A Copper(I)-Catalyzed Radical Relay Reaction Enabling the Intermolecular 1,2-Alkylborylation of Unactivated Olefins

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ABSTRACT: The first catalytic intermolecular 1,2-alkylborylation reaction via a radical-relay mechanism between unactivated olefins, bis(pinacolato)diboron, and an alkyl electrophile is reported. Successful implementation of this method requires that the competing boryl substitution of the alkyl electrophile is retarded to facilitate the radical relay. This challenge was overcome using electronically or sterically demanding alkyl electrophiles, which results in the simultaneous, and highly regioselective introduction of a *gem*-difluoro, monofluoro, tertiary, or secondary alkyl group and a boryl group across the C=C double bond.

INTRODUCTION

The transition-metal-catalyzed radical-relay strategy for the intermolecular 1,2-carbofunctionalization of widely available unactivated olefins is one of the most useful protocols for rapidly constructing complex carbon-based structures. Only a catalytic amount of a radical-generating reagent is required[1–6] and typically, this process involves a single-electron transfer (SET) from an organometallic intermediate to an electrophile. Subsequent addition of the resulting radical to an olefin occurs with high regioselectivity and is followed by radical recombination.[7–15] One of the main advantages of this protocol is that it tolerates electronically or sterically demanding alkyl electrophiles that cannot be used in catalytic 1,2-carbofunctionalization reactions that involve S_N2-type nucleophilic substitutions. Similarly, the intermolecular 1,2-carboborylation of olefins via a radical relay, a transformation that involves simultaneous installation of a C–C bond and a transformable C–B bond, would undoubtedly be highly attractive. This approach would expand the scope of synthetically accessible organoboron compounds that bear complex carbon frameworks.[16–19] Despite the significant progress that has been made in radical-relay chemistry, the intermolecular 1,2-carboborylation of olefins via a radical relay has not yet been reported.[20,21]

During the past decades, an array of copper(I)-catalyzed 1,2-alkylborylation reactions of olefins has been reported (Scheme 1).[16–19,22,23] In general, these reactions proceed via a two-electron mode, in which a borylcopper(I) intermediate reacts with an olefin followed by electrophilic substitution of the resulting alkylcopper(I) intermediate. A new C(sp^3)–B bond and a new C(sp^3)–C bond are simultaneously formed at the terminal and internal positions of the olefin, respectively. However, the scope of previously reported copper(I)-catalyzed 1,2-alkylborylation reactions with respect to the carbon electrophiles is usually limited as these reactions are capable of incorporating only primary alkyl groups (Scheme 1A).[22,23] In contrast, a radical-relay strategy would provide an alternative approach with reverse regioselectivity.[24] Ideally, this process would involve an SET from a borylcopper(I) intermediate to an alkyl electrophile. Radical addition of the resulting alkyl radical to an olefin, followed by C–B bond formation would simultaneously form a new C(sp^3)–B bond at the internal position of the olefin and a new C(sp^3)–C bond at the terminal position. In this strategy, it is feasible to use alkyl electrophiles that cannot be employed in traditional 1,2-alkylborylations, which represents an opportunity to increase the range of synthetically accessible organoboronates (Scheme 1B).

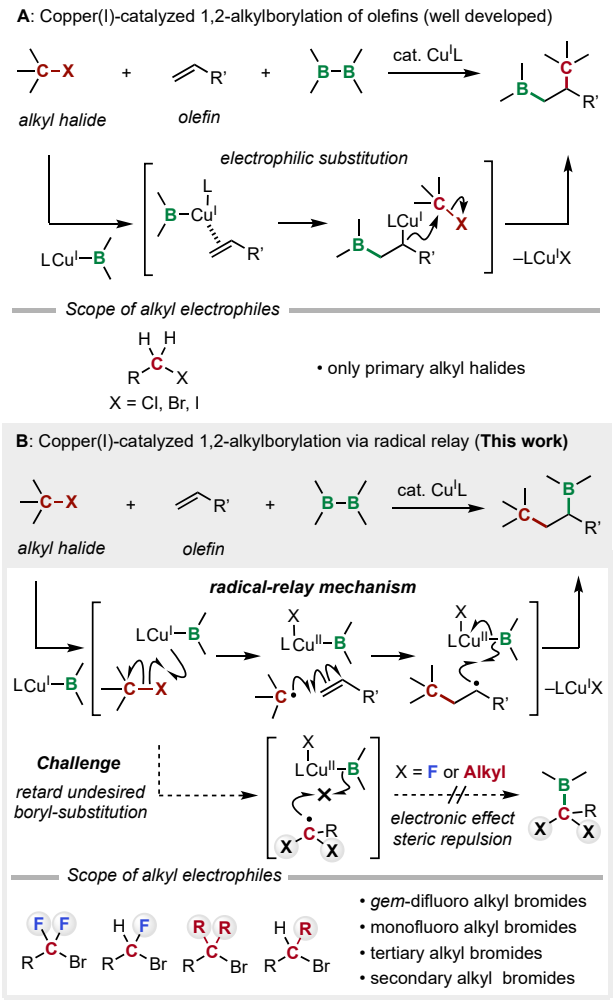
In 2012, our group and that of Marder independently reported copper(I)-catalyzed boryl substitution reactions of alkyl halides with bis(pinacolato)diboron.[25–31] These reactions proceed via an SET from a borylcopper(I) intermediate to an alkyl halide, generating an alkyl radical, followed by radical recombination to form a C–B bond. The application of these reaction mechanisms for an intramolecular borylative radical cyclization was achieved in 2017.[24] Despite this success, the intermolecular counterpart has not yet been achieved due to the difficulty in suppressing the direct coupling between the borylcopper(I) intermediate and the carbon electrophile.

