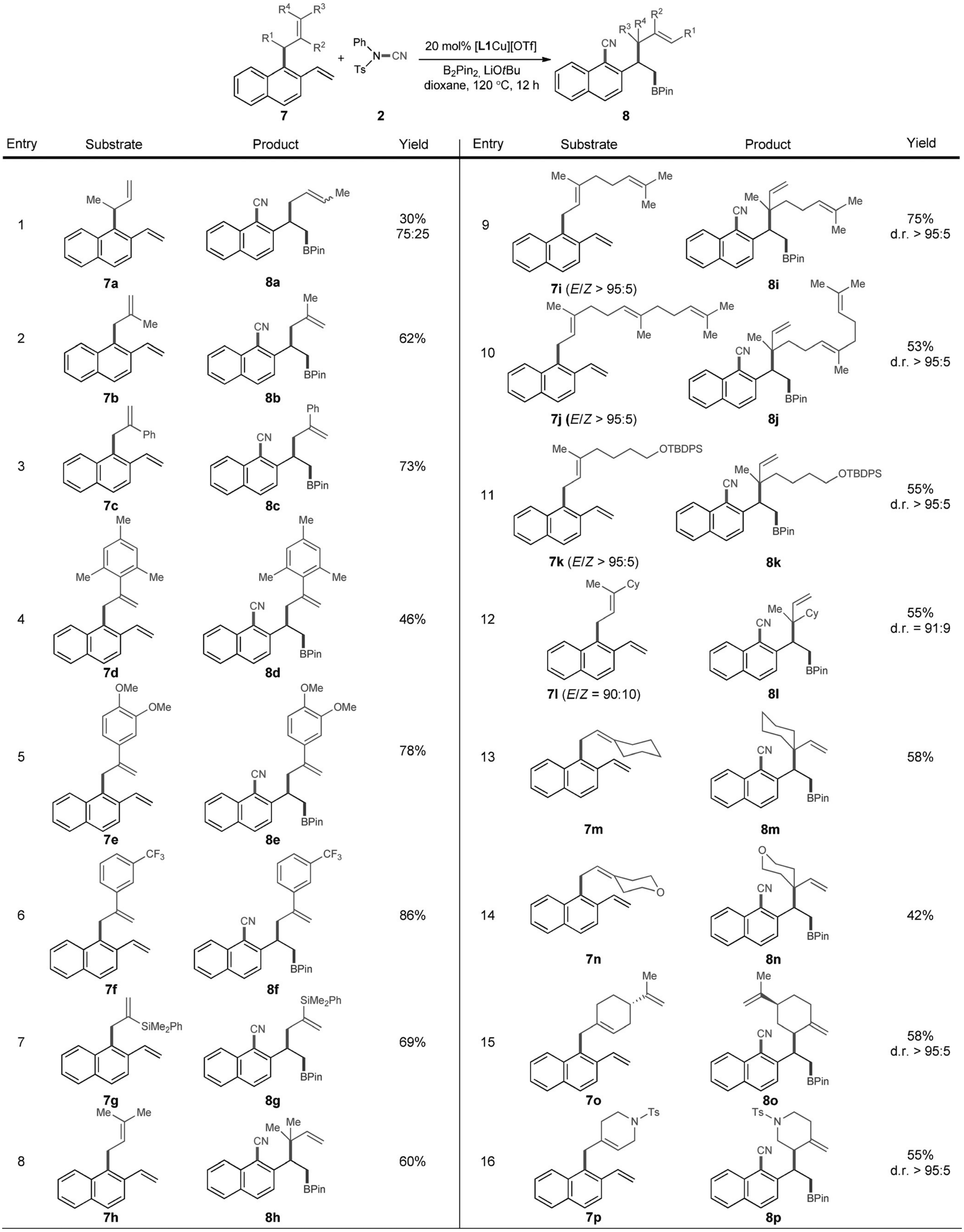
In addition, this process showed a broad substrate scope with respect to the allyl component (Scheme 3). Arenes possessing 2-substituted allyl groups (**7b**–**7g**) provided corresponding products in good to excellent yields. Owing to the increased steric hindrance proximal to the cyanated carbon, **7a** furnished the cyanation/allyl transfer products in moderate yield as a 75:25 mixture of olefin stereoisomers. Furthermore, 3,3-disubstituted allyl components were also compatible with the current reaction (**7h**–**7l**). In the case of 3,3-unsymmetrically disubstituted allyl substrates, the stereochemical information of the olefin geometry was fully transferred to the product in the form of relative configuration of the newly formed vicinal stereocenters (**7i**–**7l**). Cyclic variant **7m** and its heterocyclic analogue **7n** also represent viable substrates for this reaction. Finally, allylvinylarenes bearing an endocyclic C=C double bond (**7o** and **7p**) could be successfully transformed into the cyanation/allyl migration product with excellent diastereoselectivity.



