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Copper-Catalyzed Recycling of Halogen Activating Groups via 1,3-Halogen Migration

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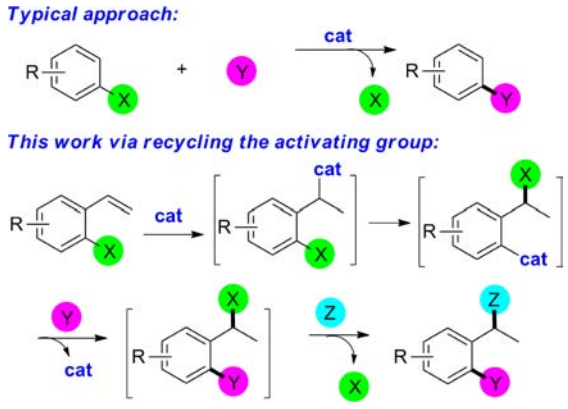
Supporting Information

ABSTRACT: A Cu(I)-catalyzed 1,3-halogen migration reaction effectively recycles an activating group by transferring bromine or iodine from a sp^2 to a benzylic carbon with concomitant borylation of the Ar−X bond. The resulting benzyl halide can be reacted in the same vessel under a variety of conditions to form an additional carbon−heteroatom bond. Cross-over experiments using an isotopically enriched bromide source support intramolecular transfer of Br. The reaction is postulated to proceed via a Markovnikov hydrocupration of the *o*-halostyrene, oxidative addition of the resulting Cu(I) complex into the Ar−X bond, reductive elimination of the new sp^3 C−X bond, and final borylation of an Ar−Cu(I) species to turn over the catalytic cycle.

The ability to functionalize aromatic rings is an important part of the synthetic chemist's repertoire.[1] Typically, aryl halides or pseudohalides are employed to provide reliable regioselectivity (Scheme 1, top). However, use of an activating group imbues these transformations with less-than-ideal atom economy, as only one new bond is formed at the expense of the waste product. Direct C−H functionalization eliminates the need for preactivation, yet the need for additives in many of these reactions means it is not a foregone conclusion that this approach is less wasteful.[2] Important advances have recently been made toward more practical and general directing groups for C−H functionalization,[3] but the use of halide or pseudohalide activating groups remains the most convenient and commonly employed route to aryl functionalization. We felt that the use of activating groups might be more attractive if a way to "recycle" the halide could be developed.[4] In this Communication, we report a Cu-catalyzed 1,3-halogen migration/borylation reaction that permits a halogen activating group to be used for the sequential formation of two new carbon−heteroatom bonds.

Scheme 1. Traditional Cross-Coupling Approach vs a New Mode of Arene Functionalization



Conventional arene functionalization utilizes a range of transition metal catalysts and coupling partners to transform aryl−X bonds into new carbon−carbon or carbon−heteroatom bonds, as represented by C−Y in Scheme 1. Conceptually, our approach differs in that the catalyst does not interact with the C−X bond directly, but rather with a functional group, such as an olefin. Activation of the C−X bond then occurs with subsequent transfer of X to a new carbon in the molecule, followed by the formation of C−Y. The activating group X is recycled by the construction of a final C−Z bond.

The work described herein arose from our attempts to prepare **3** from **1** using a reported CuCl/dppbz catalyst (Table 1, entry 1).[5] While none of the desired hydroboration was noted, due mainly to polymerization of the styrene, we observed small amounts of unexpected byproduct **2**. Curious as to whether **2** might be obtained exclusively, we undertook an investigation of several mono- and bidentate ligands for CuCl (Table 1).

