Very Important Publication

Copper-Catalyzed 1,6-Hydrodifluoroacetylation of *para*-Quinone Methides at Ambient Temperature with Bis(pinacolato)diboron as Reductant

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Received: September 7, 2016; Revised: November 28, 2016; Published online: ■■ ■■, 0000

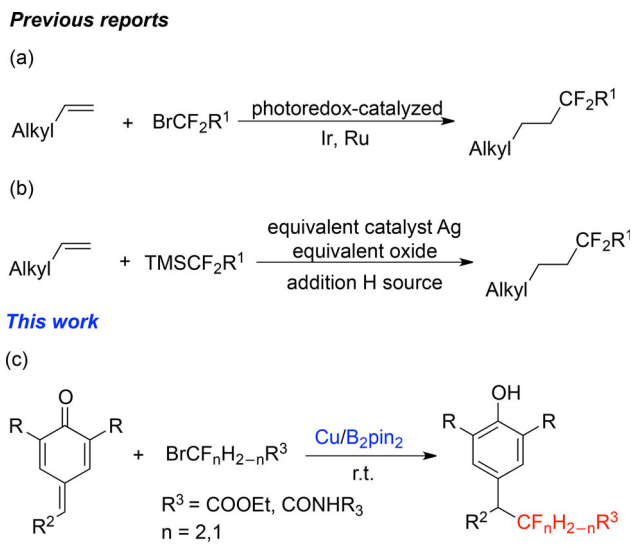
Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600991.

Abstract: An original and efficient copper-catalyzed 1,6-hydrodifluoroacetylation of *para*-quinone methides with difluoroalkyl bromides has been described with bis(pinacolato)diboron (B_2pin_2) as reductant. In this reaction, a new C(sp^3)–CF_2 bond is constructed under smart conditions. A broad substrate scope of *para*-quinone methides (*p*-QMs) make this protocol very practical and attractive. Preliminary mechanistic studies manifested that a difluoroalkyl radical pathway was involved in this reaction. Also the presence of the diboron reagent was an essential requisite in this transformation.

Keywords: bis(pinacolato)diboron (B_2pin_2); hydrodifluoroacetylation; *para*-quinone methides (*p*-QMs); radical pathway

The introduction of fluorine atoms into organic molecules has attracted great attention because of the dramatic improvements in biological and physicochemical properties of the parent molecules.[1–3] Among them, the difluoromethylene group (CF_2) can be regarded as a bioisostere for an oxygen atom, carbonyl group and methylene group due to its excellent stability in metabolism, and the electron-withdrawing property.[4] At the same time, the CF_2 group also affects the electronic property, chemical property and reaction activity of substituents on its *ortho* position as well.[5] Therefore, enormous effort has been made for the development of new synthetic methods for the incorporation of the CF_2 group into molecules.[6,7]

In the past five years, the fluoroalkyl radical addition over a π acceptor has become one of the most straightforward methods to construct C–CF_2 bond.[8–11] Great advances have been achieved in this field.[12,13] However, compared to the prevailing C(sp^2)–CF_2 formation, the incorporation of a difluoromethyl group into diverse skeletons to construct a new C(sp^3)–CF_2 bond is underdeveloped. To the best of our knowledge, there are only very few examples on this topic. For instance, photoredox catalysts (Ir and Ru) were reported to promote fluoroalkylation of alkenes to render C(sp^3)–CF_2 bond formation (Scheme 1a).[14,15] However, the alkenes were limited to aliphatic terminal alkenes. Compared to photoredox catalysts, the examples of constructing C(sp^3)–CF_2 bonds *via* transition metal catalysts are very scant.[16,17] In 2014, Hao and co-workers reported a stoichiometric Ag salt-mediated fluoroalkylation of alkenes rendering the formation of new C(sp^3)–CF_2 bonds, once again, only aliphatic terminal alkenes were applicable under the conditions with a stoichiometric oxidant required for the success of the transformation.[17b] Therefore, it is highly attractive yet very challenging to exploit new catalytic systems for the incorporation of di- or mono-