During related studies on the copper(I)-catalyzed borylation of alkyl halides, we have encountered a problem where, despite observing consumption of the starting materials, substrates with electronically or sterically demanding substituents did not afford the desired boryl substitution products. We hypothesized that this outcome could be due to the boryl copper(II) intermediate being inaccessible to the alkyl radical intermediate on account of electronic effect or steric repulsion. Inspired by these results, we suspected that the reaction of an unactivated olefin with bis(pinacolato)diboron and an electronically or sterically demanding alkyl electrophile might offer an alternative pathway to enable the intermolecular 1,2-alkylborylation reaction. We speculated that this reaction could proceed via a radical-relay strategy since the boryl substitution reaction would be retarded using these electrophiles (Scheme 1B).[25–27]

Herein, we report the first example of an intermolecular 1,2-alkylborylation of unactivated olefins via a radical-

relay strategy. The key to the success of this protocol is the use of electronically or sterically demanding alkyl electrophiles to retard undesired boryl-substitution reactions. Notably, our reaction can be applied to a variety of electrophiles including *gem*-difluoro alkyl bromides, a monofluoro alkyl bromide, as well as secondary and tertiary alkyl bromides, which cannot be employed in under any other hitherto reported 1,2-alkylborylation reaction conditions.[22,23]

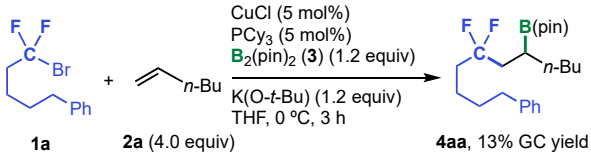
Scheme 1. A Comparison of Methods for Copper(I)-Catalyzed Intermolecular 1,2-Alkylborylation Reactions.



RESULTS AND DISCUSSION

As a proof-of-concept, we selected α,α-difluoro alkyl bromide **1a** as the alkyl electrophile; applying our previously reported catalysts system, **1a** did not furnish the corresponding boryl substitution product.[24,25] Surprisingly, the trial experiment delivered the desired 1,2-alkylborylation product (**4aa**) in 13% gas chromatography (GC) yield in the presence of CuCl/PCy_3, our efficient catalyst for the boryl substitution of alkyl halides, under concomitant formation of unidentified byproducts (Scheme 2).[24]

Scheme 2. Initial Attempt of the 1,2-Alkylborylation.[a]

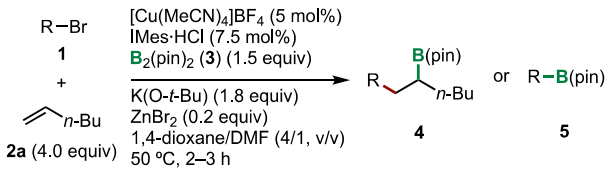


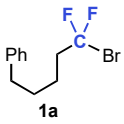
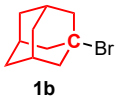
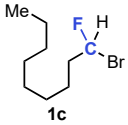
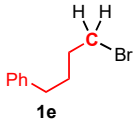
[a]Conditions; **1a** (0.1 mmol), **2a** (0.4 mmol), **3** (0.12 mmol), CuCl (0.005 mmol), PCy_3 (0.005 mmol), K(O-*t*-Bu) (0.12 mmol), THF (200 μL). The yield of **4aa** was determined by GC analysis of the crude reaction mixture with $C_{13}H_{28}$ as the internal standard.

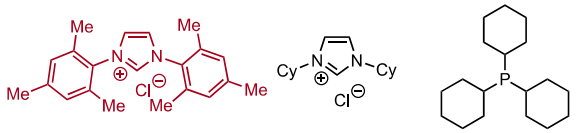
This initial success prompted us to conduct an extensive optimization study of the reaction conditions.[32] We found that **4aa** could be obtained in a 79% GC yield using a $[Cu(MeCN)_4]BF_4$/IMes·HCl catalyst system with $B_2(pin)_2$, K(O-*t*-Bu), and a catalytic amount of $ZnBr_2$ as an additive in 1,4-dioxane/DMF (4/1, v/v) at 50 °C (Table 1, entry 1). Using the optimized conditions, we then investigated several other alkyl bromides to understand which electrophiles are suitable for the intermolecular 1,2-alkylborylation (Table 1, entries 2–5). The reaction with 1-adamantyl bromide (**1b**), a tertiary alkyl bromide, also delivered the 1,2-alkylborylation product in good yield, while the corresponding boryl-substitution product (**5**) was not detected (Table 1, entry 2). These results indicate that the electronic effect and/or steric repulsion play an essential role in preventing the boryl-substitution reaction and facilitate the radical-relay mechanism efficiently. Furthermore, we found that the intermolecular 1,2-alkylborylation reactions of olefins with a monofluoro alkyl bromide (**1c**) and a secondary alkyl bromide (**1d**) proceeded when an excess of olefin was used (Table 1, entries 3 and 4). The lower yields of these reactions relative to those with difluoro- or tertiary alkyl bromides are mainly due to the competing inevitable boryl-substitution reactions. It should be noted here that the intermolecular 1,2-alkylfunctionalizations of olefins via a radical-relay mechanism with secondary alkyl electrophiles are usually difficult to achieve due to competing coupling reactions.[7–14] In contrast, a primary alkyl bromide (**1e**) predominantly furnished the boryl-substitution product, and only trace amounts of the 1,2-alkylborylation product were obtained (Table 1, entry 5).