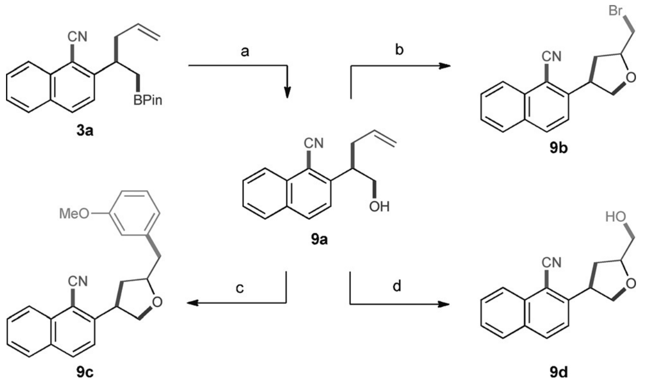
Scheme 2. Substrate scope with respect to the arenes. Reaction conditions: **5** (0.20 mmol), **2** (0.24 mmol), **4** (0.040 mmol), B_2Pin_2 (0.22 mmol), LiO*t*Bu (0.24 mmol), dioxane (0.50 mL), 120 °C, 12 h. Yields of isolated product are reported. The yields in parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture with 1,1,2,2-tetrachloroethane as an internal standard. The isolated yields were 5–20% lower than ^{1}H NMR yields owing to product decomposition on silica gel.

To further demonstrate the synthetic utility of this transformation, several derivatization reactions were carried out (Scheme 4). Oxidation of cyanoboronate **3a** under mild conditions afforded alcohol **9a** in 90% yield.[12] By taking advantage of the olefin and alcohol functional groups present in **9a**, an array of olefin difunctionalization reactions, including bromoetherification[13] (**9b**), palladium-catalyzed oxyarylation,[14] (**9c**) and dioxygenation[15] (**9d**), were successfully accomplished to furnish various complex 2,4-disubstituted tetrahydrofurans in excellent yields.

In an effort to gain insight into the mechanism of the reaction described above, we prepared deuterated substrate

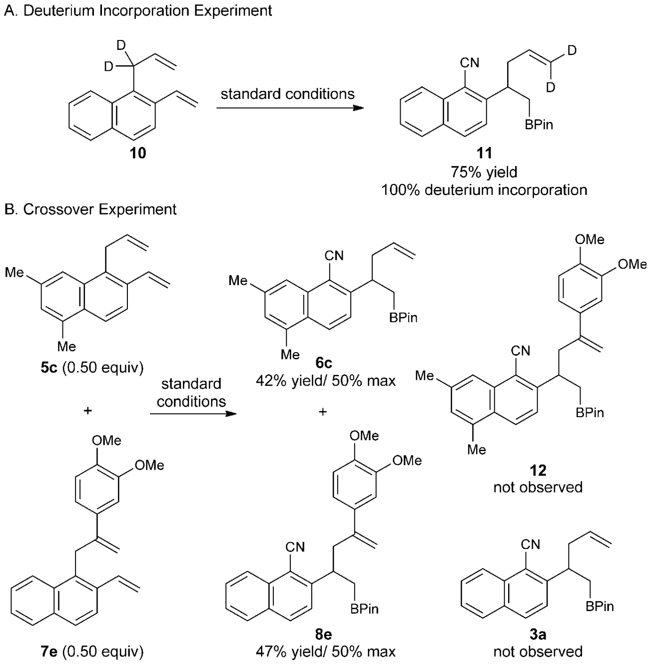


Scheme 3. Substrate scope of the migrating allyl groups. Reaction conditions: **7** (0.20 mmol), **2** (0.24 mmol), **4** (0.040 mmol), B$_2$Pin$_2$ (0.22 mmol), LiO*t*Bu (0.24 mmol), dioxane (0.50 mL), 120 °C, 12 h. Yields of isolated product are reported. These yields were usually 5–15% lower than ^{1}H NMR yields owing to product decomposition on silica gel.



