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Perspective

1,3-Halogen Migration as an Entry to Aryl Coppers from an Unintuitive Starting Material

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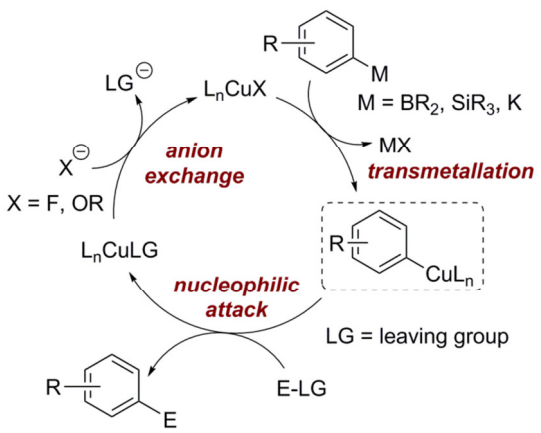
A copper(I) catalyzed 1,3-halogen migration/borylation migrates a bromine from an sp^2 carbon to a benzylic carbon with concomitant borylation of the aryl-bromine bond. This transformation proceeds *via* an aryl copper intermediate which can be accessed independently and then trapped with electrophiles. As such, copper-catalyzed 1,3-halogen migration provides unique and mild access to an aryl copper species that allows for rapid aromatic functionalization from an unconventional starting material.

Introduction

Organocopper species have been studied extensively as soft nucleophiles since their discovery over 60 years ago.[1] In the last several years, great efforts have been taken to utilize these species as reactive intermediates in catalytic transformations.[2] Unfortunately, this goal has remained elusive due to challenges associated with both the catalytic generation and subsequent functionalizations of arylcopper(I) (ArCu) intermediates.

A general catalytic cycle involves the generation of an ArCu species, followed by nucleophilic attack on an electrophile and then anion exchange to regenerate the active catalyst (Scheme 1). Three main strategies have been used for the catalytic generation of ArCu species which involve the transmetallation of (1) copper-fluoride or alkoxide with an organosilane,[3] (2) a copper-halide with a metal carbanion[4] or (3) a copper-alkoxide with a boronic ester.[5] A range of electrophiles have been successfully reacted with ArCu in a variety of transformations that include carboxylation,[6] electrophilic amination[7] and cross-coupling.[8] In order to effect catalytic turnover, either stoichiometric alkoxide bases or fluorides are added or an alkoxide is produced during the turnover step using an appropriate choice of electrophile.

Scheme 1: General catalytic cycle using arylcopper species.

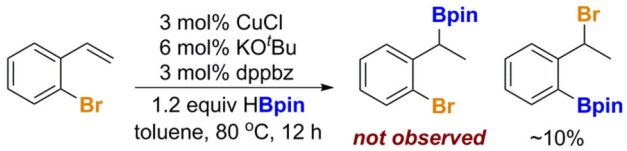


Notably, all of the above strategies rely on transmetallation to generate ArCu reactive intermediates, a strategy which usually requires long reaction times, high temperatures, or both. In this Perspective, we will discuss a novel approach to the generation of arylcopper(I) species *via* 1,3-halogen migration from aryl halides under mild conditions.

Discussion

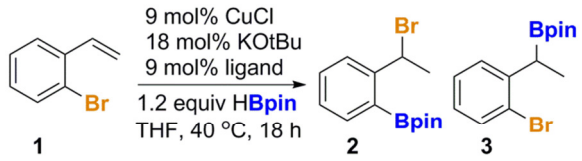
Our interest in the field of arylcopper chemistry began with a serendipitous discovery that 2-bromostyrenes undergo an unusual rearrangement in the presence of a dppbz-supported copper hydride (dppbz = 1,2-bis(diphenylphosphino)benzene) and pinacolborane (HBpin).[9] We expected to obtain a benzyl boronic ester,[10] but the observed product appeared to result from a 1,3-halogen migration[11] with concomitant borylation of the carbon-bromine bond (Equation 1). The unique nature of this transformation warranted further investigation.

Equation 1: Attempt to synthesize benzyl boronic ester.



In the process of optimizing the reaction, we found that 1,3-halogen migration was viable under a number of conditions (solvent, temperature, time), but was highly sensitive to the identity of the ligand. Despite investigating numerous ligands (a small selection is shown in Table 1), only two ligands yielded the 1,3-halogen migration product (entries 1, 6). Most ligands degraded the starting material, while producing no identifiable products, presumably due to atom-transfer radical polymerization.[12] Nitrogenated ligands, such as phenanthroline (entry 4), resulted in no reaction. Only one ligand, dCype,

Table 1: Ligand optimization of 1,3-halogen migration.

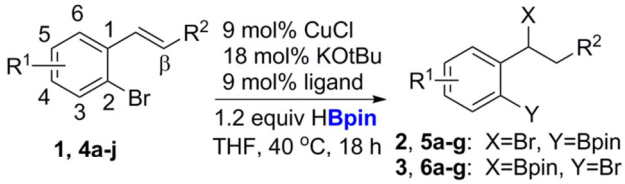


entry	ligand	1	2	3
1	dppbz	<10%	0%	<10%
2	PCy_3	60%	29%	0%
3	dppe	30%	0%	0%
4	phen	94%	0%	0%
5	Xantphos	1%	72%	0%
6	dCype	0%	0%	70%

performed well (entry 6) and was pursued in further investigations.