We also evaluated the other reaction parameters under the optimal conditions. Notably, the choice of ligand had a marked influence on the product yields (Table 1, entries 6 and 7). Using ICy·HCl gave the desired product in moderate yield (Table 1, entry 6), while using a phosphine ligand such as PCy_3 resulted in the formation of a complex product mixture and decreased the yield (Table 1, entry 7). The effects of other parameters were also investigated (Table 1, entries 8–13). Decreasing the quantity of olefin slightly diminished the product yield of the target (Table 1, entries 8 and 9), which indicates that the use of an excess of olefin is of critical importance to efficiently trap the highly reactive radical intermediate. Using THF as the solvent resulted in a similar outcome (Table 1, entry 10). Using other additives such as $MgBr_2$ is not crucial for the reaction (Table 1, entry 11) and, even though the product could be obtained without an additive, the yield drastically decreased to 20% (Table 1, entry 12).[33] In the absence of the copper catalyst, the reaction did virtually not proceed, which indicates that the copper catalyst is essential for this reaction (Table 1, entry 13). In all cases where **1a** was the electrophile, the simple boryl substitution product (**5**) was not detected.

Table 1. Screening the Reaction Conditions.[a]



Entry	Electrophile	Deviation from the standard conditions	Yield (%) 4[b]	5[d]
1	 **1a**	None	79	n.d.
2[c,f,g]	 **1b**	–	71[d]	n.d.
3[f,h]	 **1c**	20 equiv of the olefin	43[d]	31[e]
4[f,h]	 **1d**	20 equiv of the olefin	31[d]	20
5[f,h]	 **1e**	20 equiv of the olefin	trace	84
6	**1a**	ICy·HCl as the ligand	55	n.d.
7	**1a**	PCy_3 as the ligand	11	n.d.
8	**1a**	3.0 equiv of the olefin	71	n.d.
9	**1a**	2.0 equiv of the olefin	58	n.d.
10	**1a**	THF as the solvent	49	n.d.
11	**1a**	$MgBr_2$ instead of $ZnBr_2$	27	n.d.
12	**1a**	No $ZnBr_2$	20	n.d.
13	**1a**	No Cu cat.	trace	n.d.



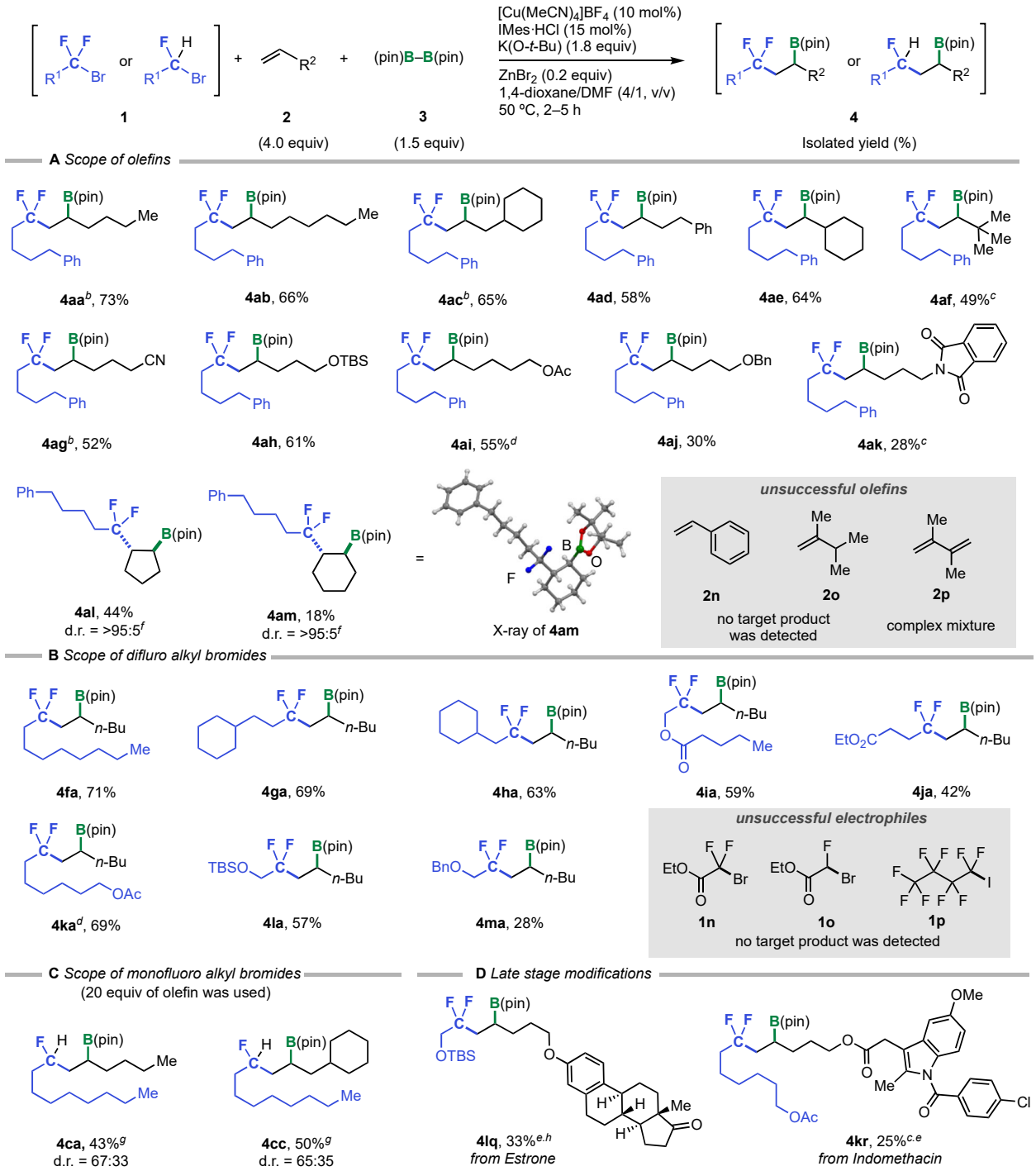
[a]Conditions: **1** (0.1 mmol), **2a** (0.4 mmol), **3** (0.15 mmol), $[Cu(MeCN)_4]BF_4$ (0.005 mmol), IMes·HCl (0.0075 mmol), K(O-*t*-Bu) (0.18 mmol), $ZnBr_2$ (0.02 mmol) in 1,4-dioxane (200 μL) and DMF (50 μL) (for details, see the Supporting Information). [b]Determined by GC analysis of the crude reaction mixture with $C_{13}H_{28}$ as the internal standard. [c]0.2 mmol scale. [d]Isolated yield. [e]Determined by ^{19}F NMR analysis with fluorobenzene as the internal standard. [f]10 mol% of Cu cat. and 15 mol% of IMes·HCl were used. [g]The ratio of 1,4-dioxane/DMF was 6/1 (v/v). [h]The reaction was conducted on the 0.5 mmol scale using 20 equiv of the olefin in 1,4-dioxane/DMF (5/1, v/v).

