Chemistry Letters

Copper(I)-Catalyzed Stereoselective Defluoroborylation of Aliphatic *Gem*-Difluoroalkenes

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Advance Publication on the web August 22, 2018
doi:10.1246/cl.180656

Copper(I)-Catalyzed Stereoselective Defluoroborylation of Aliphatic *Gem*-Difluoroalkenes

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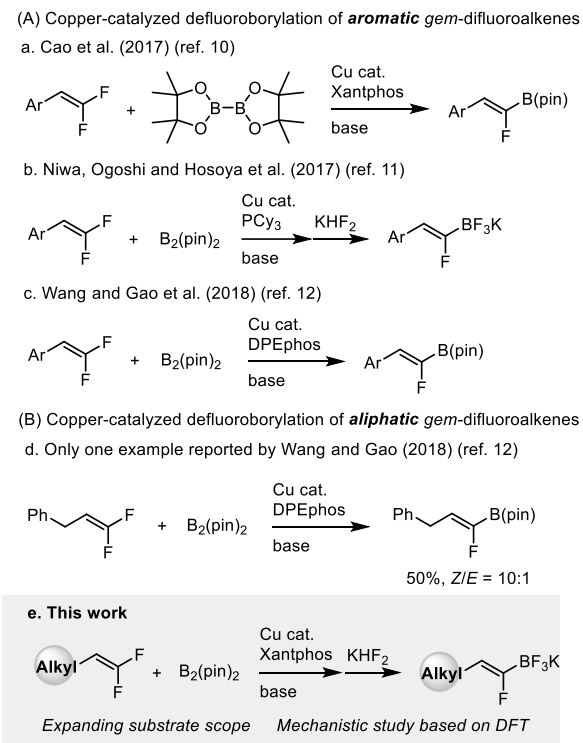
This study reports a method for the stereoselective copper(I)-catalyzed defluoroborylation of aliphatic *gem*-difluoroalkenes to afford (*Z*)-monofluoro-substituted borylalkenes. *Gem*-difluoroalkenes bearing a variety of functional groups were efficiently borylated with high stereoselectivity. A theoretical study of the reaction mechanism is also described.

Keywords: Copper, Fluoroalkene, Borylation

Fluorine has distinctive properties, with the introduction of a fluorine atom able to greatly alter the properties of bioactive compounds.[1–5] Of the many existing fluorinated motifs, monofluoroalkenes are of particular interest, especially in medicinal chemistry, because they have the potential to act as amide bond isosteres and enol mimics.[6] Therefore, the development of efficient and stereoselective synthetic methods for preparing such organofluorine compounds is highly desirable.

Organoboron compounds are widely recognized as powerful building blocks in synthetic chemistry because they can be readily applied to stereospecific functionalization.[7–9] Consequently, monofluoro-substituted borylalkenes have received considerable attention as useful intermediates for the preparation of various monofluoroalkene derivatives through a stereospecific boron functionalization process.[10–12] In 2017, Cao and coworkers reported the copper(I)-catalyzed stereoselective synthesis of (*Z*)-monofluoro-substituted borylalkenes using a diboron compound and aromatic *gem*-difluoroalkenes via a β-fluoroelimination process (Scheme 1a).[10] Subsequently, Niwa, Ogoshi, and Hosoya reported the copper(I)-catalyzed defluoroborylation of aromatic *gem*-difluoroalkenes and its application to the synthesis of a fluoroalkene mimic of an antihyperlipidemic drug (Scheme 1b).[11] More recently, Wang and Gao developed a similar defluoroborylation of aromatic *gem*-difluoroalkenes (Scheme 1c).[12] As for the borylation of aliphatic *gem*-difluoroalkenes, only one example has been reported, by Gao and Wang in 2018, where the defluoroborylation of a *gem*-difluoro-substituted allyl benzene proceeded in the presence of a copper(I) catalyst to give the corresponding borylation product in moderate yield (Scheme 1d).[12] However, the scope of aliphatic alkenes has yet to be investigated. Herein, we report the stereoselective defluoroborylation of various aliphatic *gem*-difluoroalkenes using a diboron compound in the presence of a copper(I)/Xantphos complex catalyst (Scheme 1e). *Gem*-difluoroalkenes bearing various functional groups were efficiently borylated with high stereoselectivity. A theoretical study of the reaction mechanism is also described.