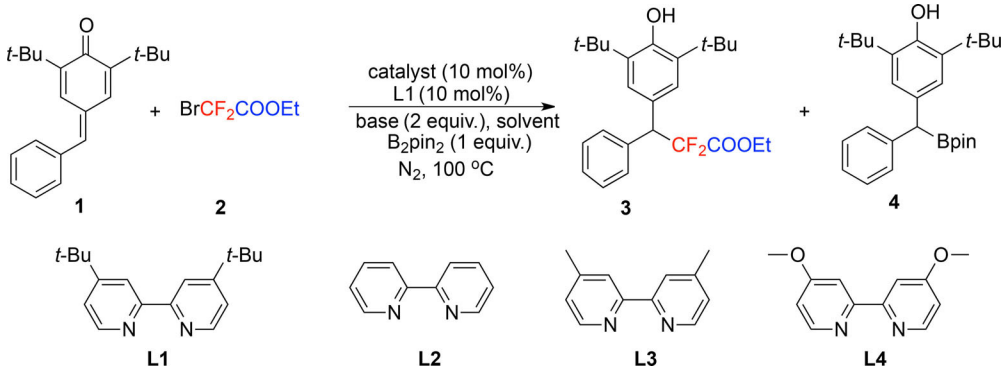
Scheme 1. Difluoroalkylation of arylalkenes.

fluoroalkyl groups into target molecules to construct new C(sp^3)–CF_2 bonds with broad substrate scope, such as to multi-substituted arylalkenes. As an earth abundant, low toxic and cost-effective transition metal, a Cu-catalyzed difluoroalkylation of alkenes for the construction of C(sp^3)–CF_2 bond has not yet been reported (Scheme 1b). Recently, a novel and efficient Cu/B_2pin_2 [B_2pin_2 = bis(pinacolato)diboron] catalytic system was developed in our group.[18] By comparison to conventional Cu catalysts, higher reactivity and potential practical value were merged and featured in this Cu/B_2pin_2 catalytic system.[10c,11c,d,18]

para-Quinone methides (*p*-QMs), which are structurally characterized by the unique assembly of carbonyl and olefinic moieties, are known as versatile building blocks and widely used in the synthesis of natural products and bioactive molecules.[19,20] Furthermore, to expand universality in Cu/B_2pin_2-catalyzed difluoroalkylation to a π acceptor, we envisioned the feasibility of Cu/B_2pin_2-catalyzed difluoroalkylation of *para*-quinone methides with difluoroalkyl halides for the construction of C(sp^3)–CF_2 bonds and recovery of aromatization (Scheme 1c).

Initially, we investigated the difluoroalkylation of *p*-QMs **1** with bromide **2** as a benchmark reaction with $CuBr_2$ as catalyst, **L1** as ligand, and B_2pin_2 (30 mol%) as reductant. Only target product **3** was obtained with 26% isolated yield with a bit of by-product **4** (Table 1, entry 1). Interestingly, it was found that the yield (55%) of **3** was dramatically improved with one equivalent of B_2pin_2. According to our previous work, B_2pin_2 not only acted as a reductant, but served as an activator of water to provide protons.[18] After an extensive screening of the catalysts (Table 1, entries 2–5), $Cu(OAc)_2·H_2O$ gave the best result (83% GC yield, 78% yield on isolation; Table 1, entry 4). Next, a screening of the ligands was carried out (Table 1, entries 6–8), and it indicated that ligand **L1** was optimal from the price point of view by comparison of **L1** with **L3**, furnishing **3** in 78% isolated yield (Table 1, entry 4). Furthermore, a series of bases was tested (Table 1, entries 9–11), obviously,