In addition to the above investigations, we sought to explore the scope of the unactivated olefins in the reaction with α,α-difluoro alkyl bromide (Table 2A). A wide range of unactivated terminal olefins furnished the corresponding γ,γ-*gem*-difluoro *α*-alkylboronates that bear either an *n*-butyl (**4aa**), *n*-hexyl (**4ab**), allyl cyclohexyl (**4ac**), or phenethyl (**4ad**) group in good yield. The more sterically hindered olefins also reacted under the optimal conditions to give products that bear cyclohexyl (**4ae**) and *t*-butyl (**4af**) groups, although the yield was slightly lower in these cases. Functional groups such as a cyano (**4ag**), a *t*-butyl dimethylsilyl ether (**4ah**), and an acetyl group (**4ai**), were tolerated in the position distal to the C=C double bond. The reactions with benzyl ether (**4aj**) and phthalimide (**4ak**) represent exceptions. Furthermore, the reaction of an internal strained olefin afforded the corresponding product (**4al**) in moderate yield with high diastereoselectivity, which was likely controlled by the steric hindrance around the secondary alkyl radical generated after the radical addition reaction. Moreover, the reaction with cyclohexene furnished **4am** in low yield. The relative stereochemistry of **4am** was determined by X-ray crystallography. Unfortunately, aromatic olefin **2n** did not react under the optimized conditions, because the boryl-copper(I) intermediate reacts preferentially with the aromatic olefine rather than with the alkyl bromides. Additionally, 2,2-disubstituted olefin **2o** and diene **2p** did not afford any target products and only complex mixtures were obtained.

Next, we turned our attention to the scope of the α,α-difluoro alkyl bromides, which can be readily prepared from the terminal olefins in a single step (Table 2B).[34] Using aliphatic substrates that bear *n*-octyl or cyclohexyl groups, the corresponding products **4fa**, **4ga**, and **4ha** were obtained in good yield. Substrates that bear esters also reacted with an olefin to give **4ia** and **4ja** in moderate yield. In addition, protecting groups such as acetyl (**4ka**), and *t*-butyl dimethyl silyl ether (**4la**) were tolerated, although a substrate bearing a benzyl ether furnished the corresponding product (**4ma**) in decreased yield. Unfortunately, fluorinated alkyl bromo esters **1n** and **1o** furnished complex mixtures under these reaction conditions and did not afford the target products. The targeted 1,2-alkylborylation product was not detected in the reaction using perfluoroalkyl iodide **1p**. On the other hand, the reaction is compatible with α-monofluoro alkyl bromide **1c** when an excess of olefin is used. Then, γ-monofluoro α-alkylboronates that bear either an *n*-butyl (**4ca**) and allylcyclohexyl group (**4cc**) are obtained in moderate yield (Table 2C). Furthermore, we conducted late-stage modifications of complex molecules such as derivatives of estrone and indomethacin, as exemplified by the efficient preparation of **4lq** and **4kr**, both of which are large molecules that bear a further transformable boron moiety (Table 2D).

