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Perfluoroalkylative pyridylation of alkenes *via* 4-cyanopyridine-boryl radicals†

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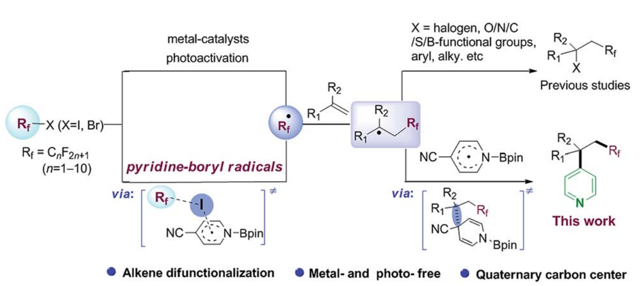
A metal-free and photo-free method for the perfluoroalkylative pyridylation of alkenes has been developed *via* a combination of computational and experimental studies. Density functional theory calculations and control experiments indicate that the homolysis of R_f–X (X = Br, I) bonds by the 4-cyanopyridine-boryl radicals *in situ* generated from 4-cyanopyridine and B_2pin_2 is the key step. Sequential addition of R_f radicals to alkenes and the selective cross-coupling of the resulting alkyl radicals and 4-cyanopyridine-boryl radicals gives alkene difunctionalization products with a quaternary carbon center. This method exhibits a broad substrate scope and good functional group compatibility.

Introduction

Difunctionalization of C═C bonds is a powerful strategy for the construction of complex compounds with various functional groups.[1] In particular, building two C–C bonds tandemly in a single step is highly deserved in terms of structure diversity, step and atom economy. Incoporation of a perfluoroalkyl group in this tandem reaction would be attractive with potential applications in medicinal chemistry, agrochemistry, materials science.[2] Along this line, radical-mediated perfluoroalkylative difunctionalization of alkenes, through transition-metal catalysis,[3] photoredox catalysis,[4] or visible-light activation of electron donor–acceptor (EDA) complexes,[5] has played privileged roles in these transformations (Scheme 1, up). Developing a metal- and photo-free method for difunctionalization of alkenes remains an important synthetic goal.

Pyridine skeletons are often served as "privileged" scaffolds in drug design and discovery.[6] Radical pyridylation is a useful synthetic methodology for the synthesis of value-added pyridine derivatives, due to the good functional group tolerance and broad substrate scope of these methods.[7] The challenge is how to tune the reactivity and selectivity of various radicals in a system. The direct hydroarylation of alkenes with pyridines has also been investigated by transition-metal catalysts.[8] However, the simultaneous introduction of the pyridine moiety and other functional groups to alkenes has been rarely reported, which might be attributed to the low reactivity and site-selectivity of the pyridine group.[9] Herein, we describe a metal- and photo-free protocol for perfluoroalkylative pyridylation of alkenes, which is mediated by *in situ* 4-cyanopyridine-boryl radicals (Scheme 1, down).

Our investigation began with the ^{19}F NMR observation of heating the mixture of perfluorobutyl iodide **1a**, 4-cyanopyridine and B_2pin_2 at 80 °C (Scheme 2a, see details in ESI†), based on previous report that pyridine-stabilized boryl radical could be easily derived from 4-cyanopyridine and diboranes.[10] It was found that the ^{19}F NMR chemical shift at ~60 ppm (which corresponds to the signal of $-CF_2I$ group) disappeared, implying that the formation of the perfluorobutyl radical might be induced by the 4-cyanopyridine-boryl radicals. The perfluorobutyl radical could be trapped by 1,1-diphenylethene in the presence of 4-cyanopyridine, perfluorooctyl iodide **1g**, B_2pin_2, and 1,4-dihydromesitylene (as a hydrogen source) under the similar conditions (Scheme 2b). These results indicated that the 4-cyanopyridine-boryl radicals can activate the perfluoroalkyl iodides to generate perfluoroalkyl radicals. Inspired



Scheme 1 Alkene perfluoroalkylation.