These preliminary studies revealed that neither monodentate phosphine ligands (entries 2, 3) nor electron-poor bidentate ligands (entries 4−8) were capable of promoting the desired reaction. Phenanthroline (entry 9) gave only recovered starting material. Interestingly, the *trans*-spanning Xantphos ligand (entry 10) gave exclusively the hydroboration product **3** in 72% yield, while a similar DPEphos ligand (entry 11) gave no **2** or **3**. Finally, we found that the electron-rich and bulky bidentate phosphine ligand, bis(dicyclohexylphosphino)ethane (dCype, entry 12), exclusively promoted the desired 1,3-halogen migration.[6]

Further reaction optimization was undertaken using the dCype ligand (Table 2). THF (entry 1) proved superior to toluene, CH_2Cl_2, Et_2O, CH_3CN, and $CHCl_3$ (entries 3−7), although dioxane (entry 2) gave similar results. Lowering the temperature to 40 °C (entry 8) did not increase the yield compared to entry 1, but improved the mass balance. Finally, scaling the reaction to 5 mmol (entry 9) reproducibly increased the yield to 94% of **2**.

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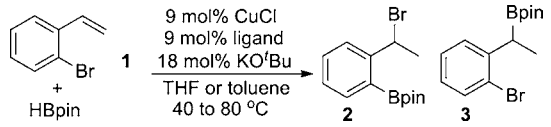
Table 1. Initial Ligand Screen[a]



entry	ligand	1 : 2 : 3
1	dppbz	<10% : <10% : 0%
2	PPh_3	50% : 0% : 0%
3	PCy_3	60% : 0% : 29%
4	dppm	51% : 0% : 41%
5	dppe	30% : 0% : 0%
6	dppp	19% : 0% : 0%
7	dppb	68% : 0% : 0%
8	dppf	0% : 0% : 0%
9	phen	94% : 0% : 0%
10	Xantphos	1% : 0% : 72%
11	DPEphos	42% : 0% : 0%
12	**dCype**	**0% : 70% : 0%**

[a]NMR yields using 1,1,1,2-tetrachloroethane as internal standard.

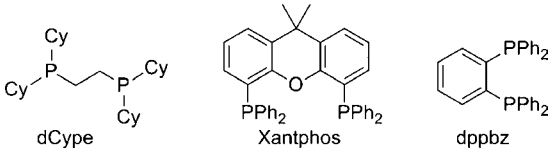
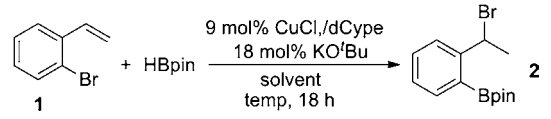


Table 2. Reaction Optimization[a]

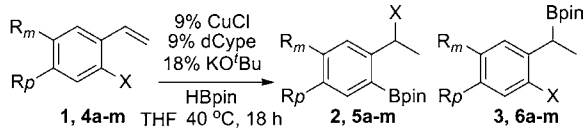


entry	solvent	temp (°C)	2 : 1
1	THF	70	73% : 2%
2	dioxane	70	68% : 0%
3	toluene	70	41% : 0%
4	CH_2Cl_2	70	54% : 6%
5	Et_2O	70	40% : 3%
6	CH_3CN	70	0% : 2%
7	$CHCl_3$	70	0% : 12%
8	THF	40	60% : 27%
9[b]	**THF**	**40**	**94% : 0%**

[a]NMR yields using 1,1,1,2-tetrachloroethane as internal standard. [b]Isolated yield from the reaction on a 5 mmol scale.

With optimized conditions in hand, we explored the scope of the reaction (Table 3). In general, 1,3-bromine migration was favored with a variety of substrates. However, placing electron-withdrawing halogen groups *meta* to the olefin (entries 2, 3) diminished the 1,3-halogen migration and resulted in significant hydroboration. Other groups at this position favored trans-position. Curiously, if a bromide group (entry 8) was placed *para* to the olefin, the hydrocupration did not occur at all. Neutral and electron-donating substituents F, Ph, ^{t}Bu, and OMe (entries 9–12) *para* to the alkene yielded predominantly the 1,3-halogen migration products. For some of these cases, the benzyl bromide products were sensitive to elimination and were trapped with propargyl alcohol prior to isolation, illustrating the potential of this chemistry in cascade reactions to construct more complex compounds. Consistent with prior observations,[5a] the 4-methoxy substrate (entry 12) reacted slowly. Finally, substitution on the β carbon of the styrene