The conditions were also found to be applicable to reactions that use different tertiary alkyl bromides as the electrophiles. For example, the reactions between 1-adamantyl bromide (**1b**) and several different olefins afforded β-adamantyl α-alkyl boronates that bear *n*-butyl (**4ba**), cyclohexyl (**4bc**), or phenyl ethyl groups (**4bd**) (Table 3A). Furthermore, functionalized olefins that bear a *t*-butyl dimethyl silyl ether (**2h**), an acetyl (**2i**), or an ethyl ester group (**2s**) reacted smoothly with 1-adamantyl bromide to give the corresponding products (**4bh**, **4bi**, and **4bs**) in good yield. Other tertiary alkyl bromides (**1q**–**1u**) also furnished the corresponding γ,γ-dialkyl α-alkyl boronates (**4qa**–**4ua**), albeit in diminished yield (Table 3B). Finally, we demonstrated the synthetic utility of this protocol by applying the reaction employing 1-adamantyl bromide to the late-

Table 2. Scope with Respect to Difluoro or Monofluoro Alkyl Bromides[a]

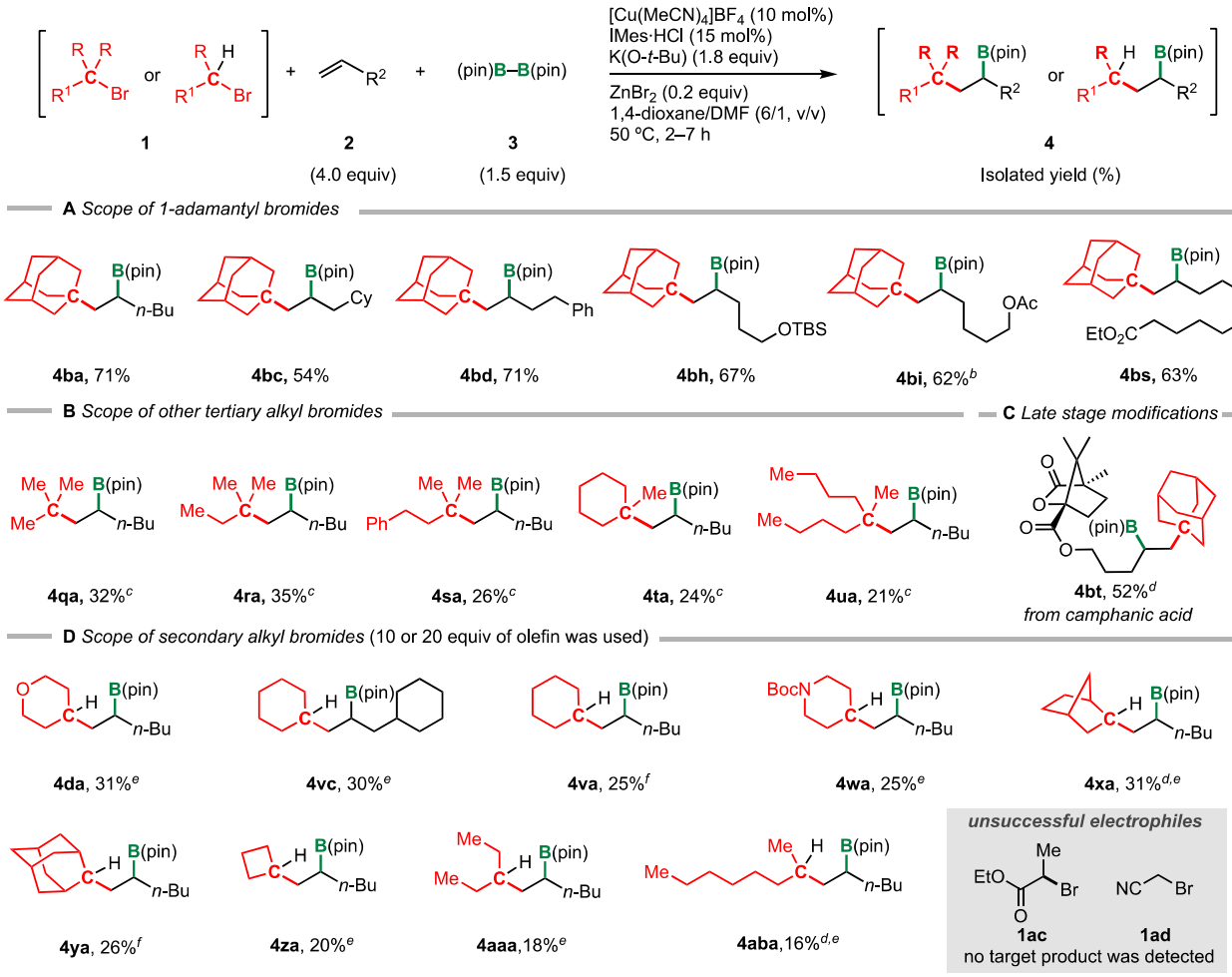


[a]Same conditions as in entry 1 of Table 1 except that catalyst loadings of 10 mol% for the Cu cat. and 15 mol% of IMes·HCl were used. [b]5 mol% of Cu cat. and 7.5 mol% of IMes·HCl were used. [c]Contaminated with small amounts of impurities. [d]1.2 equiv of $B_2(pin)_2$ was used. [e]The ratio of 1,4-dioxane/DMF was 5/2 (v/v). [f]Determined by GC analysis of the crude reaction mixture. [g]The reaction was conducted on the 0.5 mmol scale with 20 equiv of the olefin. The ratio of 1,4-dioxane/DMF was 5/1 (v/v). The d.r. ratio was determined by ^{19}F NMR analysis of the crude reaction mixture. [h]The d.r. ratio was not determined.

stage modification of camphanic acid (**2t**) to provide **4bt** (Table 3C).