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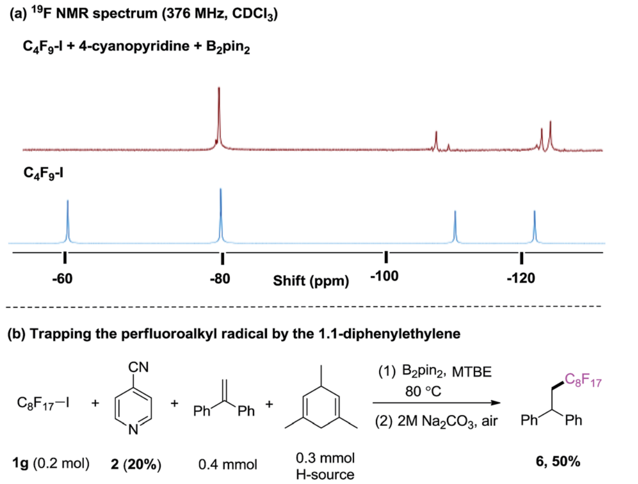
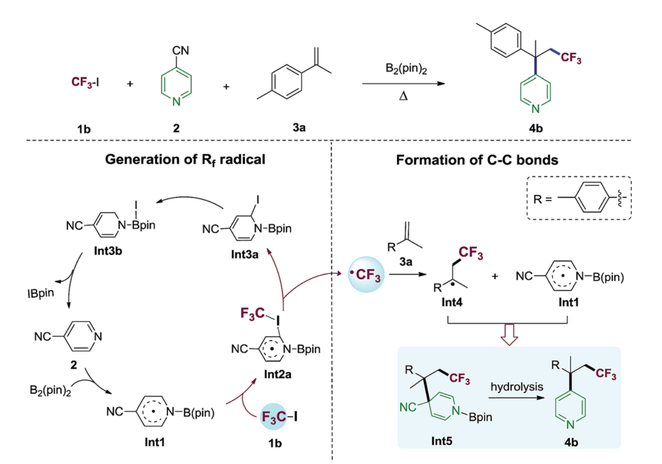


Scheme 2 (a) 4-cyanopyridine boryl radicals-mediated C–I bond homolysis of perfluorooctyl iodide **1a** monitored by ^{19}F NMR; (b) radical trapping experiment.

by this observation and recent progress from Studer[11] and Liu[12] groups that R_f–X (X = I, Br) reagents can act as inexpensive perfluoroalkyl radical precursor for difunctionalization of alkenes, we envisioned that the perfluoroalkyl radical generated from homolysis of perfluoroalkyl halides R_f–X (X = I, Br) promoted by 4-cyanopyridine radicals might be trapped by alkenes, and selective cross-coupling of the resulting alkyl radicals with the persistent 4-cyanopyridine-boryl radicals might lead to the perfluoroalkylative pyridylation of alkenes (Scheme 1, down).[13]

Results and discussion

The proposed reaction mechanism of the alkene perfluoroalkylative pyridylation was postulated in Scheme 3. The following steps may be involved: (1) 4-cyanopyridine-boryl radicals (**Int1**) are generated from the homolytic cleavage of the B–B bond of B_2pin_2 by 4-cyanopyridine; (2) **Int1** activates the



Scheme 3 Proposed 4-cyanopyridine-boryl radicals-mediated alkene difunctionalization.

C–I bond of CF_3I (**1b**) to produce the CF_3 radical and **Int3a**, and regenerate 4-cyanopyridine; (3) CF_3 radical adds to 4-methylisopropenylbenzene (**3a**), forming a new alkyl radical (**Int4**); (4) the selective cross-coupling of **Int1** and **Int4** by persistent radical effect,[14] yields the intermediate **Int5**, which is hydrolysed to give the alkene perfluoroalkylation product **4b**. Notably, **Int1** not only catalyze the C–I bond homolysis of perfluoroalkyl halides R_f–X (X = I, Br), but also serves as the pyridine precursor.

