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Allylic C–H alkylation with a CF_3-containing nucleophile†‡

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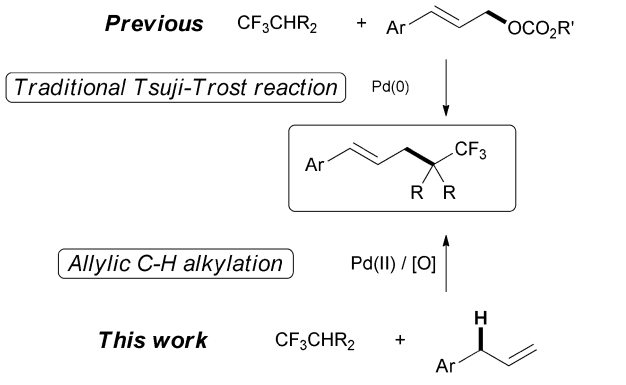
Lun Li, Qing-Yun Chen* and Yong Guo*

Allylic C–H alkylation of allylarenes with dimethyl 2-trifluoromethylmalonate was successfully developed. The reactions were carried out at room temperature in the presence of a catalytic amount of $Pd(OAc)_2$/Ph_3P and a stoichiometric amount of 2,6-dimethylbenzoquinone. The reactions avoided defluorination successfully, providing a new method to construct a CF_3-containing all-carbon quaternary center.

Due to the unique properties of fluorine atom(s), introduction of a trifluoromethyl group to organic compounds has aroused wide interest in recent years and the majority of approaches focus on direct trifluoromethylation.[1–3] Trifluoroethylation (CF_3CH_2– or CF_3CR_2–) has been thought as a synthetic challenge because β-defluorination competes with the reaction with nucleophiles when an α-CF_3 carbanion is generated.[4] In 2012, Hu *et al.* reported a Pd-catalyzed cross-coupling reaction of boronic derivatives with CF_3CH_2I.[5] An extensional study of terminal alkynes was reported very recently.[6] At the end of last year, Chen *et al.* developed a method to synthesize $ArXCHClCF_3$ (X = O, S) by Cu-mediated reactions of 1,1-dichloro-2,2,2-trifluoroethane (HCFC123) with phenoxides or thiophenoxides.[7] The existence of electron-withdrawing groups in an α-CF_3 carbanion can greatly help to stabilize the carbanion.[4a] The generation of β-fluorinated carbanion is fast and in reversible equilibrium while β-elimination of HF is slow but irreversible.[1c] The certain lifetime of the carbanion allows a fast nucleophilic reaction to occur without defluorination. Based on this rule, a few protocols have been elegantly developed, including Ir or Ru-catalyzed addition of CF_3-containing nucleophiles to alkenes[4b] and Pd-catalyzed allylic alkylation of carbonates with CF_3-containing nucleophiles.[8]

The Tsuji–Trost reaction was discovered in 1969 and has been well-developed.[9,10] However, in a traditional Tsuji–Trost reaction a preoxidized allylic substrate is required for ionization to form a π-allylpalladium intermediate. C–H activation is among the most active research topics in current organic chemistry.[11] Shi, White and Trost *et al.* have reported several methods for allylic C–H alkylation by carbon nucleophiles.[12–16] However, it is unknown whether the C–H activation protocol can be applied to fluorinated nucleophiles to avoid the serious defluorination issue. With this in mind, we began our research on the first α-CF_3-carbanion-involved allylic alkylation using the C–H activation protocol, to construct a CF_3-substituted all carbon quaternary center which is an interesting structural motif in drug design (Scheme 1).[2c,17]