The reactions of secondary alkyl bromides (**1d**, **1v**–**1ab**) proved more challenging than those of the tertiary alkyl bromides as the boryl-substitution product was typically formed. Nevertheless, using an excess of olefin afforded the corresponding 1,2-alkylborylation products (**4da**, **4vc**, **4va**–**4aba**) (Table 3D). The efficiency of the reaction with those electrophiles remains to be improved, and corresponding research efforts are currently in progress in our laboratory. Unfortunately, alkyl

Table 3. Scope with Respect to Tertiary or Secondary Alkyl Bromides[a]



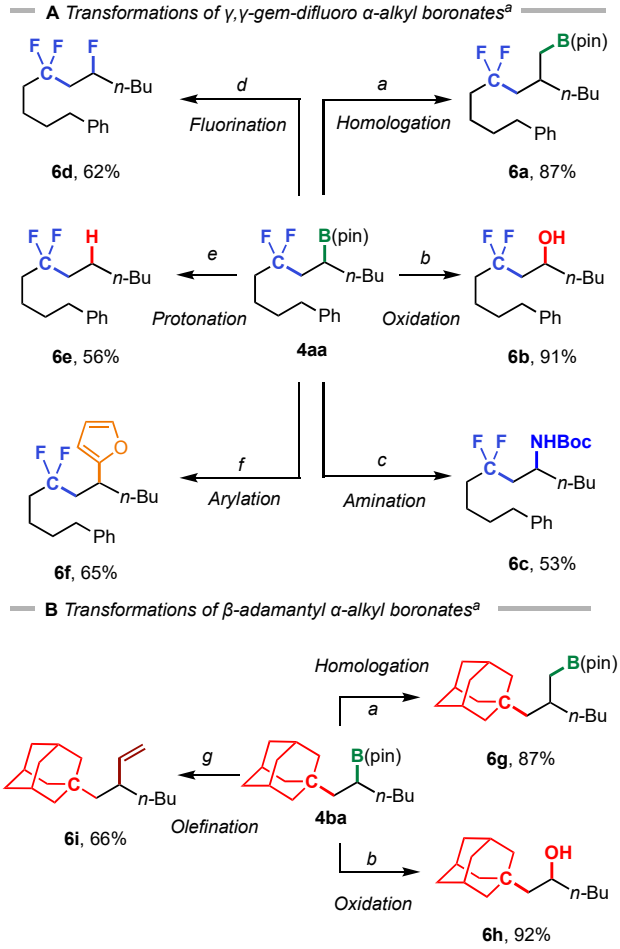
[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]1.2 equiv of $B_2(pin)_2$ was used. [c]0.4 mmol scale. The ratio of 1,4-dioxane/DMF was 4/1 (v/v). [d]The d.r. ratio was not determined. [e]The reaction was conducted on the 0.5 mmol scale with 20 equiv of the olefin. The ratio of 1,4-dioxane/DMF was 5/1 (v/v). [f]The reaction was conducted on the 0.5 mmol scale with 10 equiv of the olefin. The ratio of 1,4-dioxane/DMF was 4/1 (v/v).

bromides that bear an α-ethoxycarbonyl (**1ac**) or cyano group (**1ad**) were not suitable under the applied basic reaction conditions.[12]

The synthetic utility of this method was further highlighted by an array of transformations using the boron moiety (Scheme 3). First, fluorinated boronate **4aa** was subjected to a homologation with a halomethyl lithium reagent,[35] oxidation, or amination with methoxyamine[36] to give the corresponding alkylboronate (**6a**), alcohol (**6b**), or secondary amine (**6c**) in good yield (Scheme 3A). Further transformations of **4aa** undertaken include a fluorination,[37] a protonation,[38] and an oxidative coupling with furan[39] to deliver several functionalized *gem*-difluoro compounds in moderate yield (**6d-f**). Notably, the *gem*-difluoromethylene group has recently attracted attention as a valuable fluorinated motif that could be applicable in pharmaceuticals and biologically active compounds.[40–51] Additionally, β-adamantyl α-alkyl boronate **4ba** was subjected to an oxidation, a homologation, and an olefination,[52] which afforded the corresponding alkyl boronate (**6g**), alcohol (**6h**), and olefin (**6i**) in good yield (Scheme 3B).