To verify whether the proposed mechanism is thermodynamically or kinetically feasible, we performed DFT calculations with the M06-2X[15] functional to explore the free energy profile of the proposed mechanism for the model reaction of **1b** and **3a** in the presence of **Int1** as a reactive intermediate. The reaction mechanism of generating **Int1** was reported in our previous works.[10c,d,j,k] The calculated free energy profile and transition state structures are listed in Fig. 1 (the optimized structures of all minimum species are shown in Fig. S1†). First, the association between the iodine atom of **1b** and the carbon atom at the C2 position of the radical **Int1** forms an encounter complex (**Int2a**), which is endergonic by 7.2 kcal mol^{-1}. Then, the transfer of the iodine atom from **1b** to **Int1** to give the CF_3 radical and **Int3a** involves a barrier of 32.6 kcal mol^{-1} (*via* **TS1**) and is endergonic by 20.2 kcal mol^{-1} (relative to the isolated reactants **Int1** and **1b**). It should be mentioned that the homolytic dissociation energy of C–I bond in CF_3I is 49.1 kcal mol^{-1}. There results indicate that the homolysis of C–I bond in CF_3I is indeed assisted by **Int1**. Subsequently, CF_3 radical adds to the alkene **3a** to generate a new alkyl radical **Int4** *via* **TS2**, being exothermic by 11.3 kcal mol^{-1} with a barrier of 29.2 kcal mol^{-1} (with respect to the separated reactants **Int1**, **3a** and **1b**). Finally, the C–C coupling between **Int1** and **Int4** produces an intermediate **Int5** through **TS3** with a barrier of 6.8 kcal mol^{-1} (relative to **Int4** and **Int1**), and the whole process is exothermic by 30.1 kcal mol^{-1} (with respect to the reactants **Int1**, **1b** and **3a**). In addition, the hydrolysis of the intermediate **Int5** will produce the final product **4b**. The results indicate that the proposed alkene perfluoroalkylation is thermodynamically favorable. Alternatively, the C–I bond homolysis by the 4-cyanopyridine-boryl radicals at the C4 position is also investigated (shown in Fig. S2†). This process is endergonic by 31.0 kcal mol^{-1}, with a barrier of 37.7 kcal mol^{-1} (relative to **Int1** and **1b**), suggesting that the pathway is less favorable. Furthermore, we also calculate the isomerization reaction of **Int3a** (see Fig. S3†). Starting from **Int3a**, the intramolecular migration of the iodine atom from C2 atom to B atom *via* **TS4**, could yield another isomer **Int3b**, which further proceeds through the breaking of the B–N bond (*via* **TS5**) to regenerate 4-cyanopyridine. Overall, the rate-determining barrier height of this process is 10.1 kcal mol^{-1} and endergonic by 2.9 kcal mol^{-1} (relative to **Int3a**), indicating that the C–I bond homolysis is a catalytic process by 4-cyanopyridine. Moreover, our calculations suggest that the direct single electron transfer (SET) process between 4-cyanopyridine-boryl radicals and CF_3I is highly endergonic by 60.0 kcal mol^{-1} (see Fig. S4†). Thus, the SET mechanism is unlikely responsible for the generation of the perfluoroalkyl radicals in the reaction.

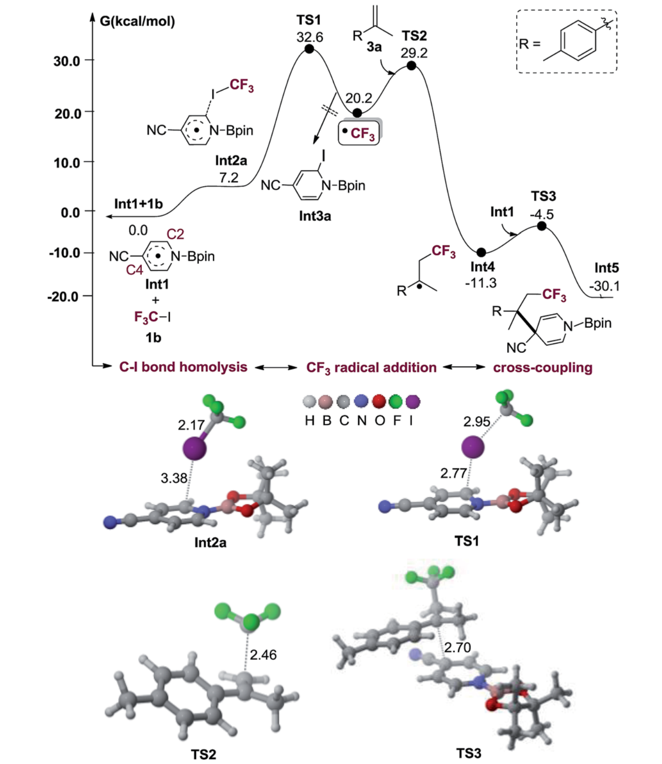
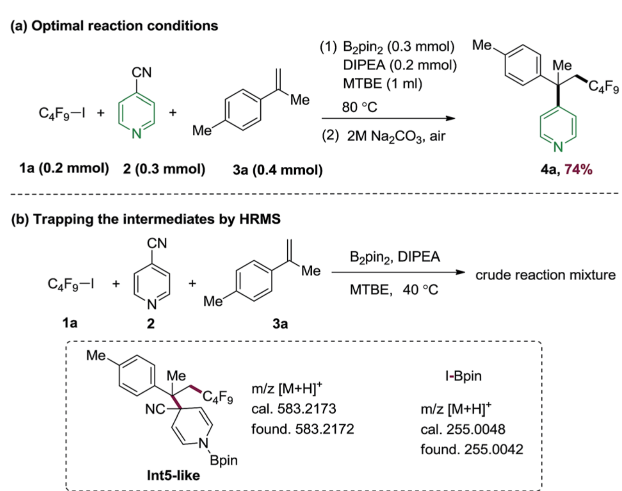