Table 3. Substituent Effects on 1,3-Halogen Migration[a]



entry		R_m	R_p	yield
1	**1**	H	H	94% **2**, 0% **3**
2	**4a**	Br	H	57% **5a**, 31% **6a**
3	**4b**	F	H	49% **5b**, 28% **6b**
4	**4c**	Ph	H	73% **5c**, 0% **6c**
5	**4d**	1-Napth	H	69% **5d**,[b] 0% **6d**
6	**4e**	4-$MeOC_6H_4$	H	67% **5e**, 0% **6e**
7	**4f**	OMe	H	87% **5f**, 0% **6f**
8	**4g**	H	Br	0% **5g**, 0% **6g**
9	**4h**	H	F	89% **5h**, 0% **6h**
10	**4i**	H	Ph	66% **5i**,[b] 12% **6i**
11	**4j**	H	^{t}Bu	65% **5j**,[b] 0% **6j**
12	**4k**	H	OMe	36% **5k**,[b,c] 0% **6k**
13	**4l**	H	H	75% **5l**, 0% **6l**
14	**4m**	H	H	59% **5m**,[b,e] 0% **6m**

[a]X = Br except for entry 14, where X = 1. [b]Product was trapped with propargyl alcohol prior to isolation. [c]79% conversion. [d]Substrate was 1-bromo-2-((1*E*)-prop-1-en-1-yl)benzene. [e]87% conversion.

(entry 13) was tolerated in the 1,3-halogen migration, as *trans*-β-methylstyrene **4l** gave **5l** in 75% yield. Although 2-chlorostyrenes underwent halogen transposition with poor conversions, it was found that 2-iodostyrene **4m** did produce the transposed product (entry 14), although only partial conversion was observed. The sensitive benzyl iodide had to be trapped with propargyl alcohol to give **5m** in moderate yield. The reactivity of 2-bromo-3-methylstyrene and 2-bromo-6-methylstyrene was also examined. While 1,3-halogen migration was observed, the conversion was low. Less bulky catalysts are being developed for sterically encumbered substrates.

The benzyl boronic esters that result from the typical hydroboration of styrenes are often utilized as synthons for benzylic carbanions.[7] In contrast, the 1,3-halogen migration observed in our chemistry allows access to intermediates that are electrophilic at the benzylic carbon. Facile recycling of the activating group was demonstrated by transforming **1** into a variety of benzyl-substituted boronic esters (Scheme 2). For example, propargyl and *p*-methoxybenzyl alcohols, aniline, and sodium azide were all suitable nucleophiles for reacting with the benzyl bromide to yield **7**–**9**. These reactions represent formal Cu-catalyzed hydroalkoxylation and hydroaminations that are typically accomplished using more expensive precious metal catalysts including Pd, Rh, or Au.[8,9]

In addition to functionalization at the benzylic carbon, the boronic ester could also be transformed into either a carbon–heteroatom or carbon–carbon bond. For example, treatment of **1** under Cu catalysis, followed by reaction with 3-phenylpropan-1-ol and an oxidative workup using H_2O_2, yielded the phenol **10**.[10] Recycling the bromine activating group also provided a flexible platform for convergent syntheses of heterocycles. Tandem 1,3-halogen migration/functionalization/Suzuki couplings of **1** were accomplished using (*Z*)-3-iodopent-2-en-1-ol and 2-iodobenzyl alcohol to yield the heterocyclic dihydroxepins **11** and **12**.[11] Finally, halogen migration followed by reaction with 2-iodoaniline and

