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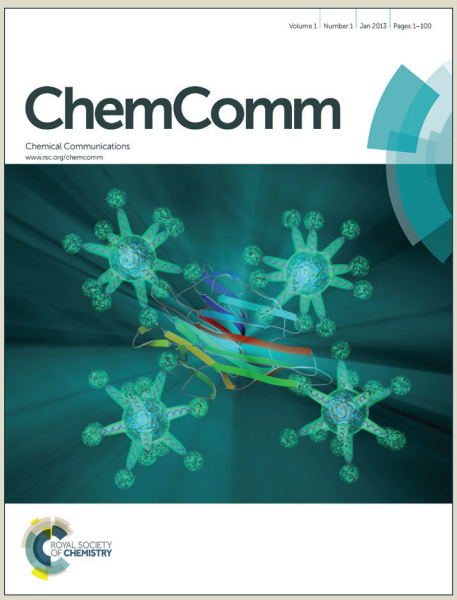





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# Pd(0)-Catalyzed Radical Aryldifluoromethylation of Activated Alkenes

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**A Pd(0)-catalyzed intramolecular aryldifluoromethylation of activated alkenes under mild reaction conditions has been developed. This reaction provides a new method for construction of a variety of difluoromethylated oxindoles. Mechanistic investigations indicated that a difluoromethyl radical, which was triggered by Pd(0), initiated the cascade sequence through an addition to alkene.**

Organofluorine compounds are widely used in medicine and agriculture, as well as in life- and material sciences because of their unique metabolic stability, lipophilicity and biological properties.[1] Therefore, the development of new methods for the introduction of fluorine or fluorinated moieties into organic molecules is of widespread importance. Since the difluoromethyl group ($CF_2H$) could act as a bio-isostere of alcohols and thiols and as a lipophilic hydrogen-bond donor,[2] it has been realized as a valuable structure motif with great potential in pharmaceuticals, agrochemicals, and materials because of the special biological properties.[3]

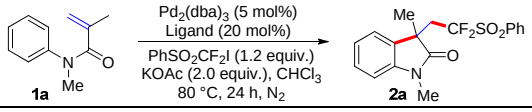
In the past decades, considerable efforts have been devoted to develop the practical methods to synthesize difluoromethylated organic compounds.[4] While transition metal mediated or catalyzed trifluoromethylation has been demonstrated as a powerful strategy to incorporation $CF_3$ group into organic molecules,[5] there are still few examples of transition metal-promoted difluoromethylation. The Amii group reported a sequential cross-coupling/hydrolysis/decarboxylation to difluoromethylarenes route catalysed by copper.[6] Hu and co-workers described a copper-mediated difluoromethylation of propargyl chlorides and alkynyl halides to afford $HCF_2$-containing allenes and alkynes.[7] With their own developed Togni-type I(III)-$CF_2SO_2Ph$ reagent, the Hu group reported also copper-catalyzed vinylic[8] and allylic[9] difluoromethylation from α,β- and β,γ-carboxylic acids, respectively, through decarboxylative fluoroalkylation. The Hartwig[10] and Prakash[11] groups described the direct copper-mediated difluoromethylation of iodoarenes with $HCF_2TMS$ and $HCF_2SnBu^n_3$, respectively. Liu and co-workers reported an iron-catalyzed decarboxylative difluoromethylation of cinnamic acids with zinc difluoromethanesulfinate (DFMS).[12] Recently, the Reutrakul group described a Pd-mediated Heck-type couplings of $PhSO_2CF_2Br$ and styrene, in which a well-known Heck reaction mechanism was proposed.[13] However, this method suffered from high Pd loading (35 mol%), narrow substrate scope and low yield. Herein, we report a Pd(0)-catalyzed intramolecular aryldifluoromethylation of activated alkenes,[14,15] in which a variety of difluoromethylated oxindoles were synthesized. Mechanistic investigations indicate that the cascade sequence was initiated by an addition of a difluoromethyl radical to alkene.