Fig. 1 Computed Gibbs free energy profile of the alkene carbopyridylation *via* 4-cyanopyrodine boryl radicals. The optimized structures of transition states are also displayed. Interatomic distances are in Å.

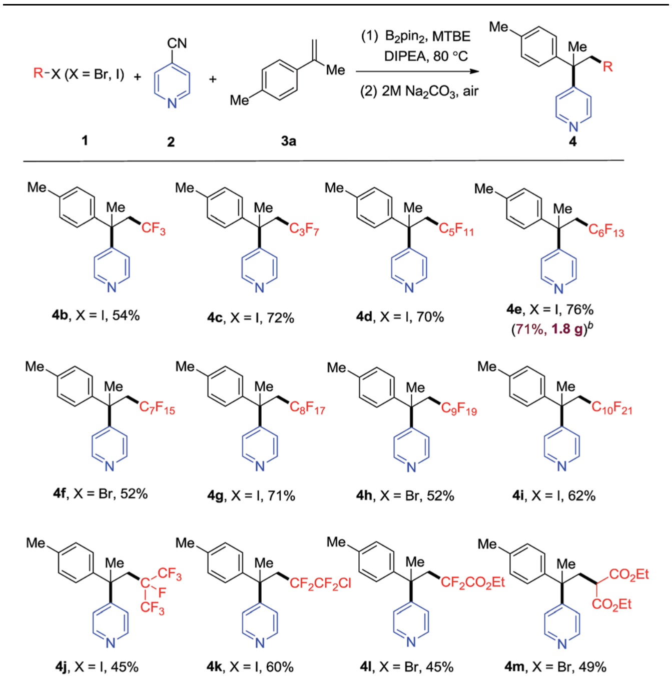
Based on the predicted reactivity, we first examined the proposed alkene difunctionalization using 4-cyanopyridine, perfluorobutyl iodide **1a**, 4-methylisopropenylbenzene **3a** as model substrates. The optimization details are given in ESI.† We found that the desired product could be obtained in 74% yield at 80 °C in the presence of B_2pin_2 with *N*,*N*-diisopropylethylamine (DIPEA) as additives (Scheme 4a). Control experiments suggest that this transformation occurs *via* a thermally induced process, as decreased yield was observed at lower temperatures. The requirement of a relatively high temperature (80 °C) are in qualitative accord with the DFT results discussed above. Moreover, the generation of intermediates **Int3a** (or its isomer **Int3b**), and the compound **7-like** (from the addition of **Int1** and the perfluorobutyl radical) in the presence of **1a**, 4-cyanopyridine and B_2pin_2 under the standard conditions were confirmed by high resolution mass spectroscopy (HRMS) experiments, which provide direct evidence on the C–I homolysis mechanism of **1a** *via* 4-cyanopyridine-boryl radicals (see Fig. S5 and S6†). In addition, the intermediacy of the cross-coupling intermediate **Int5-like** as well as the by-product I-Bpin could be detected by the HRMS analysis of the reaction mixture of the perfluorobutyl, 4-cyanopyridine and 4-methylisopropenylbenzene **3a** under the standard conditions (Scheme 4b, Fig. S7 and S8†). Finally, the addition of the perfluoroalkyl radical to alkenes could be further confirmed by a radical clock experiment using vinyl cyclopropane **3r** as the substrate (see Fig. S9† for details). In combination, the studies revealed an unique strategy for the generation of perfluoroalkyl radicals and for subsequent perfluoroalkylative pyridylation of alkenes using the inexpensive 4-cyanopyridine/B_2pin_2 system.