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (10 mol%)	Ligand (10 mol%)	Base (2 equiv.)	Solvent (1 mL)	Yield [%] 3	4
1[b]	$CuBr_2$	**L1**	$NaHCO_3$	dioxane	26	trace
2	$CuBr_2$	**L1**	$NaHCO_3$	dioxane	55	trace
3	$CuCl_2$	**L1**	$NaHCO_3$	dioxane	60	trace
4	$Cu(OAc)_2·H_2O$	**L1**	$NaHCO_3$	dioxane	83 (78)	trace
5	CuBr	**L1**	$NaHCO_3$	dioxane	81	trace
6	$Cu(OAc)_2·H_2O$	**L2**	$NaHCO_3$	dioxane	39	trace
7	$Cu(OAc)_2·H_2O$	**L3**	$NaHCO_3$	dioxane	83	trace
8	$Cu(OAc)_2·H_2O$	**L4**	$NaHCO_3$	dioxane	67	trace
9	$Cu(OAc)_2·H_2O$	**L1**	Na_2CO_3	dioxane	65	trace
10	$Cu(OAc)_2·H_2O$	**L1**	K_2CO_3	dioxane	83	trace
11	$Cu(OAc)_2·H_2O$	**L1**	NaOAc	dioxane	15	32
12	$Cu(OAc)_2·H_2O$	**L1**	K_2CO_3	toluene	89	trace
13	$Cu(OAc)_2·H_2O$	**L1**	K_2CO_3	CH_3CN	88	trace
14[c]	$Cu(OAc)_2·H_2O$	**L1**	K_2CO_3	CH_3CN	95(88)	trace

[a] *Reaction conditions:* **1** (0.1 mmol), $BrCF_2COOEt$ (2, 0.2 mmol), B_2pin_2 (1 equiv.), catalyst (10 mol%), ligand (10 mol%), base (2 equiv.), solvent (1 mL), under N_2 for 16 h at 100 °C.

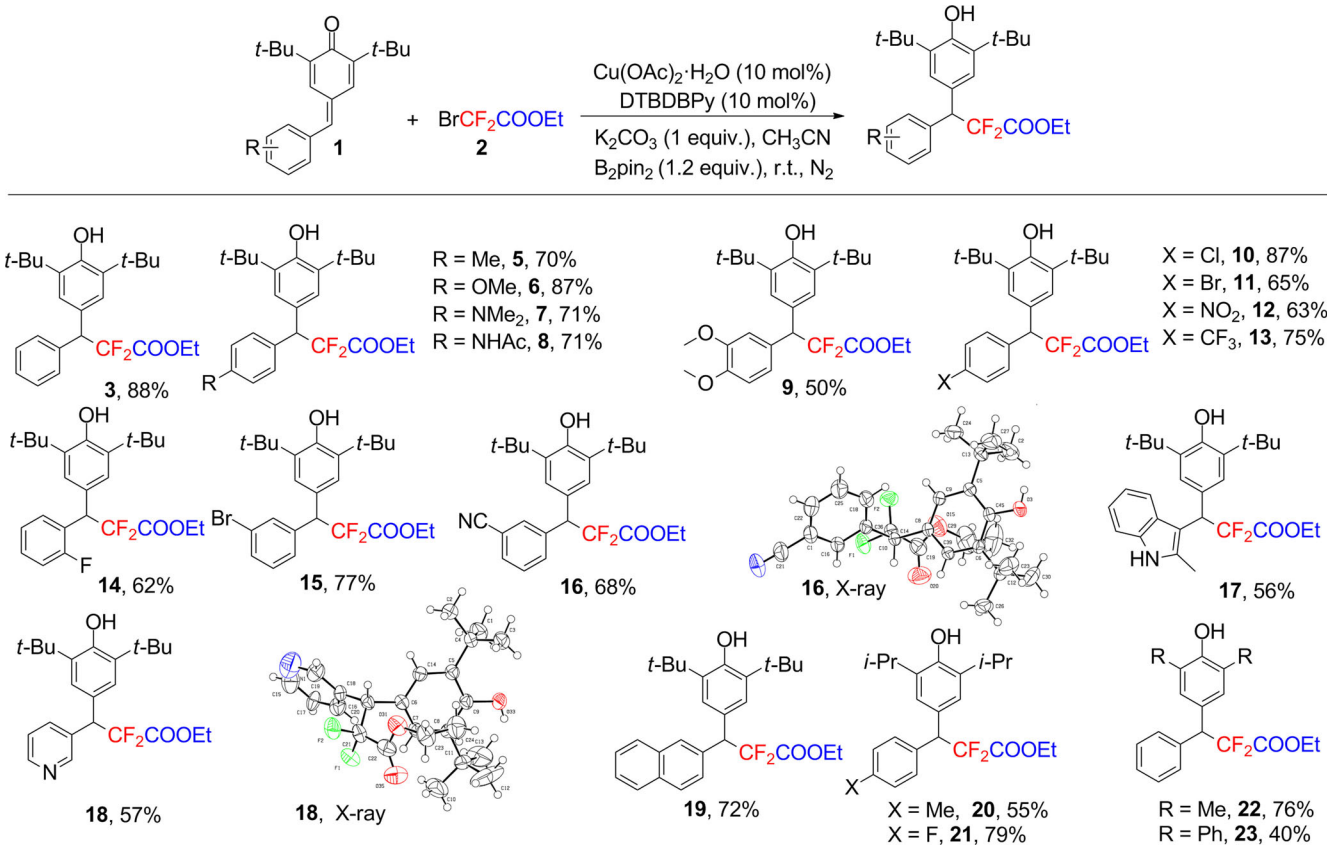
[b] B_2pin_2 (30 mol%).

