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Iron-Catalyzed Radical Aryldifluoromethylation of Activated Alkenes to Difluoromethylated Oxindoles

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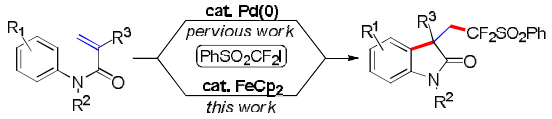
An iron-catalyzed aryldifluoromethylation of activated alkenes under mild reaction conditions has been developed, which is a rare example with cosolvent used to improve the reaction yield along with Fenton reagent and thus provides an economic and green method for the synthesis of a variety of difluoromethylated oxindoles. Priliminary mechanistic investigations indicate a radical addition path.

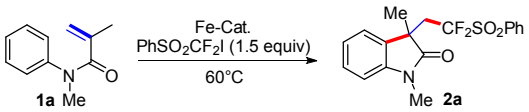
Fluorine-containing organic compounds are of significant interests in various fields, especially in medicine, agriculture, and life- and material sciences because of their specific physical and chemical properties.[1] For example, the introduction of the difluoromethyl group (CF_2H), a bio-isostere of alcohols (thiols) and a more lipophilic hydrogen bond donor, into organic molecules often improves their membrane permeability, binding affinity and bioavailability.[2] As a result, the development of new methodologies for the incorporation of CF_2H group into molecules has attracted increasing interests.[3]



Scheme 1 Aryldifluoromethylation of activated alkenes

Oxindole has long been realized as an important scaffold employed in medical and biological chemistry for the unique bioactivities,[4] which makes the incorporation of fluoroalkyl groups into this structure a feasible way to design bioactive molecules.[5] While a variety of known methods focused on the synthesis of trifluoromethylated oxindoles,[6] it is still of big interests to develop new strategies to construct the closely related difluoromethylated derivatives. We recently reported the only example of Pd(0)-catalyzed difluoromethylation of activated alkenes to construct HCF_2-oxindoles (Scheme 1), in which a radical addition path was indicated by mechanistic investigation.[7] However, this method still suffered from high catalyst loading, substrate scope limitation, toxicity and high cost of palladium. To address these issues, iron was considered as the best choice due to the potential economic, environmental and avirulent merits compared with the transition metals.[8] Within our continuous efforts to develop new methods to synthesize fluorine-containing organic compounds,[9] we herein report an iron-catalyzed radical aryldifluoromethylation of activated alkenes, affording a variety of difluoromethylated oxindoles under mild reaction conditions.

Table 1 Optimization of reaction conditions[a,b]



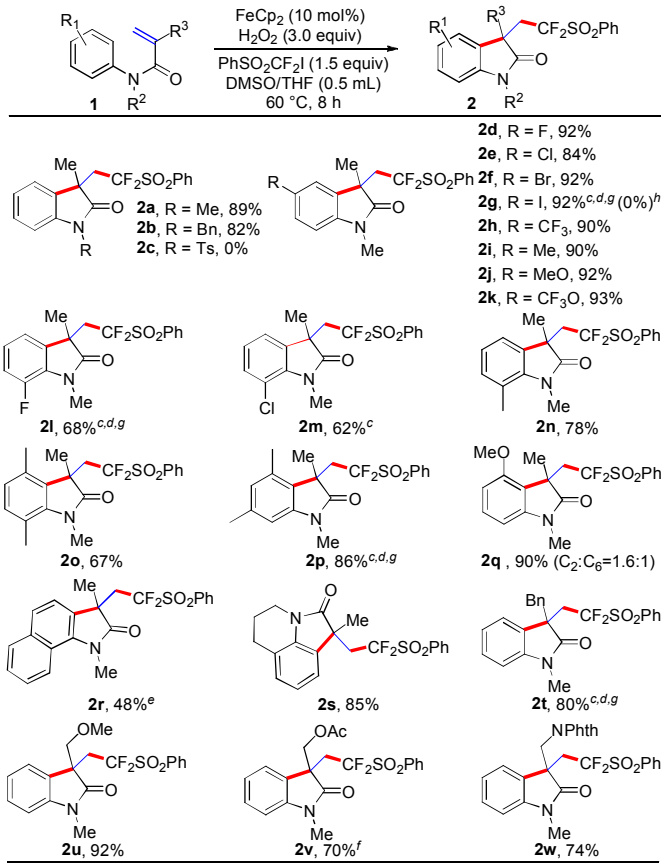
Entry	Fe	Oxidant (eq.)	Solvent	t (h)	yield (%)
1	$FeSO_4{\cdot}7H_2O$	H_2O_2 (5.0)	DMSO	6	56
2	$FeSO_4{\cdot}7H_2O$	DTBP (5.0)	DMSO	6	N.R.
3	$FeSO_4{\cdot}7H_2O$	TBHP (5.0)	DMSO	6	N.R.
4	$FeSO_4{\cdot}7H_2O$	DDQ (5.0)	DMSO	6	N.R.
5	$FeSO_4{\cdot}7H_2O$	$K_2S_2O_8$ (5.0)	DMSO	6	Trace
6	$FeSO_4{\cdot}7H_2O$	BPO (5.0)	DMSO	6	N.R.
7	$FeSO_4{\cdot}7H_2O$	H_2O_2 (3.0)	DMSO	6	57
8	$FeCp_2$	H_2O_2 (3.0)	DMSO	6	75
9	$FeCl_2$	H_2O_2 (3.0)	DMSO	6	67
10	FeF_2	H_2O_2 (3.0)	DMSO	6	72
11	$Fe(OAc)_2$	H_2O_2 (3.0)	DMSO	6	73
12	$FeCl_3$	H_2O_2 (3.0)	DMSO	6	74
13	$FeBr_3$	H_2O_2 (3.0)	DMSO	6	50
14	$FeCp_2$	H_2O_2 (3.0)	DMSO/DCE (1/4)	6	65
15	$FeCp_2$	H_2O_2 (3.0)	DMSO/DCE (1/4)	8	78
16	$FeCp_2$	H_2O_2 (3.0)	DMSO/THF (1/4)	8	87
17[c]	$FeCp_2$	H_2O_2 (3.0)	DMSO/THF (1/4)	8	**89**