The scope of the 1,3-halogen migration reaction was fairly general (Table 2). However, more electron poor substrates tended to favor formation of the hydroboration side product (entries 2-3).

Table 2: Selected substrate scope of 1,3-halogen migration.



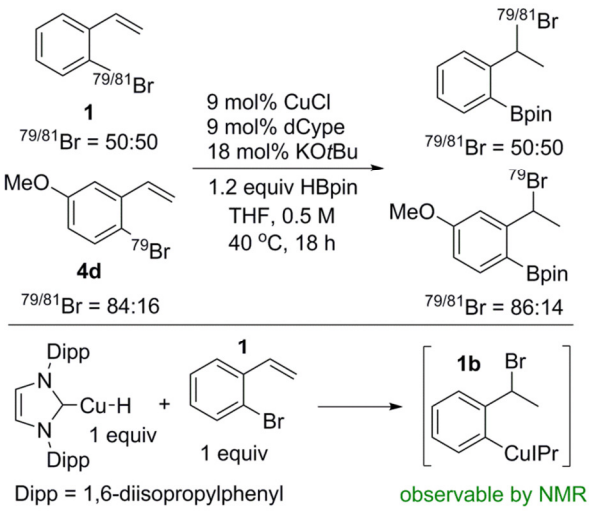
entry	substrate	yield		yield	
1	H	94%	**2**	0%	**3**
2	5-Br	57%	**5a**	31%	**6a**
3	5-F	49%	**5b**	28%	**6b**
4	5-Ph	73%	**5c**	0%	**6c**
5	5-OMe	87%	**5d**	0%	**6d**
6	4-F	89%	**5e**	0%	**6e**
7	4-*t*Bu	65%[a]	**5f**	0%	**6f**
8	β-Me	75%	**5g**	0%	**6g**

[a] trapped with propargyl alcohol before isolation

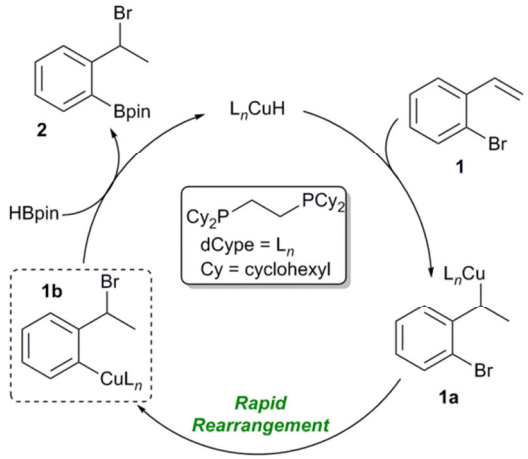
Our preliminary mechanistic studies have shown that 1,3-halogen migration is likely an intramolecular process that proceeds through an arylcopper(I) species. When styrene **1** and ^{79}Br-enriched styrene **4d** were subjected to the reaction conditions, there was no crossover of the bromine isotopes, indicating an intramolecular migration (Scheme 2, top). Additionally, if styrene **1** is added to a solution of IPrCuH, arylcopper(I) species **1b** is the only observed species in solution (Scheme 2, bottom).

We believe that a copper(I)-hydride is generated *in situ* as the active catalyst. The copper hydride then adds to an olefin to forming a benzyl copper(I) species **1a** (Scheme 3). The benzyl copper(I) undergoes rapid rearrangement to form the aryl copper(I) intermediate **1b**, which then reacts with HBpin to regenerate the copper hydride catalyst and yield the product. In our proposed mechanism, the generation of the ArCu, as well as the regeneration of the active catalyst, proceeds through a completely different pathway than the majority of mechanisms that are proposed to involve aryl copper species.

Scheme 2: Mechanistic studies.



Scheme 3: Mechanism of Cu-catalyzed 1,3-halogen migration.

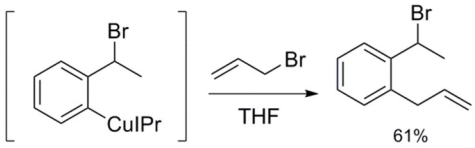


A big question that remains is the pathway by which **1a** (Scheme 3) is transformed to **1b**. A thorough mechanistic study is currently being conducted using a combination of experimental and computational approaches; results will be reported in due course.