Then, we examined the substrate scope of the carbon radical precursor with 4-methylisopropenylbenzene **3a** as the radical acceptor (see Table 1). With perfluoroalkyl iodides (C_nF_{2n+1}–I), the corresponding α-perfluoroalkyl-β-pyridylation product could be obtained in moderate to good yields (**4a–4e**, **4g**, **4i**).



Scheme 4 Control experiments.

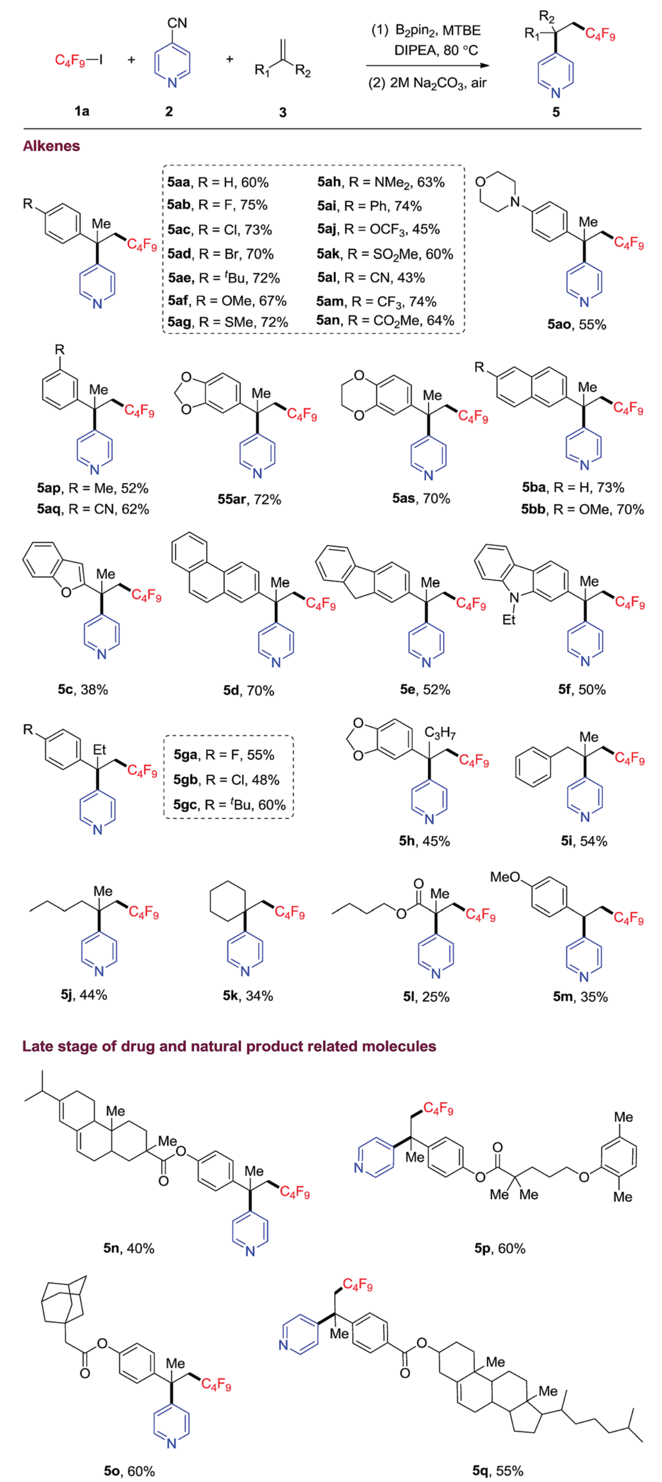
Table 1 Substrate scope for the radical precursor[a]



[a] Reaction conditions: **1** (0.2 mmol), $B_2(pin)_2$ (0.3 mmol), 4-cyanopyridine **2** (0.3 mmol), 4-methylisopropenylbenzene **3a** (0.4 mmol), MTBE (1.0 mL), DIPEA (0.2 mmol), 24 h, 80 °C. Isolated yield. [b] 5 mmol scale. **1e** (5 mmol), $B_2(pin)_2$ (7.5 mmol), 4-cyanopyridine (7.5 mmol), MTBE (15.0 mL), DIPEA (5.0 mmol), 24 h, 80 °C. Me = methyl, Et = ethyl.