[c] $Cu(OAc)_2·H_2O$ (10 mol%), **L1** (10 mol%), K_2CO_3 (1 equiv.), B_2pin_2 (1.2 equiv.) under N_2 for 12 h at room temperature. GC yield by using *n*-dodecane as an internal standard. The isolated yield is given in parenthesis.

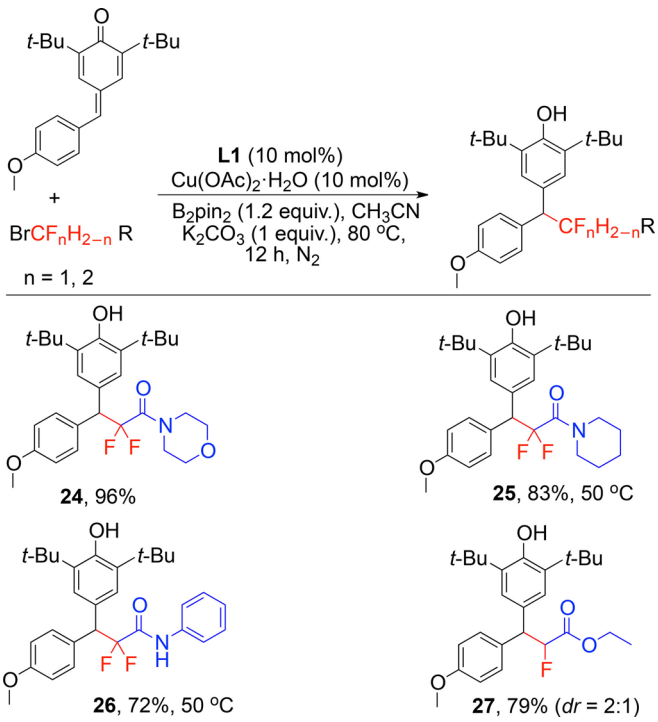
K_2CO_3 exhibited the best catalytic activity (Table 1, entry 10). However, the side product **4** became the major one with 32% isolated yield on using NaOAc as the base (Table 1, entry 11). Further optimization on solvents demonstrated that toluene could be an alternative one to CH_3CN since it gave a similar result as the latter did in the reaction (entry 12 *vs.* entry 13 in Table 1). But other unknown by-products were generated as well, leading to separation difficulty with toluene as solvent. We also tested other parameters, such as temperature, the loading of B_2pin_2, the loading of bases etc., and eventually the optimal result was achieved (Table 1, entry 14, see the Supporting Information). Control experiments suggested that B_2pin_2, $Cu(OAc)_2{\cdot}H_2O$, and ligand **L1** are prerequisites for the success of the reaction (Table S6, see Supporting Information). Also only 10% of **3** was obtained in the absence of K_2CO_3.