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), Fe (20 mol%), $PhSO_2CF_2I$ (1.5 equiv), 60 °C. [b] Isolated yield. [c] $FeCp_2$ (10 mol%) was used.

Our study commenced by examing the difluoromethylation of *N*-methyl-*N*-phenyl-methacrylamide (**1a**) and $PhSO_2CF_2I$[10] in the presence of catalytic $FeSO_4{\cdot}7H_2O$ and H_2O_2 (5.0 equiv), known as

Fenton reagent,[11] in DMSO at 60 °C under an air atmosphere. To our delight, the desired product (**2a**) was obtained in 56% yield after 6 hours (entry 1, Table 1). Considering the key role of oxidant to generate the difluoromethyl radical, a variety of oxidants were next examined in this reaction system, but all of them showed almost no reactivity (entries 2-6). To increase the yield further, different kinds of Iron species were investigated, which indicated both Fe(II)and Fe(III) catalysts gave the similar catalytic efficiency with about 75% yields (entries 8-13). Interestingly, though the addition of DCE as the cosolvent afforded a slightly drop of the yield (entry 14), prolonging the reaction time to 8 hours increased the yield back to 78% (entry 15). To our excitement, THF provided the best performance as the optimal cosolvent with 87% yield (entry 16), which is a rare example that cosolvent used to improve the yield along with Fenton reagent. Importantly, when the $FeCp_2$ catalyst was reduced to 10 mol%, the yield could even give a little rise to 89% (entry 17).

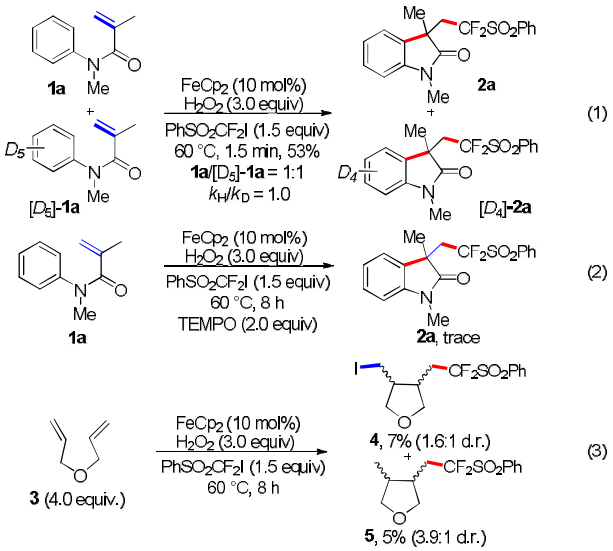
Table 2 Substrate scope[a,b]



[a] Unless other noted, the reaction conditions were as follows: **1a** (0.2 mmol, 1.0 equiv), $FeCp_2$ (10 mol%), $PhSO_2CF_2I$ (1.5 equiv) and DMSO/THF (v/v = 1/4, 0.5 mL) at 60 °C for 8 h. [b] Isolated yield. [c] $FeCp_2$ (20 mol%). [d] $PhSO_2CF_2I$ (2.0 equiv). [e] 6 h. [f] 4 h. [g] 12 h. [h] Performed with Pd(0)-catalytic system.[7]