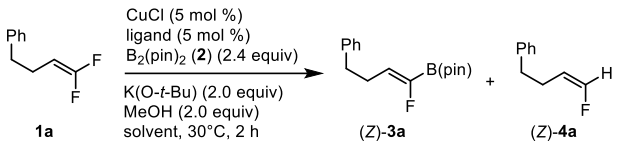


Scheme 1. Copper(I)-catalyzed defluoroborylation of *gem*-difluoroalkenes.

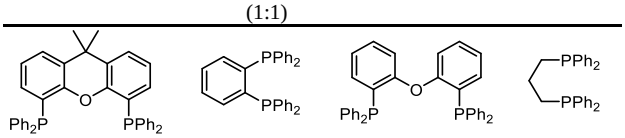
We have previously reported that a copper(I)/Xantphos complex efficiently catalyzed the formal hydrodefluorination of aromatic *gem*-difluoroalkenes using a diboron reagent.[13,14] This reaction presumably proceeds through borylcupration of the alkene, followed by β-fluoroelimination to form (*Z*)-monofluoro-substituted borylalkenes as a key intermediate. Therefore, we wondered whether this catalytic system could be used for the stereoselective defluoroborylation of aliphatic *gem*-difluoroalkenes. Pleasingly, we found that the reaction of *gem*-difluoroalkene **1a** with 2.4 equivalent of bis(pinacolato)diboron (**2**) in the presence of 5 mol% CuCl, 5 mol% Xantphos as ligand, 2.0 equivalent of K(O-*t*-Bu), and 2.0 equivalent of MeOH[15] in THF afforded the desired (*Z*)-monofluoro-substituted borylalkene **3a** in good yield with excellent stereoselectivity (64%, >95:5 *Z*/*E*, Table 1, entry 1). Other phosphine ligands, such as 1,2-bis(diphenylphosphino)benzene (dppbz) and bis[2-(diphenylphosphino)phenyl] ester (DPEphos) were also investigated, but gave poor results (entries 2–6). No product was obtained when 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) was used

as a ligand (entry 7). We found that the choice of reaction solvent significantly affected the reactivity (entries 8–14). Using toluene afforded desired product (*Z*)-**3a** and protonated byproduct (*Z*)-**4a** in 28% and 18% yields, respectively (entry 8), while using 1,2-dimethoxyethane (DME) improved the product yield (75%, entry 10). Interestingly, highly polar solvents, such as 1,3-dimethyl-2-imidazolidinone (DMI), provided protonated product (*Z*)-**4a** as the major product (entry 12). Finally, we found that using a mixed solvent (THF/DMF = 1:1, *v/v*) afforded the highest product yield with excellent stereoselectivity (85%, >95:5 *Z*/*E*, entry 14). While the minor *E* isomer was produced under the conditions used by Wang and Gao, our reaction showed near-perfect stereoselectivity (>95:5 *Z*/*E*).

Table 1. Optimization of reaction conditions for the copper(I)-catalyzed defluoroborylation of aliphatic *gem*-difluoroalkenes.[a]