With the optimized conditions in hand, the scope of *p*-QMs was investigated (Scheme 2). A series of *p*-QMS bearing electron-donating groups (R = 4-Me, 4-OMe, 4-NMe_2, 4-NHAc, 3,4-dimethoxy) could be difluoroacetylated smoothly in this transformation with high efficiencies (**5**–**9**). Substrates with halo groups such as Cl and Br were good candidates, giving the corresponding products in good yields (**10** and **11**), which might be employed for further structural manipulations. Electron-withdrawing groups (R = 4-NO_2, 4-CF_3) were competent under the standard conditions as well and provided the desired products in good yields (**12** and **13**). Also, *o*- and *m*-substituents have less impact on the reaction, albeit with slightly lower yields (**14**–**16**). Gratifyingly, heteroaromatic *p*-QMs were proven to be good substrates in this transformation and the desired products were obtained with moderate yields (**17** and **18**). Furthermore, it was found that the benzene ring could also be effectively replaced by a naphthalene moiety (**19**). 2,6-Dimethyl, phenyl and isopropyl *p*-QMs were also suitable candidates for this transformation, with the corresponding products obtained in decent to reasonable yields (**20**–**23**).

Next, different difluoromethylated and monofluoromethylated bromides as reagents with *p*-QMs were also tested (Scheme 3). Gratifyingly, the transformation was found to be compatible with a variety of bromodifluoroacetamides with excellent yields (**24**–**26**). To our delight, the corresponding monofluorinated *p*-QM was obtained with good yield using monofluoroacetyl bromide (**27**).



Scheme 2. Substrate scope of *p*-QMs for difluoroacetylation. *Reaction conditions:* *p*-QM **1** (0.2 mmol, 1 equiv.), **2** (0.4 mmol, 2.0 equiv.), B_2pin_2 (1.2 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), **L1** (10 mol%), K_2CO_3 (0.2 mmol,1.0 equiv.), and CH_3CN (1 mL), room temperature for 12 h. All yields are those of isolated products.

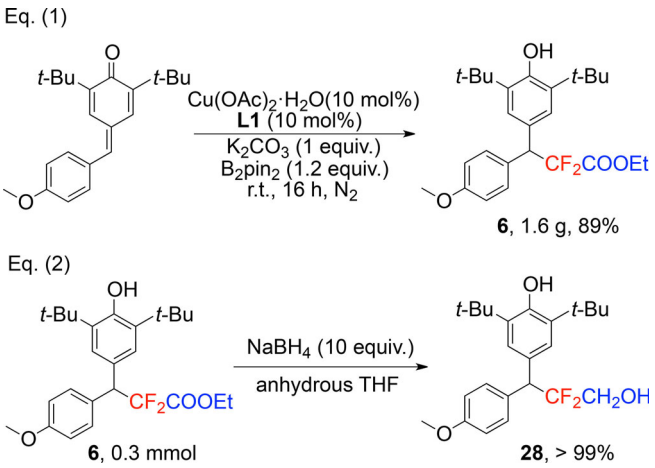


Scheme 3. Scope of fluoromethylated bromides. *Reaction conditions:* *p*-QM (0.2 mmol, 1 equiv.), ethyl fluoroacetate reagent (0.4 mmol, 2.0 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), **L1** (10 mol%), K_2CO_3 (0.2 mmol,1.0 equiv.), CH_3CN (1 mL), room temperature for 12 h. All yields are of islolated products.

Importantly, the cost-effectiveness and mild conditions afforded a scale-up opportunity for the potential practical application. A gram-scale experiment has been completed using 4-OMe *p*-QM with difluoroacetyl bromide. Noteworthily, a 4 mmol preparative-scale synthesis of the corresponding difluorinated *p*-QM **6** could be acquired while sustaining a high isolated yield of 89% as well, thus certifying the robustness of our method [Scheme 4, Eq. (1)]. To further expand the application of our protocol, the alcohol **28** was obtained in the presence of sodium borohydride with excellent yield [Scheme 4, Eq. (2)].