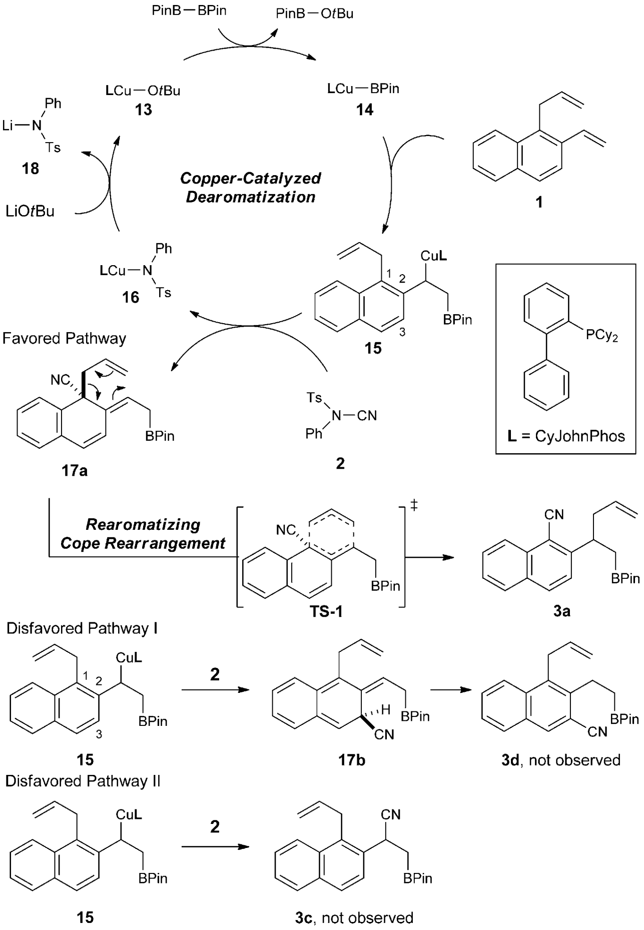
Scheme 4. Derivatization of borylation/cyanation/allyl transfer products. Conditions: a) $NaBO_3 \cdot 4H_2O$, THF/H_2O, RT, 2 h (90%). b) NBS, $NaHCO_3$, CH_2Cl_2/H_2O, RT, 12 h (97%, d.r. = 78:22). c) 2.5 mol% $[(allyl)PdCl]_2$, 10 mol% SPhos, 3-bromoanisole, NaO*t*Bu, toluene, 110°C, 12 h (71%, d.r. = 62:38). d) mCPBA, CH_2Cl_2, RT, 48 h (96%, d.r. = 50:50). Isolated yields were reported. NBS = *N*-bromosuccinimide, mCPBA = *m*-chloroperoxybenzoic acid.

10 and subjected it to the standard reaction conditions (Scheme 5). It was found that both deuterium atoms were fully incorporated into product **11** at the terminal position of the olefin. This finding suggests that an overall 1,3-transposition of the allyl moiety has taken place. Furthermore, having confirmed that **5c** and **7e** reacted at similar rates, we conducted a crossover experiment with these two substrates. Careful examination of the ^1H NMR spectrum revealed that neither of the crossover products **12** and **3a** was present in the crude reaction mixture, whereas the yield of the unimolecular allyl migration products **6c** and **8e** remained essentially unaffected. This observation is consistent with an intramolecular 1,3-allyl group migration mechanism.



Scheme 5. Mechanistic studies.

Based on these findings, a plausible reaction mechanism is shown in Scheme 6. Transmetalation of the monodentate phosphine ligated copper catalyst **13** with the diboron reagent provides the copper boryl complex **14**, which undergoes borocupration with **1** to provide the benzylcopper species **15**.



Scheme 6. Proposed mechanism.

Electrophilic cyanation of **15** affords the dearomatized product **17a**, eventually leading to the formation of **3a** through the rearomatizing Cope rearrangement. Complete regio- and stereospecificity is ensured by the highly organized chair-like transition state of this [3,3]-sigmatropic rearrangement. We believe that the electron-rich CyJohnPhos (**L1**) greatly enhances the nucleophilicity of **15** and is thus critical in promoting this challenging quaternary carbon-forming dearomatization process. Cyanation at the C3 position (**17b**) would disrupt the aromaticity of both benzene rings and is thus thermodynamically disfavored. Computational investigations are being performed to gain further insight into the preferred C1 cyanation over the benzylic cyanation, as well as the nature of the transition state for this rearomatizing Cope rearrangement.

In summary, we have developed a novel catalytic borylation/*ortho*-cyanation/Cope rearrangement sequence. This cascade process features the overall regio- and stereospecific 1,3-allyl transposition, which proceeds through a rearomatizing [3,3]-sigmatropic rearrangement triggered by the copper-catalyzed electrophilic cyanative dearomatization. This protocol provides an effective means to access a broad range of synthetically useful building blocks that can be easily transformed into a variety of complex molecular scaffolds. The results presented herein may serve as a platform for the development of an enantioselective allyl transposition reaction, as well as other rearrangement processes initiated by dearomatization.

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