At first, reaction of **2** with 1.5 equivalents of **1** in the presence of 5% $Pd(OAc)_2$ and 10% Ph_3P in NMP for 12 h by using benzoquinone (BQ) and a balloon of oxygen as the oxidant at 60 °C was carried out, giving the allylic C–H alkylated CF_3-containing product **3a** in 38% yield (Table 1, entry 1). We chose $Pd(OAc)_2$ because OAc^- was reported to be the necessary counter ion for the allylic C–H alkyation.[16b] This was also supported by the fact that no **3a** was found with the use of $Pd(PPh_3)_2Cl_2$, (Table 1, entry 2). Later, several phosphine ligands were tested. When using $(2\text{-}MeOC_6H_4)_3P$ or $(2\text{-furyl})_3P$, the yield was 23% or 19%, respectively (Table 1, entries 3 and 4). Other ligands, such as $(c\text{-hex})_3P$, $(4\text{-}MeOC_6H_4)_3P$, BINAP, XPhos, *t*-BuPhos, and $(C_6F_5)_3P$ only gave trace amount of **3a** (Table 1, entries 5–10). Based on the above comparison, Ph_3P was thought as a suitable ligand for further screening of the



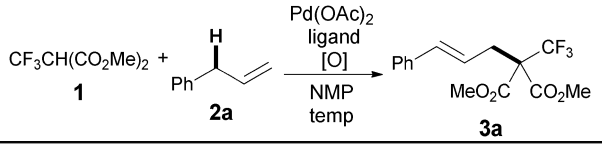
Scheme 1 Allylic C–H alkylation protocol.

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China. E-mail: yguo@sioc.ac.cn; Fax: +86 21 64166128; Tel: +86 21 54925462

† Dedicated to Prof. Jean'ne M. Shreeve on the occasion of her 80th birthday.

‡ Electronic supplementary information (ESI) available: Experimental details and copies of ^1H NMR, ^{19}F NMR and ^{13}C NMR spectra for all products. See DOI: 10.1039/c3cc43120g

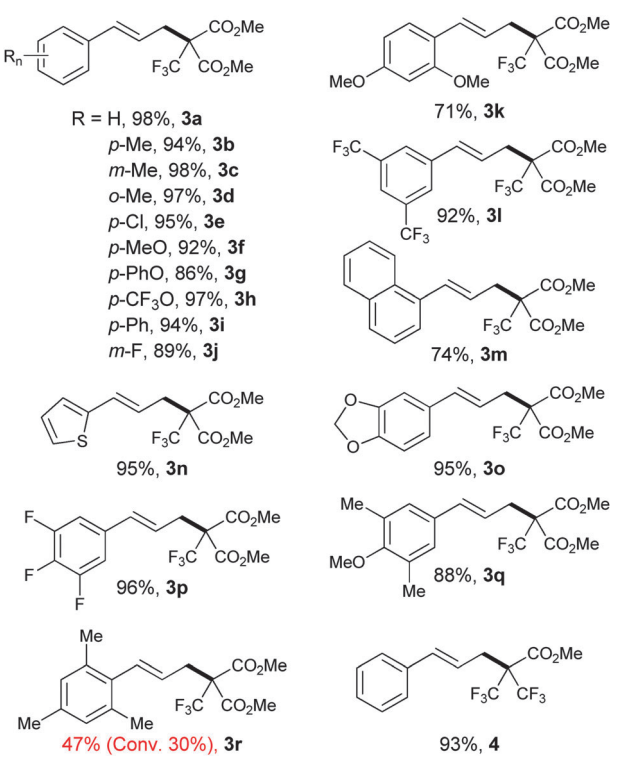
Table 1 Screening of conditions for allylic C–H alkylation[a]