To gain insight into the mechanism, several radical trapping experiments were conducted. It was found that no desired product **6** was detected when the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added under our standard conditions, and the TEMPO-CF_2COOEt adduct was formed, suggesting that a difluoroalkyl radical is indeed generated during the reaction [Scheme 5, Eq. (3)].

To further confirm that a free difluoroalkyl radical existed in the reaction, a radical-clock experiment was carried out. As illustrated in Eq. (4), the known ring-expanded product **29** was observed between α-cyclopropylstyrene and difluoroacetyl bromide under our standard conditions. Thus, these results demonstrated that a free difluoroalkyl radical pathway was participating in the reaction [Scheme 5, Eq. (4)].



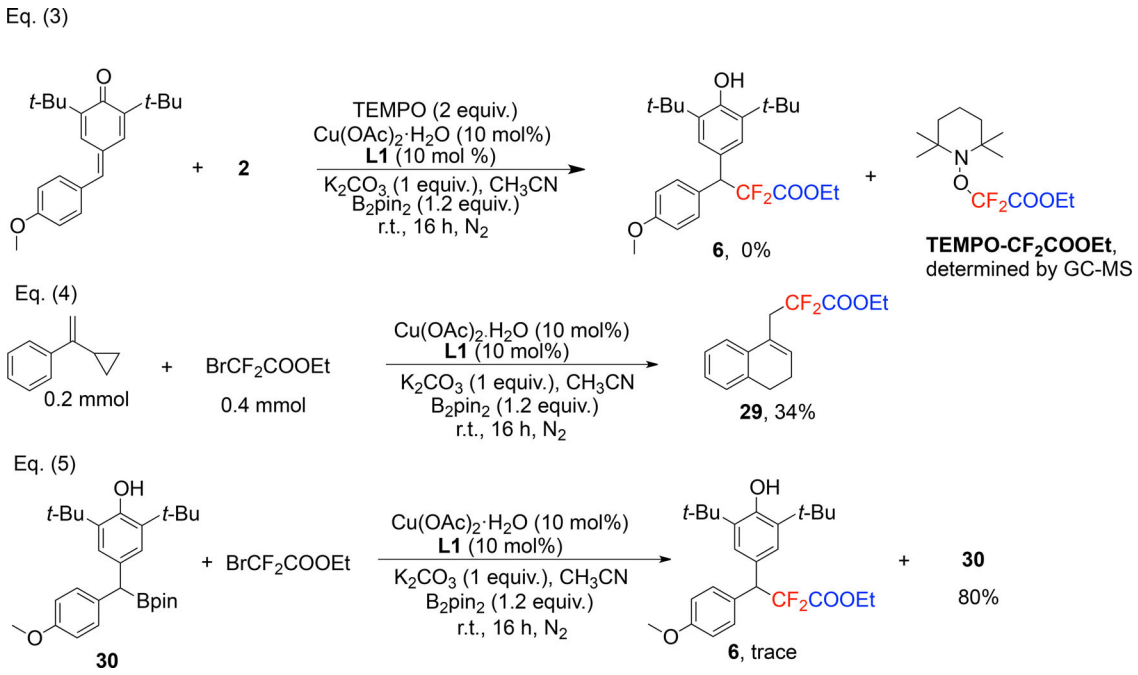
Scheme 4. Application to the difluoroalkylation of *p*-QMs.