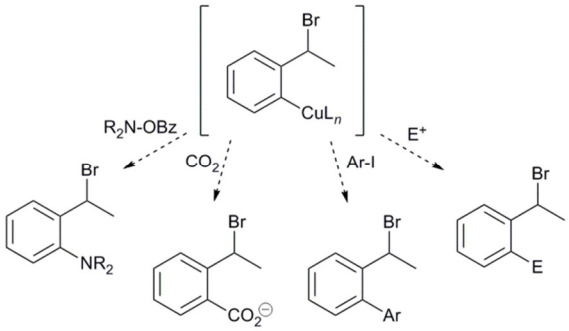
The synthetic utility of Cu-catalyzed 1,3-halogen migration is also being pursued in our laboratories. In our initial report, we demonstrated that the benzyl bromide could be transformed into a wide range of products *via* nucleophilic displacement of the bromide, as well as coupling of the aryl boronic ester.[9] A more efficient approach would be to directly intercept the arylcopper(I) species with a variety of different coupling partners to reveal new catalytic reactions that produce a wide range of benzyl- and aryl-functionalized products. For example, treatment of the arylcopper(I) generated from the reaction between a copper hydride and 2-bromostyrene with allyl bromide promotes C-C bond formation to yield the aryl-functionalized product in 61% yield (Equation 2) and regenerates a L_nCuBr species. Current work focuses on rendering this reaction catalytic, as well as developing tandem reactions that can utilize the benzyl bromide for further

functionalization. Finally, we are focused on investigating the reactivity of our ArCu species with electrophiles described in the work of Ball,[13] Lalic,[14] Daugulis,[15] Sadighi,[16] Giri,[17] and others to expand the scope of C-C and carbon-heteroatom bond-forming reactions that can be achieved using 1,3-halogen migration as a key step. Scheme 4 shows a selection of coupling partners that are currently under investigation to provide a wide range of synthetically useful products. For example, trapping of our arylcopper(I) intermediate with benzoyloxyamines, carbon dioxide, aryl halides, and other electrophiles could be envisaged.

Equation 2: Trapping arylcopper with allyl bromide.



Scheme 4: Potential arylcopper(I) reactivity.



The bromine activating group in our strategy is 'recycled'[18] in order to deliver the benzyl bromide. As the product itself is an excellent electrophile, cascade reactions are being designed to provide products resulting from functionalization at both the aryl and benzylic carbons, including cyclic scaffolds with drug-like properties. The challenges of facilitating turnover to the copper hydride and minimalizing atom transfer radical polymerization will be crucial to enabling catalytic versions of this interesting chemistry.

Conclusions

Copper(I) catalyzes a 1,3-halogen migration/borylation cascade that proceeds under mild conditions to recycle the bromine activating group. This 1,3-halogen migration represents a unique entry to arylcopper(I) species, which are typically formed *via* transmetallation. Mechanistic studies support an intramolecular migration leading to an arylcopper(I) species. Future developments will focus on a better understanding of the mechanism of this unusual transformation and harnessing the reactivity of this intermediate for powerful C-C and carbon-heteroatom bond-forming reactions that can functionalize both aryl and benzylic carbons.

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Notes and references

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1 H. Gilman, R. G. Jones, L. A. J. Woods, *J. Org. Chem.* 1952, **17,** 1630-1634.
2 N. Yoshikai, E. Nakamura, *Chem. Rev.* 2012, **112,** 2339-2372.
3 J. R. Herron, V. Russo, E. J. Valente, Z. T. Ball, *Chem. Eur. J.* 2009, **15,** 8713-8716.
4 H.-Q. Do, R. M. Kashif Kahn, O. Daugulis, *J. Am. Chem. Soc.* 2008, **130,** 15185-15192.
5 A. M. Whittaker, R. P. Rucker, G. Lalic, *Org. Lett.* 2010, **12,** 3216-3218.
6 T. Ohishi, M. Nishiura, Z. Hou, *Angew. Chem. Int. Ed.* 2008, **47,** 5792-5795.
7 R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *Angew. Chem. Int. Ed.* 2012, **51,** 3953-3956.
8 S. K. Gurung, S. Thapa, A. S. Vangala, R. Giri, *Org. Lett.* 2013, **15,** 5378-5381.
9 R. D. Grigg, R. Van Hoveln, J. M. Schomaker, *J. Am. Chem. Soc.* 2012, **134,** 16131-16134.
10 D. Noh, H. Chea, J. Ju, J. Yun, *Angew. Chem. Int. Ed.* 2009, **48,** 6062-6064.
11 For an example of a copper-catalyzed 1,3-hydrogen migration see: Y. Yang, S. Buchwald, *Angew. Chem. Int. Ed.* 2014 DOI: 10.1002/anie.201402449.
12 J.-S. Wang, K. Matyjaszewski, *Macromolecules,* 1995, **28,** 7901-7910.
13 J. R. Herron, Z. T. Ball, *J. Am. Chem. Soc.* 2008, **130,** 16486-16487.
14 R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.* 2012, **134,** 6571-6574.
15 H. Tran-Vu, O. Daugulis, *ACS Catal.* 2013, **3,** 2417-2440.
16 N. P. Mankad, T. G. Gray, D. S. Laiter, J. P. Sadighi, *Organometallics,* 2004, **23,** 1191-1193.
17 S. K. Gurung, S. Thapa, A. Kafle, D. A. Dickie, R. Giri, *Org. Lett.* 2014, **16,** 1264-1267.
18 J. M. Schomaker, R. D. Grigg, *Synlett.* 2013, **24,** 401-407.