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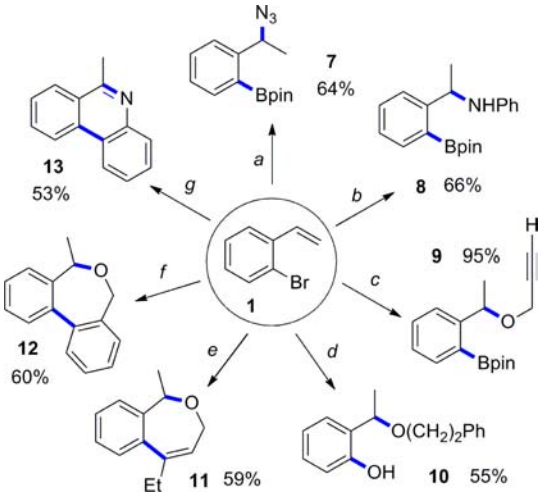
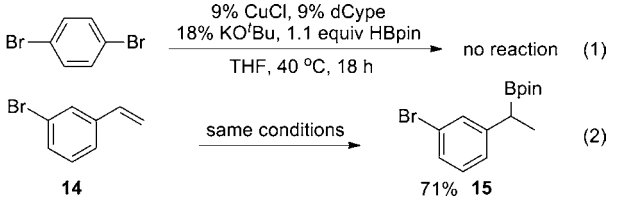
Scheme 2. Recycling of the Activating Group[a]



[a]Cu-catalyzed halogen transposition was followed by addition of the following: (a) 1.1 equiv of NaN_3, DMSO. (b) 1.2 equiv of aniline, 0.2 equiv of 18-crown-6, 1.5 equiv of K_2CO_3. (c) 1.2 equiv of propargyl alcohol, 0.2 equiv of 18-crown-6, 1.5 equiv of K_2CO_3. (d) $Ph(CH_2)_2OH$, 0.2 equiv of 18-crown-6, 1.0 equiv of K_2CO_3, then H_2O_2/NaOH. (e) (Z)-3-Iodopent-2-en-1-ol, 1.2 equiv of K_2CO_3, 0.2 equiv of 18-crown-6, then 10 mol% $PdCl_2dppf$, 3 equiv of $K_3PO_3{\cdot}H_2O$, 9:1 DME:H_2O. (f) 2-Iodobenzyl alcohol, 1.2 equiv of K_2CO_3, 0.2 equiv of 18-crown-6, then 10 mol% $PdCl_2dppf$, 3 equiv of $K_3PO_3{\cdot}H_2O$, 9:1 DME:H_2O. (g) 2-Iodoaniline, 0.2 equiv of 18-crown-6, 1.5 equiv of K_2CO_3, then 10 mol% $PdCl_2dppf$, 3 equiv of $K_3PO_3{\cdot}H_2O$, 9:1 DME:H_2O, followed by H_2O_2.

subsequent Pd-catalyzed coupling/oxidation gave the biologically active phenanthridine core of **13**.[12]

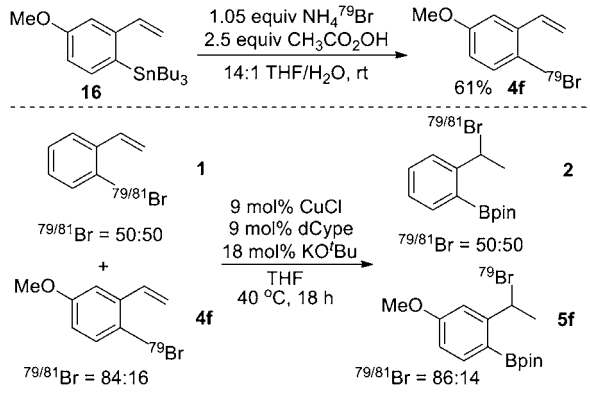
We wanted to ensure that we were not observing direct borylation of the Ar−Br bond, followed by an unexpected bromination of the alkene. Examples of aryl bromides that undergo Cu-catalyzed borylation in the absence of a directing group have been reported, but these reactions are rare.[13] In our case, when both 1,4-dibromobenzene and **14** were subjected to the reaction conditions (eqs 1 and 2), no borylation of either