Entry	Phosphine ligand	Oxidant	T (°C)	Yield of **3a**[b] (%)
1	Ph_3P	BQ, O_2	60	38
2[c]	$Pd(PPh_3)_2Cl_2$	BQ, O_2	60	0
3	$(2\text{-}MeOC_6H_4)_3P$	BQ, O_2	60	23
4	$(2\text{-Furyl})_3P$	BQ, O_2	60	19
5	$(c\text{-Hex})_3P$	BQ, O_2	60	Trace
6	$(4\text{-}MeOC_6H_4)_3P$	BQ, O_2	60	Trace
7	BINAP	BQ, O_2	60	Trace
8	XPhos	BQ, O_2	60	Trace
g	*t*-BuPhos	BQ, O_2	60	Trace
10	$(C_6F_5)_3P$	BQ, O_2	60	Trace
11[d]	Ph_3P	BQ, O_2	60	51
12[d]	Ph_3P	BQ, N_2	60	73
13[d]	Ph_3P	DMBQ, N_2	60	100
14	**Ph_3P**	**DMBQ, N_2**	**rt**	**100**
15[e]	Ph_3P	DMBQ, N_2	rt	88
16[f]	Ph_3P	DMBQ, N_2	rt	11
17	Ph_3P	DMBQ, O_2	rt	36

[a] The reactions of **2a** with 1.5 equivalents of **1** in the presence of 5 mol% $Pd(OAc)_2$, 10 mol% phosphine ligand and 1.5 equivalents of quinone oxidant in NMP were carried out at varied temperatures for 12 h under an oxygen or nitrogen atmosphere. [b] The yields were determined by ^{19}F NMR by using benzotrifluoride as an internal standard. [c] Using $Pd(PPh_3)_2Cl_2$ instead of $Pd(OAc)_2/Ph_3P$. [d] The reaction time was 24 h and 3 equivalents of **1** were used. [e] 1 equivalent of **1** was used. [f] 1% $Pd(OAc)_2$ and 2% Ph_3P were used.

Table 2 The substrate scope of alkenes

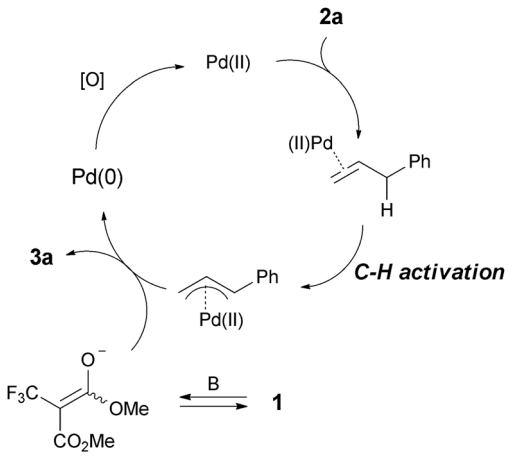


oxidant system. The utilization of three equivalents of **1** and a reaction time of 24 h increased the yield to 51% (Table 1, entry 11). Interestingly, when the reaction was carried out under a nitrogen atmosphere, the yield was improved to 73% (Table 1, entry 12), suggesting that the quinone derivative was the true oxidant for the Pd(0)/Pd(II) regeneration cycle under these conditions. Luckily, further investigation of oxidants revealed that DMBQ gave a quantitative yield of **3a** (Table 1, entry 13), even when the amount of **1** was 1.5 equivalents and the reaction time was shortened to 12 h (Table 1, entry 14). Subsequently, the use of only one equivalent of **1** gave rise to a decrease in the yield of **3a** slightly (88% yield) (Table 1, entry 15). When 1% $Pd(OAc)_2$ was used, the yield dropped greatly probably due to generation of Pd black to cease the catalytic cycle (Table 1, entry 16). Usually, the reaction solution was red after the reaction finished, but in the case of entry 16, the color of the solution turned yellow, which also suggested that $Pd(OAc)_2$ was insufficient. Entry 17 shows that the yield decreased in the presence of oxygen.