In order to determine the key intermediates of the reaction, compound **30** was treated with difluoro reagent **2** under the standard condition, the desired product was only obtained in less than 5% yield with 80% of the compound **30** remaining [Scheme 5, Eq. (5)], this suggested that borated alkane **30** was not the key intermediate. On the basis of these results, a plausible mechanism as depicted in Scheme 6 was proposed. Firstly, copper salt LCuX is reduced by B_2pin_2 in the presence of base to afford the copper(I)-Bpin species **A**.[18,21] Subsequently, oxidative addition of **A** into bromodifluoro reagent *via* SET produces complex **B**,[18,21b] elimination of X-Bpin from complex **B** leads to R-Cu-Ln **C**, which further is trapped by *p*-QM to form the *C*-centered radical **D**, subsequently isomerizing into *O*-centered radical **E**. Finally, hydrolysis of complex **E** with water under the basic conditions leads to the desired product as well as completion of the catalytic cycle.[17a]

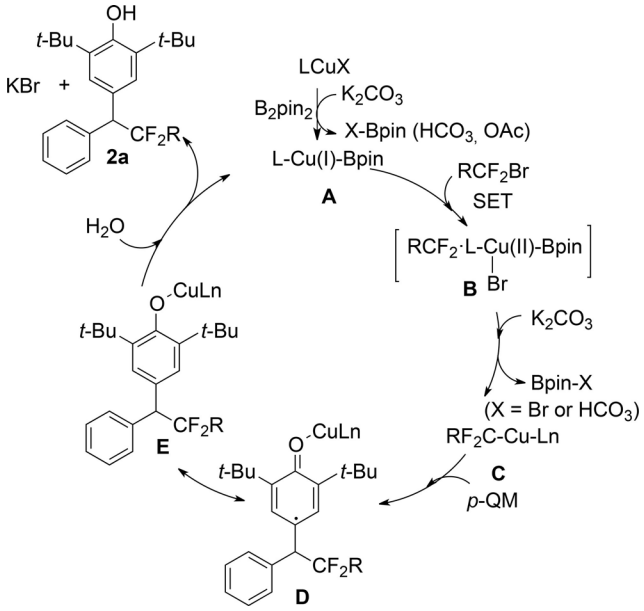
Experimental Section

Synthesis of *p*-QMs (1a–1s)

Phenol (5.0 mmol) and the corresponding aldehyde (6.0 mmol) in toluene (50 mL) were heated to reflux in a round-bottomed flask. Piperidine (10 mmol, 0.8 mL) was dropwise added within 20 min. The reaction mixture was further heated to reflux for 6–24 h. After cooling just below the boiling point of the reaction mixture, acetic anhydride (50.0 mmol, 2.55 g) was added and stirring was continued for 15 min. Then the reaction mixture was poured onto ice-water (500 mL) and extracted with EtOAc (3×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent of the filtrate was removed under reduced pressure. The crude products were purified by flash



Scheme 5. Preliminary mechanistic studies.



Scheme 6. Preliminary mechanism.

column chromatography and further recrystallized from *n*-hexane, affording the desired *p*-QMs **1a**–**1s**.

General Procedure for the Difluoroalkylation of *p*-QMs

p-QM (0.2 mmol), bis(pinacolato)diboron (0.24 mmol, 60.9 mg), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%, 4.0 mg), 4, 4′-dibutyl-2, 2′-bipyridyl (10 mol%, 5.4 mg), and K_2CO_3 (0.2 mmol, 27.7 mg) were added to a 25-mL Schlenk tube under air. Then the mixture was evacuated and backfilled with N_2 (3 times). Ethyl bromodifluoroacetate (0.4 mmol, 52 μL) and CH_3CN (1 mL) were added subsequently. The Schlenk tube was screw-capped. And the mixture was stirred at room temperature for 12 h. The crude product mixture was diluted with ethyl ethylate and then washed with NaCl solution (3×5 mL). The organic layers were dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by flash column chromatograph to give the pure products. The structures of compounds **16** (CCDC 1482472) and **18** (CCDC 1482210) have deen deposited. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21202049), the Recruitment Program of Global Experts (1000 Talents Plan), Natural Science Foundation of Fujian Province (2016J01064), Fujian Hundred Talents Program, the Program of Innovative Research Team of Huaqiao University (Z14X0047), and Graduate Innovation Fund of Huaqiao University (for M. Ke) are gratefully acknowledged. We also thank Mr. Weiqun Liu and Yuntao Zhou for the preparation of some substrates and Instrumental Analysis Center of Huaqiao University for analysis support.

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