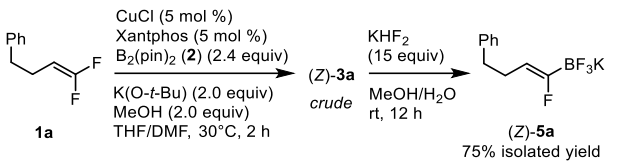


Entry	Ligand	Solvent	Yield of **3a** [%][b]	Yield of **4a** [%][b]	*Z*/*E* of **3a**[b]
1[c]	Xantphos	THF	64	<5	>95:5
2	dppbz	THF	<5	<5	–
3	DPEphos	THF	29	<5	80:20
4	dppp	THF	<5	<5	–
5	PPh_3	THF	<5	<5	–
6	PCy_3	THF	<5	<5	–
7	IPr・HCl	THF	<5	<5	–
8	Xantphos	toluene	28	18	>95:5
9	Xantphos	Et_2O	43	<5	>95:5
10	Xantphos	DME	75	<5	>95:5
11	Xantphos	DMF	46	<5	>95:5
12	Xantphos	DMI	25	32	>95:5
13	Xantphos	DME/DMF (1:1)	46	<5	>95:5
14	Xantphos	THF/DMF (1:1)	85	<5	>95:5



[a]Conditions: **1a** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), bis(pinacolato)diboron **2** (1.2 mmol), K(O-*t*-Bu) (1.0 mmol), and MeOH (1.0 mmol) in solvent (1.0 mL). [b]Determined by NMR analysis with an internal standard.

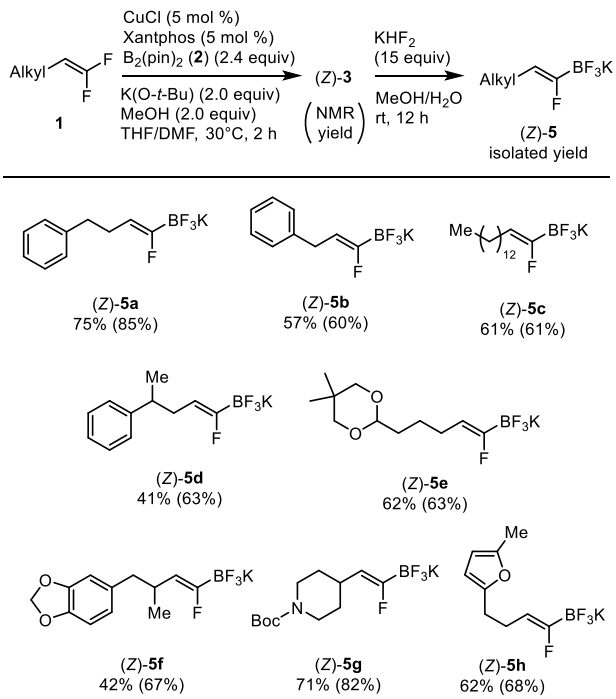
Next, we attempted to isolate the (*Z*)-monofluoro-substituted borylalkenes, which tend to be partially decomposed by silica gel column chromatography. The borylation product (*Z*)-**3a** could be purified and isolated by converting into the corresponding trifluoroborate (*Z*)-**5a**[16] through treatment with KHF_2 (Scheme 2).



Scheme 2. Isolation of the borylation product.

With the optimized reaction conditions in hand, we proceeded to investigate the substrate scope (Table 2). Simple aliphatic substrates **1a**–**1d** were efficiently borylated to afford corresponding trifluoroborates (*Z*)-**5a**–**5d** in good to high yields. *Gem*-difluoroalkenes bearing acetal **1e**, benzoxazole **1f**, Boc-protected amine **1g** and furan **1h** moieties were tolerate and provided the desired borylation products (*Z*)-**5e**–**5h** in good yields. Notably, no *E* isomers were produced under these reaction conditions.

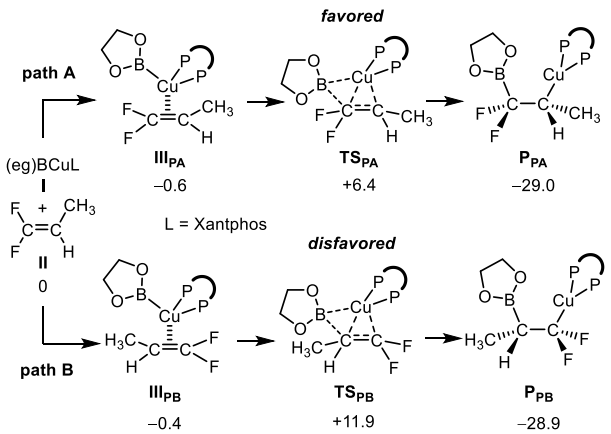
Table 2. Substrate scope for the copper(I)-catalyzed defluoroborylation of aliphatic *gem*-difluoroalkenes.[a,b]