Using the optimal conditions (Table 1, entry 16), we tested the scope of alkenes (Table 2). The substrate with one (**3a**–**3j**), two (**3k**, **3l**) or three substituents (**3p**, **3q**) at the phenyl group gave a good to excellent yield of the product. The functional group with different electron-withdrawing or -donating abilities also did not affect the yield significantly (**3a**–**3j**). The aryl substituent could also be thienyl (**3n**) or naphthyl (**3m**). However, the sterically crowded mesitylene derivative **3r** was obtained in a low yield with a low conversion of alkene. Based on all the examples in Table 2, we found that the allylic C–H alkylation with CF_3-nucleophile **1** has a wide substrate scope in terms of various aryl substituents at the allylic position of alkenes and the electronic effect was less essential than the steric effect. In these reactions, we never found branched-substituted products probably due to bulkiness of the trifluoromethylated nucleophile. This reaction can be applied to $(CF_3)_2CHCO_2Me$ to give product **4** in 93% yield, but failed with CF_3CH_2CN. In the previous reports,[8,18] an allylic alkylation by a fluorinated nucleophile normally required a preoxidized allylic substrate, such as carbonate. This report, to the best of our knowledge, is the first example of C–H activation in allylic nucleophilic displacement by a fluorinated nucleophile, whose stability is relatively low because of the innate tendency of defluorination.

In 2008, Shi,[14] White,[15] Trost[16] and Fristrup[11b,19] reported their creative studies on direct allylic alkylation *via* the catalysis of Pd(II), providing much mechanistic evidence for the C–H activation. According to the results mentioned above, a plausible mechanism is proposed in Scheme 2. Palladium(II) is ligated to alkene in a reversible way and then a rate-determining C–H activation happens to give the π-allylpalladium complex. The complex is attacked by the nucleophilic carbanion of **1**, affording product **3a** and Pd(0). Pd(0) is oxidized to re-generate Pd(II). The C–H activation is hard in the formation of **3r** because of the steric hindrance of two *ortho*-methyl substituents.

The palladium-catalyzed allylic alkylations with α-CF_3 containing nucleophiles and preoxidized allylic substrates were reported.[8] Those reactions proceeded through allylpalladium intermediates similar to the one for allylic C–H alkylation. Based on the observations of Kitazume and his co-workers, defluorination of ethyl 3,3,3-trifluoropropionate ($CF_3CH_2CO_2Et$)



Scheme 2 Plausible mechanism.

in palladium-catalyzed allylic alkylations did not occur. In contrast, elimination of fluoride with 2-substituted 3,3-difluoropropionates (for example $HCF_2CH(Me)CO_2CH_2CH_2Ph$) was found to give *E*-fluoroolefins and they thought it might be due to the fact that the C–F bond length in the CHF_2 group is longer than that of the CF_3 group.[8a] This means that the stability of a nucleophile is essential for a successful reaction without defluorination. In the decarboxylative allylations of α-trifluoromethyl β-keto esters reported by Cahard and Shibata, the defluorinations were not observed.[17b] The authors thought that this clearly demonstrated that the allylation proceeded faster than the β-elimination reaction. In our experiments, because of three electron-withdrawing groups within **1**, the stability of the anion of **1** should be higher than the ones with two electron-withdrawing groups.[4a] Thus, the carbanion of **1** has a longer lifetime and remains intact before alkylation. Moreover, quinone acts as a proton acceptor as well as an oxidant for the conversion of Pd(0) to Pd(II).[11b] This allows the reaction to happen without additional bases and leads to a slow generation of the carbanion of **1** and suppression of defluorination under the optimal conditions.

In the early research on allylic C–H alkylations, White and Shi always used the bis(sulfoxide) ligand in order to get a good experimental result.[14,15] However, the bis(sulfoxide) ligand is relatively complex and not common. During our study, Ph_3P was proved to be an excellent ligand and with this ligand we could conduct our experiment at room temperature and get a quantitative yield. This result is consistent with the previous discovery by Trost and his co-workers, where phosphorus-based ligands successfully promoted allylic C–H alkylation with 1,4-dienes and allylarenes.[16]

In summary, we have found a facile method to introduce a CF_3-containing nucleophile to allylarenes through Pd-catalyzed allylic C–H alkylations, providing a series of aromatic products with a quaternary carbon center, which may be useful for drug discovery.

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