Oxindoles have long been realized as one of the important scaffolds used in medical and biological chemistry because of their unique bioactivities.[16] Liu and co-workers reported an impressive approach to synthesis trifluoromethylated oxindoles, in which a Pd-catalyzed intramolecular oxidative aryltrifluoromethylation of *N*-arylacrylamides was developed (Scheme 1).[17] Recently, Sodeoka[18] , Nevado[19] and Zhu[20] reported copper-catalyzed or photoinduced $CF_3$• radical cyclization of this kind of acrylamides to oxindoles with Togni reagent, respectively. Though the difluoromethyl moiety ($CF_2H$) has long been realized as an important bioactive fluoroalkyl group different from $CF_3$, the synthesis of $CF_2H$-containing oxindoles has never been explored. We envisioned that a difluoromethyl radical could be trapped by the activated double bonds of *N*-arylacrylamides, thus giving the corresponding oxindoles after C−C bond-forming cyclization.

Our study commenced with *N*-methyl-*N*-phenyl-methacrylamide (**1a**) as the pilot substrate and $PhSO_2CF_2I$, a well established difluoromethylation reagent developed by Prakash and Hu,[21] as the coupling partner in the presence of catalytic $Pd_2(dba)_3$ (5 mol%) at 80 °C. To our excitement, the desired aryldiflroromethylation product **2a** was obtianed in 89% yield with XantPhos used as the ligand in chloroform (entry 1, Table 1). In contrast to XantPhos, most other ligands, including diphosphine ligands (dppe, dppf and BINAP) and monophosphine ligands ($PPh_3$, S-Phos and X-Phos), showed almost no or markedly reduced catalytic reactivity (entries 2-7). Unsurprisingly, diphosphine ligand DPE-Phos, which has the similar structure as XantPhos, gave the difluoromethylated product with a slightly diminished yield (entry 8). Importantly, when the Pd catalyst loading was reduced to 5 mol% (2.5 mol% $Pd_2(dba)_3$), approximately the same yield could be obtained (entry 9). Notably, the investigation of ratio of Pd/ligand showed 2 equivalent of

XantPhos to Pd was necessary to give high yield, which indicated that the electron-rich tetraphosphine-ligated palladium species was crucial to initiate the transformation (entries 9-11). Lastly, control experiments confirmed that only trace quantities of the desired product was detected with $PhSO_2CF_2Br$[13] used as difluoromethylated reagent source (entry 12).

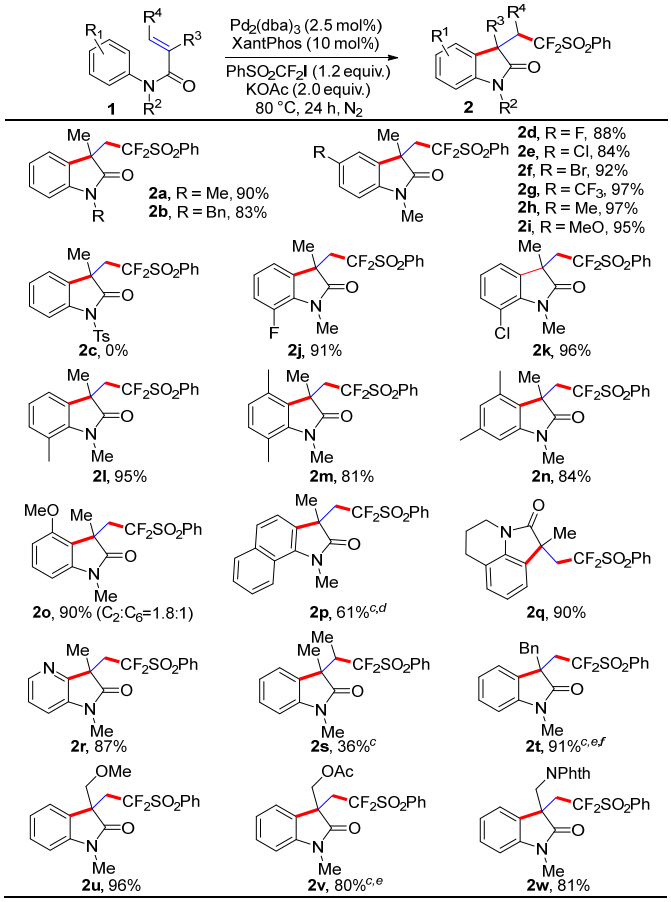
**Table 1** Optimization of reaction conditions[a,b]