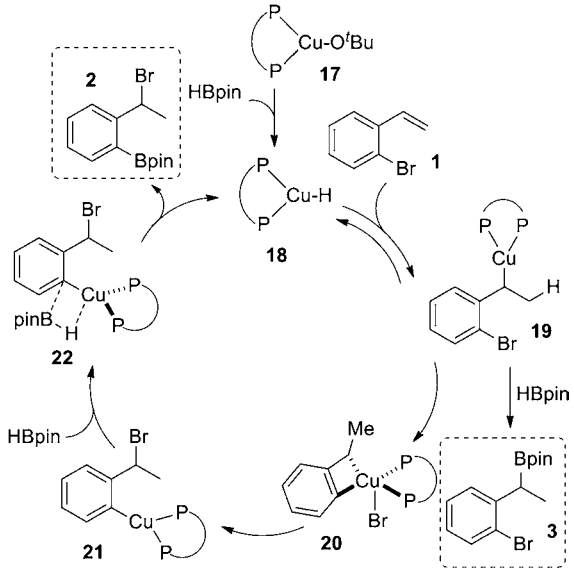
C−Br bond was observed. Subjecting the typical hydroboration product **3** to the reaction conditions also did not lead to **2**, indicating direct borylation of **1** is not a likely reaction pathway.

We also demonstrated that the 1,3-halogen migration is likely an intramolecular process by performing a cross-over experiment using isotopically enriched ^{79}Br. The enriched aryl bromide **4f** (Scheme 3) was prepared by reacting the tributylaryltin **16** with ∼85% isotopically enriched $NH_4{}^{79}Br$ (see the Supporting Information for further details).[14] After we ensured that the unlabeled styrenes **1** and **4f** reacted at comparable rates, reaction of **4f** in the presence of non-isotopically enriched **1** showed no additional incorporation of ^{79}Br into **2** or degradation of the $^{79/81}Br$ ratio in the conversion of **4f** to **5f** within statistical error.

Scheme 3. Cross-Over Experiment Using Isotopically Enriched ^{79}Br



Scheme 4. A Potential Mechanism for the Cu-Catalyzed 1,3-Halogen Migration



One proposed mechanism for the 1,3-halogen migration is illustrated in Scheme 4. Reaction of the precatalyst **17** with HBpin generates the active, phosphine-supported Cu−H species **18**.[15] In the absence of an *ortho* C−Br bond, reversible Markovnikov hydrocupration of the styrenic double bond of **1** with **18** would be followed by reaction with HBpin to give the typical hydroboration product **3**.[16,17] However, the presence of an *ortho* C−Br bond in **19** may promote a subsequent oxidative addition to yield a formal Cu(III) species, **20**.[18,19] Reductive elimination of **20** to **21** could then be followed by a σ-bond metathesis with HBpin to yield **2** and regenerate the active Cu−H catalyst **18**.[20] Other possibilities for the mechanism of the 1,3-migration could involve intermediate π-allyl Cu species, single-electron-transfer processes, halogen atom transfer, or π-complexation to the halide.[21] Computational and further experimental studies are in progress to shed more light on whether a Cu(I)/Cu(III) or a Cu(I)/Cu(II) cycle is more likely and will be used to guide our further exploration of this 1,3-halogen migration reaction.

In conclusion, Cu(I) promotes a cascade 1,3-halogen migration/borylation/functionalization that proceeds under mild conditions to recycle the bromine activating group. Future studies will focus on expanding the reaction scope to include

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other functional groups capable of directing the Cu catalysis and other activating groups that can be transferred. Initial promising results in enantioselective migration are being optimized. The development of other efficient cascade reactions and computational studies to better understand the mechanism of this unusual transformation are under way.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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