Notably, the sterically congested substrate, perfluoro-isopropyl iodide, reacted smoothly to afford the desired product in moderate yield (**4j**, 45%). 1-Chlorotetrafluoro-2-iodoethane could also be converted into the desired product **4k** in good yield *via* the selective cleavage of C–I bond. For the perfluoroalkyl bromides, the desired products (**4f**, **4h**, **4l**, **4m**) could be formed in moderate yields under the standard conditions. The reaction of $C_6F_{13}I$, 4-cyanopyridine and alpha-methyl styrene on a 5 mmol scale in the presence of B_2pin_2 readily afforded **4e** in 71% yield (1.8 g).

Table 2 Substrate scope for the alkenes[a]



[a] Reaction conditions: **1a** (0.2 mmol), $B_2(pin)_2$ (0.3 mmol), 4-cyanopyridine (0.3 mmol), alkene (0.4 mmol), MTBE (1.0 mL), DIPEA (0.2 mmol), 24 h, 80 °C. Isolated yield. Me = methyl, Et = ethyl, ᵗBu = *tert*-butyl.

Next, the substrate scope of alkenes was evaluated. As shown in Table 2, alpha-methyl styrene bearing a variety of functional groups (such as Br, MeS, CF_3O, $MeSO_2$, CN, CF_3, CO_2Me *etc.*) on the phenyl rings, were well compatible with this protocol, offering corresponding carbopyridylation products with quaternary carbon center (**5aa–5as**) in moderate to good yields (43–74%). Alpha-methyl naphthalenes also reacted to provide the desired products in good yields (**5ba**, 73% and **5bb**, 70%). Furthermore, other alpha-methyl arylethene containing fused heterocycles, such as benzofuran, phenanthrene, fluorene and carbazole, could be converted into the corresponding products **5c–5f** in moderate to good yields. The reactions of more sterically congested alpha-ethyl and -propyl styrenes provided the desired products (**5ga–5h**) in moderate yields. In addition, 1,1-disubstituted unactivated alkenes could also smoothly transform into the corresponding products (**5i–5k**, 45–54% yields). However, the reactions of methacrylate and 4-methoxystyrene only afforded the carbopyridylation products **5l** and **5m** in lower yields. With internal alkenes as substrates, no corresponding carbopyridylation products can be detected under standard conditions. Our DFT calculations suggest that the barrier heights for the addition of trifluoromethyl radical to internal alkene or terminal monosubstituted styrene are higher than that of disubstituted styrene by 1.2–3.4 kcal mol^{-1} (see Table S1†). This result may be responsible for the experimental facts described above. Thus, internal alkenes or terminal mono-disubstituted styrenes are not suitable for the present transformation.

Both pyridine and perfluoroalkyl groups are prevalent motifs in drugs and natural products. The simultaneous incorporation of these two groups into bioactive molecules might improve their properties, such as reactivity and metabolic stability and selectivity.[2,6] As illustrated in Table 2, four complicated alkene substrates derived from abietic acid, gemfibrozil, 1-adamantaneacetic acid, and cholesterol, readily underwent the carbopyridylation to give products **5n–5q** in moderate to good yields.

Conclusions

In summary, we reported a metal- and photo-free synthetic method for perfluoroalkylative pyridylation of alkenes. Density functional theory calculations and control experiments indicate the *in situ* prepared 4-cyanopyridine-boryl radicals from 4-cyanopyridine and $B_2(pin)_2$, which not only activates the C–I bond homolysis but also serves as a pyridine precursor, play a key role in this transformation. A high functional group tolerance and broad substrate scope were achieved. This method provides a scalable and operationally simple protocol for difunctionalization of alkenes with inexpensive 4-cyanopyridine/$B_2(pin)_2$

reagents. We anticipated that the present approach would be useful for the construction of molecules with complexity and late stage modification of drugs and natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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