[a]Conditions: **1** (0.5 mmol), CuCl (0.025 mmol), Xantphos (0.025 mmol), bis(pinacolato)diboron **2** (1.2 mmol), K(O-*t*-Bu) (1.0 mmol), and MeOH (1.0 mmol) in THF/DMF (1:1, 1.0 mL). [b]Yields of (*Z*)-**3** were determined by ^{1}H NMR analysis using an internal standard and are shown in parentheses.

This reaction presumably proceeds through an addition–elimination pathway.[10-12] However, the regioselectivity of addition of the borylcopper(I) active species to aliphatic *gem*-difluoroalkenes has not been studied.[11,17] Therefore, preliminary density functional theory (DFT) calculations using *gem*-difluoropropene as a model substrate were conducted to determine the regioselectivity of the reaction (Scheme 3). All calculations were conducted at the ωB97X-D/def2-SVP level of theory (see SI for

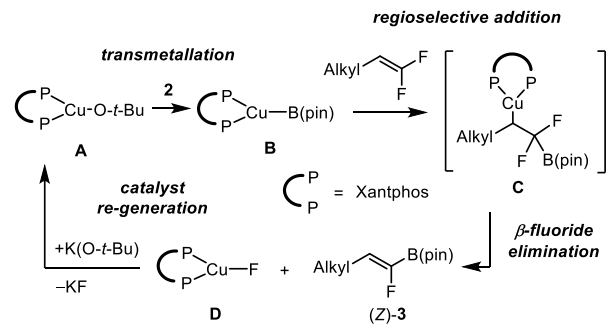
computational details and references). As shown in Scheme 3, the activation free energy for path A, where a boron atom connects with a *gem*-difluoro-substituted carbon atom, was lower than that of path B, where a copper connects with a *gem*-difluoro-substituted carbon atom, by 5.5 kcal/mol. In the transition state in path B, a transient five-coordinated geometry with highly congested environment between a boryl group and the methyl group causes destabilization of the transition state.[18] This can explain the transition state in path A having a lower barrier than that in path B.



[a]Relative *G* value (kcal/mol) at 298 K, 1.0 atm, gas phase.

Scheme 3. DFT calculations (ωB97X-D/def2-SVP) on the regioselectivity of the reaction.

On the basis of this theoretical study, we have proposed a mechanism for this process, as shown in Scheme 4. Copper(I) alkoxide **A** is formed by the reaction of CuCl, ligand, and K(O-*t*-Bu) mixture initially reacts with diboron compound **2** to form borylcopper(I) intermediate **B**. The regioselective addition of borylcopper(I) to the *gem*-difluoroalkene forms alkylcopper(I) species **C**. Subsequent *β*-fluoro-elimination affords the corresponding defluoroborylation product (*Z*)-**3** and copper fluoride **D**. Finally, copper fluoride **D** reacts with K(O-*t*-Bu), followed by transmetallation with diboron **2** to form borylcopper(I) active species **B**.[19]



Scheme 4. Possible mechanism based on the DFT study.

In summary, we have demonstrated that the copper(I)/Xantphos complex-catalyzed defluoroborylation of aliphatic *gem*-difluoroalkenes with a diboron compound proceeded efficiently to give the borylation products with excellent stereoselectivity. The products can be isolated by conversion into the corresponding trifluoroborates in good yields. A theoretical study was conducted to elucidate the regioselectivity of the reaction. We believe that the newly synthesized fluorine-containing borylalkenes will have wide applications in medicinal chemistry and drug discovery.

Acknowledgments

This work was financially supported by the Japan Society for the Promotion of Science via KAKENHI grants (JP18H03907).

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