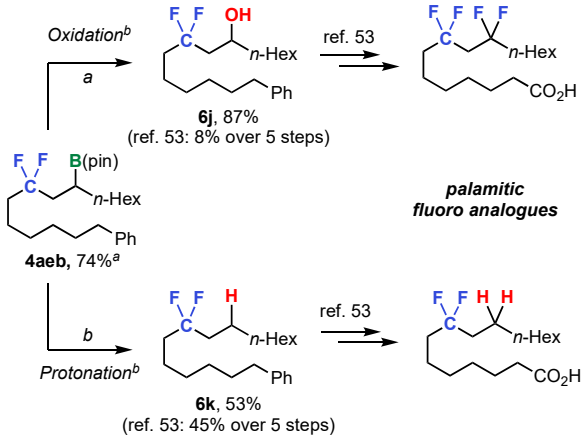
We also carried out a formal synthesis of two known *gem*-difluorinated palmitic analogues, which were synthesized by O'Hagan in multi-step syntheses for the purpose of comparing their conformational stability with that of non-fluorinated palmitic acid (Scheme 4).[53] The corresponding alcohol (**6j**) and alkyl difluorinated compound (**6k**) were synthesized in 5 steps with a total yield of 8% and 45%, respectively. In contrast, we could obtain **6j** and **6k** from the corresponding boronate **4aeb** in 87% and 53% yield, respectively. As **4aeb** was synthesized from commercially available 1-octene, the present procedure represents a synthetically useful and concise method for the synthesis of palmitic fluoro analogues.

Scheme 3. Transformations.



[a]Conditions: (a) *n*-BuLi, $BrCH_2Cl$, THF, –78 °C to rt.; (b) 3.0 M NaOH (aq), 30% H_2O_2 (aq), THF, rt.; (c) *n*-BuLi, $MeONH_2$, THF, –78 °C to 60 °C; then $(Boc)_2O$, THF, rt.; (d) PhLi, THF, 0 °C; then Selectfluor, MeCN, 0 °C; (e) TBAF·$3H_2O$, $Mn(OAc)_3·2H_2O$, TBC, Toluene, 80 °C; (f) *n*-BuLi, furan, NBS, THF, –78 °C; (g) vinyl-MgBr, I_2, NaOMe, THF, –78 °C to rt (for details, see the Supporting Information).

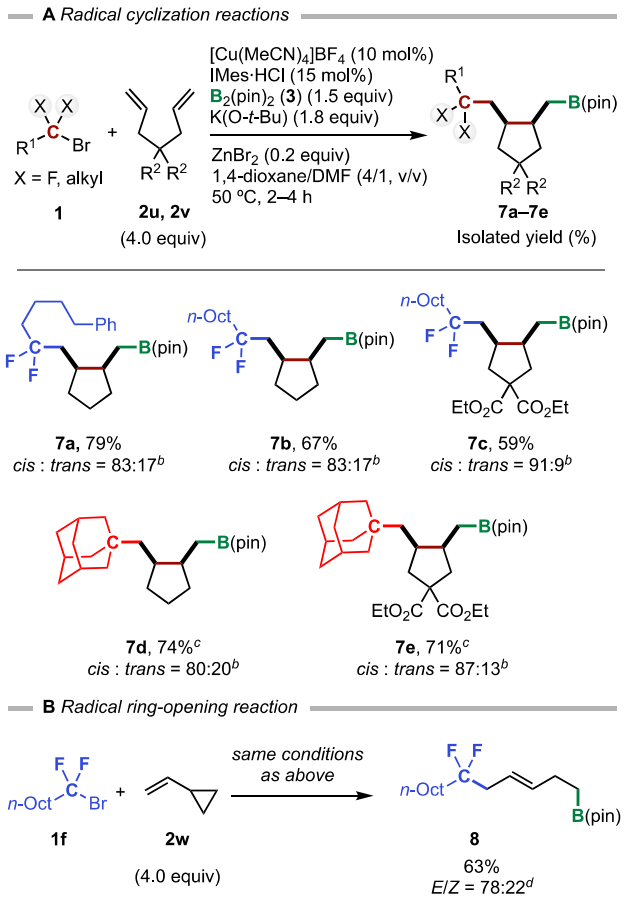
Scheme 4. Formal Synthesis of Palmitic Fluoro Analogues.



[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]Conditions: (a) 3.0 M NaOH (aq), 30% H_2O_2 (aq), THF, rt.; (b) TBAF·$3H_2O$, $Mn(OAc)_3·2H_2O$, TBC, toluene, 80 °C (for details, see the Supporting Information).

Next, we conducted several radical-clock experiments (Scheme 5). The reaction of α,α-difluoro alkyl bromide **1a** with 1,6-heptadiene (**2u**) furnished radical-cyclized **7a** with good diastereoselectivity (Scheme 5A; 79% yield, *cis*:*trans* = 83:17), indicating a radical nature for this reaction.[54] Other ring-closing borylated products were obtained using either diene **2u** or **2v** under the standard conditions (Scheme 5A; **7b**, **7c**) in addition to the cyclized borylated products obtained when 1-adamantyl bromide was used (Scheme 5A; **7d**, **7e**). The radical nature of the reaction was corroborated via a radical ring-opening reaction. The reaction of α,α-difluoro alkyl bromide **1f** with vinylcyclopropane (**2w**) provided ring-opening product **8** in good yield with moderate *E*/*Z* ratio (Scheme 5B).[55]

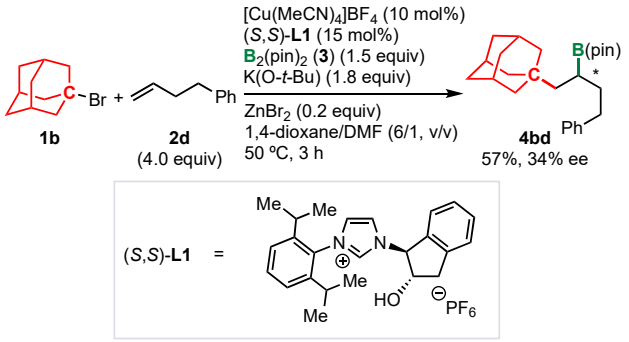
Scheme 5. Radical-Clock Experiments.[a]



[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]Determined by GC analysis. [c]The ratio of 1,4-dioxane/DMF was 6/1 (v/v). [d]Determined by ^1H NMR analysis.