| Entry | $Pd_2(dba)_3$ (mol%) | Ligand (mol%) | Yield (%) | Entry | $Pd_2(dba)_3$ (mol%) | Ligand (mol%) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | 5 | XantPhos (20) | 89 | 7 | 5 | BINAP (20) | 44 |
| 2 | 5 | $PPh_3$ (30) | 8 | 8 | 5 | DPE-Phos (20) | 82 |
| 3 | 5 | X-Phos (30) | 55 | 9 | 2.5 | XantPhos (15) | 91 |
| 4 | 5 | S-Phos (30) | Trace | 10 | 2.5 | XantPhos (10) | 90 |
| 5 | 5 | dppe (20) | 6 | 11 | 2.5 | XantPhos (5) | 71 |
| 6 | 5 | dppf (20) | 24 | 12[c] | 2.5 | XantPhos (10) | Trace |

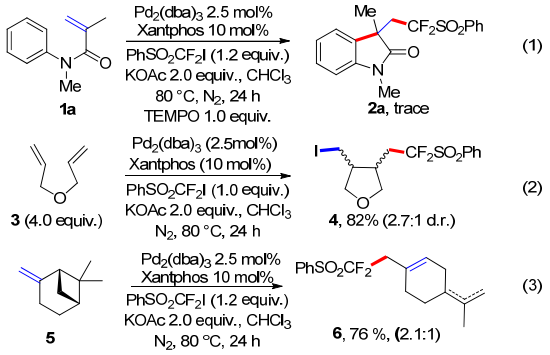
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), $Pd_2(dba)_3$ (5.0 mol%), Ligand (20 mol%), KOAc (2.0 equiv.), $PhSO_2CF_2I$ (1.2 equiv.) in $CHCl_3$ (0.5 mL) at 80 °C for 24 h. [b] Isolated yield. [c] $PhSO_2CF_2Br$ was used instead of $PhSO_2CF_2I$.

**Table 2** Substrate scope[a,b]




[a] Reaction conditions: 1 (0.2 mmol, 1.0 equiv.), $Pd_2(dba)_3$ (2.5 mol%), XantPhos (10 mol%), KOAc (2.0 equiv.), $PhSO_2CF_2I$ (1.2 equiv.) in $CHCl_3$ (0.5 mL) at 80 °C for 24 h. [b] Isolated yield. [c] $Pd_2(dba)_3$ (5.0 mol%) and Xantphos (20 mol%) were used. [d] 100 °C. [e] 120 °C. [f] $PhSO_2CF_2I$ (1.5 equiv.) were used.

With the optimized reaction conditions in hand, we next set out to investigate the substrate scope. Initially, the examination of different *N*-protecting groups revealed that methyl (**2a**) was still the best choice, while similar benzyl-protected substrate (**2b**) gave slightly reduced yield and electron-withdrawing tosyl (**2c**) afforded none of the desired product at all. The substituent effect of aryl ring ($R_1$) was next investigated. A variety of acrylamides **1** with *para*-, *meta*- as well as *ortho*-substituents were smoothly cyclized to afford the corresponding aryldifluoromethylation oxindoles **2** with good to excellent yields, yet a mixture of two expected regioisomers was obtained for *meta*-substituted substrate (**2o**, C2 : C6 = 1.8:1). Both electron-donating, such as Me and MeO, and electron-withdrawing groups, such as F, Cl, Br, $CF_3$ were compatible with the optimized conditions (**2d-i**). Notably, bromo substituent in aniline ring (**2f**), as well as inactive halides including Cl and F, offered the potential for further synthetic elaboration. Importantly, acrylamides with tetrahydroquinoline (**2q**) and pyidine ring (**2o**) were aryldifluoromethylated with excellent yields. To our satisfactory, the examination of α-substituents ($R^3$) of alkenes showed Bn, OMe, OAc, and NPhth were also well tolerated (**2t-w**). Finally, a β-substituted ($R^4$) internal alkene **2s** was also used as viable substrate for this catalytic system, albeit with lower yield.