With the optimized reaction conditions in hand, we next probed the substrate scope of this aryldifluoromethylation process. Not surprisingly, the benzyl group-protecting substrate **2b** gave almost the same yield with the methylated acrylamide **2a**, while electron-withdrawing group tosyl (**2c**) killed the reaction completely. Next, the investigation of the substitute effect of aryl ring (R) showed either the electron-donating groups or electron-withdrawing groups in the arylacrylamide's *para*-position were well tolerated, affording different difluoromethylated oxindoles in high yields (**2d-k**). Of particular note was that the iodinated acrylamide cyclized smoothly also to give the desired product in excellent yield (92%, **2g**), while none of the corresponding oxindole was obtained with our previously reported Pd(0)-catalytic system. Meanwhile, the *ortho*-substituted arylacrylamides were aryldifluoromethylated successfully, albeit with slightly reduced yields (**2l-p**), probably due to the sterichindrance of *ortho*-substituents. As expected, the substrates containing *meta*-substituents gave high yield but with moderate regioselectivity (**2q**). When we changed the benzene ring into naphthalene, we find it also can react with moderate yield (**2r**). Interestingly, the cyclization of tetrahydroquinoline derivative can generate the desired tricyclic oxindole (**2s**) in 90% yield. Notely, the examination of the diversely substituted gorup at the end of double bond (R^3), including Bn (**1t**), ether (**1u**), ester (**1v**) and phthalimide (**1w**), furnished the desired products in acceptable yields.

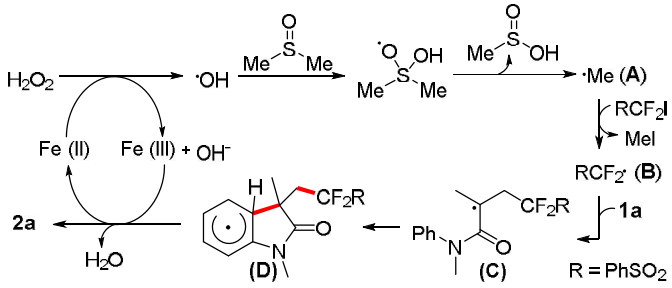
To elucidate the mechanism of this transformation, a series of experiments were carried out accordingly. First, the isotope labeling experiments were undertaken under the standard reaction conditions. An intermolecular competition experiment between *N*-methyl-*N*-phenyl-methacrylamide **1a** and its pentadeuterated analogue **1a**-d_5 exhibited a kinetic isotope effect (KIE) of 1.0, which suggested that the C-H bond cleavage is not the rate-determining step. Next, when the reaction was performed in the presence of TEMPO (2.0 equiv), a common radical scavenger, only trace of the desired difluoro(phenylsulfonyl)methyl product **2a** was obtained, which was consistent with the radical path suggested in the reactions relating with Fenton reagent. Although no coupling product of TEMPO with $PhSO_2CF_2I$ was checked out, the radical clock allyl ether **3** was employed to trap the $PhSO_2CF_2$• radical successfully, and the corresponding cyclized products **4** and **5** were obtained in 7% (1.6:1 d.r.) and 5% (3.9:1 d.r.) yields as an unseparated mixture (Eq. 3, Scheme 2), which implicated that difluoro(phenylsulfonyl)methyl radical was involved in the catalytic cycle.



Scheme 2 Experiments for mechanism study.

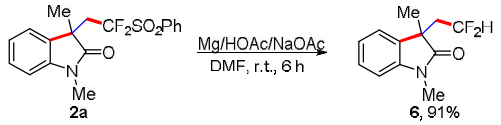
On account of the above observations and the previous reports,[12] a possible mechanism is proposed as Scheme 3. Initially, the reduction

of H_2O_2 by Fe(II) afforded the hydroxyl radical and the corresponding Fe(III) species. The hydroxyl radical was then trapped by DMSO, and followed to trigger the methyl radical **A**, which seized iodine from $PhSO_2CF_2I$ to generate the difluoromethyl radical **B**. The addition of difluoromethyl radical **B** to **1a** afforded the radical intermediate **C**, followed by C-C bond forming cyclization to give the phenyl radical **D**. Finally, the radical **D** was oxidized by Fe(III) to give the final product **2a** and the Fe (II) species to complete the catalytic cycle.



Scheme 3 Possible mechanism.

Desulfonylation of **2a** mediated by Mg with NaOAc/HOAc as proton source has been demonstrated to proceed smoothly under very mild conditions,[7,13] giving the difluoromethylated oxindole **6** in 91% yield (Scheme 4).



Scheme 4 Reductive desulfonylation.

In summary, an iron-catalyzed aryldifluoromethylation of activated alkenes under mild reaction conditions has been developed, which provides an economic and green method for the synthesis of HF_2C-containing oxindoles. Priliminary mechanistic investigations indicate a radical addition path.

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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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