The enantioselective intermolecular 1,2-alkylborylation of unactivated olefins via a radical-relay mechanism was also evaluated using a chiral NHC ligand (Scheme 6). Although the enantioselectivity of the reaction is still low (**4bd**, 57% yield, 34% ee), high enantioselectivity could potentially be induced using other suitable chiral ligands. Further studies to develop such an enantioselective 1,2-alkylborylation of olefins via the radical-relay mechanism are currently in progress in our laboratory.

Scheme 6. Reaction with a Chiral Ligand.[a]



[a]Conditions: **1b** (0.2 mmol), **2d** (0.8 mmol), **3** (0.30 mmol), $[Cu(MeCN)_4]BF_4$ (0.010 mmol), (*S*,*S*)-**L1** (0.015 mmol), K(O-*t*-Bu) (0.36 mmol), $ZnBr_2$ (0.04 mmol) in 1,4-dioxane (600 μL) and DMF (100 μL). The enantioselectivity was determined by HPLC analysis of the corresponding alcohols derived from the boronates.

Lastly, we would like to propose a catalytic cycle for this intermolecular 1,2-alkylborylation of olefins via a radical-relay mechanism (Figure 1). First, the Cu(I) salt reacts with the alkoxide base to generate a copper alkoxide intermediate, which would then react with bis(pinacolato)diboron (**3**) to give boryl copper(I) intermediate **A**. Subsequent SET between intermediate **A** and alkyl halide **1** could then result in the formation of radical intermediate **B** and a boryl copper(II) intermediate.[24–26] An electronically or sterically demanding alkyl radical (both X = F or alkyl) would not undergo a boryl substitution reaction with boryl copper(II) intermediate due to the electronic effect and/or steric repulsion. The radical addition of an unactivated olefin provides radical intermediate **C**,[56] although other electrophiles (one X = H) prefer the boryl-substitution reaction and deliver product **5**. Less electronically or sterically demanding alkyl radicals such as those from α-monofluoro alkyl bromides or secondary alkyl bromides undergo the radical addition when an excess of the olefin is used, even though the boryl-substitution reaction still proceeds in these cases. Finally, the radical recombination between intermediate **C** and the boryl copper(II) intermediate releases 1,2-alkylborylation product **4** with concomitant regeneration of the copper(I) salt for the next catalytic cycle.[27,33]

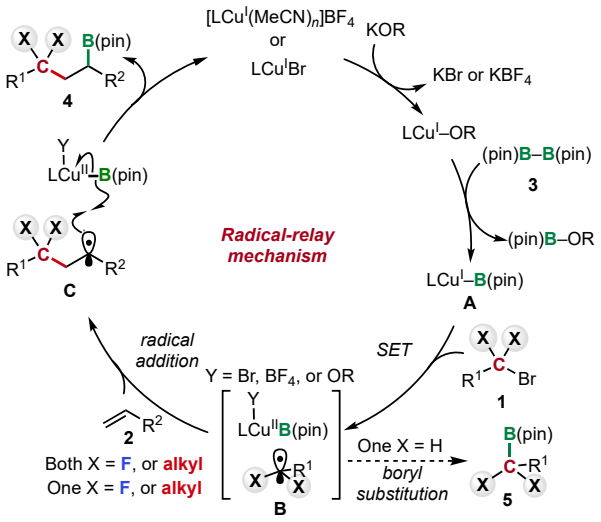


Figure 1. The proposed catalytic cycle.

CONCLUSION

In summary, we have developed the first example of an intermolecular 1,2-alkylborylation of unactivated olefins that proceeds via a radical-relay mechanism. The key to this transformation is the use of electronically or sterically demanding alkyl electrophiles, which retard the competing direct boryl-substitution reactions, thus allowing the formation of the intermolecular alkylborylation product. The products in this reaction are difficult to access via any other hitherto reported 1,2-alkylborylation approaches, which would significantly increase the number of synthetically accessible organoboron compounds. The synthetic utility of this protocol was demonstrated by versatile transformations of the resulting boryl groups to furnish valuable functionalized molecules. Future studies will focus on the evolution of the reaction with secondary alkyl electrophiles as well as an enantioselective version of this reaction.

ASSOCIATED CONTENT

Experimental procedures, characterization of new compounds, and spectroscopic data are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Note

The authors declare no competing financial interest.

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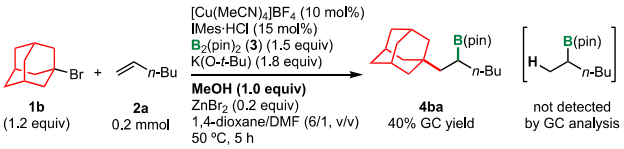

(56) Without the olefins, the alkyl halides that bear difluoro or adamantyl moieties were consumed under the optimized conditions to provide the protonated products; for details, see the Supporting Information.

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