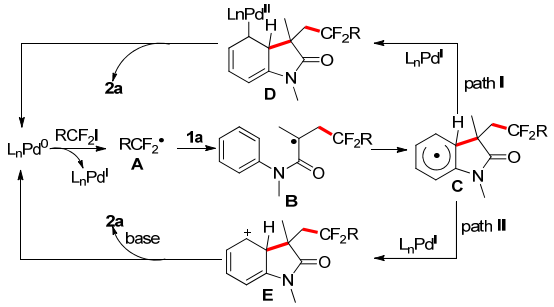



**Scheme 1** Radical trapping experiments.

To gain insight into the mechanism of this transformation, a series of experiments were carried out. First, we performed the reaction in the presence of 1.0 equiv TEMPO as a radical scavenger, and only trace of aryldifluoromethylated product was obtained, which was consistent with the hypothesis that the reaction proceeds via a radical pathway (Eq. 1, Scheme 1). Kinetic isotope experiments were next undertaken. We performed an intermolecular competition experiment between acrylamide **1a** and its pentadeuterated analogue **1a**-$d_5$ and found no kinetic isotope effect ($k_H/k_D$ = 1.0, see SI). Similarly, comparison of parallel independent reactions of **1a** and **1a**-$d_5$ showed also a KIE of 1.0 (see SI). Both observations indicated the C−H cleavage step was not rate-determining. While we failed to capture the coupling product of TEMPO with $PhSO_2CF_2I$, we were able to employ two kinds of radical clocks, allyl ether **3** and β-pinene **5**, to trap the $PhSO_2CF_2$• radical, and the cyclized product **4** and the ring-opened diene **6** were obtained in 82% yield (2.7:1 d.r.) and 76% yield (isolated as an isomeric mixture), respectively (Eq. 2-3). Both results implicated that the difluoro(phenylsulfonyl)methyl radical was involved in this process.

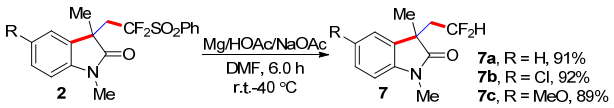
On the basis of these observations, a plausible mechanism involving a radical-type catalytic cycle is depicted in Scheme 3. Initially, reduction of $PhSO_2CF_2I$ catalyzed by Pd(0) affords Pd(I) and an electrophilic difluoro(phenylsulfonyl)methyl radical ($PhSO_2CF_2$•) **A**. Addition of **A** to the activated double bond on acrylamide **1a** results in the formation of carbon radical intermediate **B**, which is then trapped by aniline ring to give radical intermediate **C**. The subsequent C–H cleavage step could proceed through two possible pathways. Path I is similar

to Alexanian's hypothesis for Pd-catalyzed radical Heck-type reactions of alkyl iodides.[22] In this scenario, radical **C** is captured by Pd(I) to yield Pd(II) species **D**. **D** then undergoes β-hydride elimination to afford the desired product **2a** and regenerate the Pd(0) catalyst. Alternatively, in Path II, radical **C** is oxidized to cation **E** by Pd(I) followed by base-mediated deprotonation to give the final difluoromethylated product **2a**. Notably, this transformation avoids the use of potential hazardous radical initiators with Pd(0) as catalyst.




**Scheme 2** Possible mechanism.

Desulfonylation of **2a** mediated by Mg was found to proceed smoothly at r.t.,[23] affording the difluoromethylated oxindole **7a** in 91% yield (Scheme 3). Furthermore, the oxindoles with electron-deficient (**2e**) or electron-rich groups (**2i**) at the aniline ring were compatible with this method, giving the desired difluoromethyl products **7b-c** in excellent yields, respectively.




**Scheme 3** Reductive desulfonylation.

In conclusion, we have developed a Pd(0)-catalyzed intramolecular aryldifluoromethylation of activated alkenes under mild reaction conditions. Mechanistic investigations indicate that a difluoromethyl radical, which was triggered via reduction of $PhSO_2CF_2I$ by Pd(0), initiated the cascade sequence through an addition to alkene.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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