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Metal-free remote oxidative benzylic C–H amination of 4-methylanilides with *N*-fluorobenzenesulfonimide

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ABSTRACT

A metal-free remote oxidative benzylic C–H amination of 4-methylanilides with *N*-fluorobenzenesulfonimide was reported. The reaction was promoted by a hypervalent iodine reagent and can be handled under mild and neutral conditions, providing the highly regioselective benzylic C–H amination products even with multi-substituted 4-methylanilides. It provided a novel and facile method for the construction of C(sp^3)–N bonds.

1. Introduction

The construction of C–N bond has attracted much attention of organic chemists because nitrogen-containing compounds play a pivotal role in pharmaceuticals, agrochemicals, materials, and biologically relevant molecules.[1] During the past decades, direct amination of C–H bond has emerged as an important methodology for C–N bond formation.[2] However, compared with considerable achievements towards the transformation of sp^2 C–H bonds to C–N bond, fewer progress have been made for the sp^3 C–H amination.[3]

In 2006, Che and coworkers reported Pd-catalyzed sp^3 C–H amination of 8-methylquinolines with amides through cascade C–H activation/nitrene insertion.[4] Afterwards, various transition-metal catalysts such as Rh, Ir, Cu were used for directed benzylic sp^3 C–H amination (Scheme 1a).[5] Significant progress has also been made in C–H amination of the substrate without directing groups under Cu, Rh, Fe, Ni or Au catalysts (Scheme 1b).[6] However, the involvement of heavy metals and normally also extra oxidants or bases was unsatisfactory from the environmental point of view. The metal-free methods should be concerned for the pursuit of sustainable and green chemistry.[7] Oxidative amination of toluene benzylic C–H bond was also reported in recent years however large excess amount of the carbon substrate was normally necessary.[8] To overcome these problems, several strategies such as photoredox catalysis and electrochemical process were employed.[9] Recently, *N*-fluorobenzenesulfonimide (NFSI) has been widely used as a nitrogen source for C–H aminations.[10] Zhang and coworkers developed a palladium-catalyzed amide-directed amination of anilide *para*-C–H bond and 4-methylanilide benzylic C–H bond with NFSI (Scheme 1c).[11] In 2016 our group achieved the *para*-C–H amination of anilides with NFSI under metal-free conditions.[12]

As part of our continuing efforts on the development of metal-free oxidative transformations,[13] herein we report the remote oxidative benzylic sp^3 C–H amination 4-methylanilides with NFSI. The reaction was promoted by a hypervalent iodine reagent under mild and neutral conditions, providing the highly regioselective benzylic amination products (Scheme 1d).

2. Results and discussion

Initially, reaction between 4-methylacetanilide (**1a**) and NFSI (2

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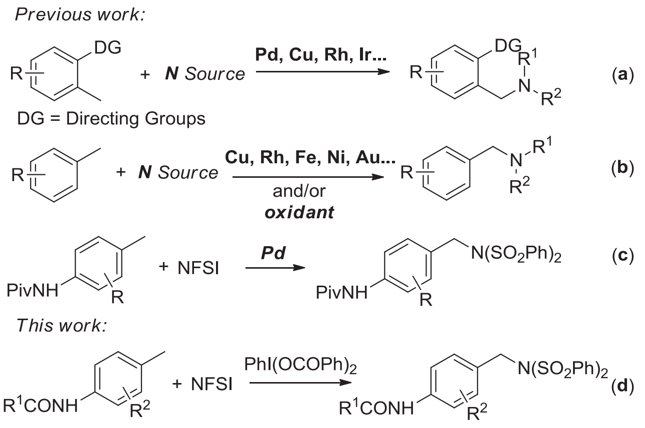
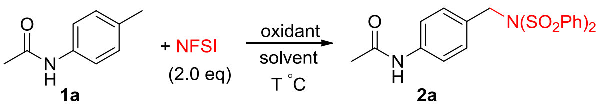


Scheme 1. Amination of benzylic C–H bonds.

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



Entry	Oxidant (equiv)	Solvent	T (°C)	Yield (%)[b]
1	$PhI(OCOPh)_2(2)$	toluene	rt	0
2	$PhI(OCOPh)_2(2)$	DME	rt	0
3	$PhI(OCOPh)_2(2)$	DCE	rt	trace
4	$PhI(OCOPh)_2(2)$	1,4-dioxane	rt	trace
5	$PhI(OCOPh)_2(2)$	PhCl	rt	trace
6	$PhI(OCOPh)_2(2)$	THF	rt	37
7	$PhI(OCOPh)_2(2)$	2-Me-THF	rt	65[c]
8	$PhI(OAc)_2(2)$	2-Me-THF	rt	37
9	$PhI(OPiv)_2(2)$	2-Me-THF	rt	35
10	TBHP(2)	2-Me-THF	rt	0
11	$K_2S_2O_8(2)$	2-Me-THF	rt	0
12	–	2-Me-THF	rt	0
13	$PhI(OCOPh)_2(1.5)$	2-Me-THF	rt	41
14	$PhI(OCOPh)_2(2.5)$	2-Me-THF	rt	65
15[d]	$PhI(OCOPh)_2(2)$	2-Me-THF	rt	47
16	$PhI(OCOPh)_2(2)$	2-Me-THF	40	60
17	$PhI(OCOPh)_2(2)$	2-Me-THF	65	50

[a] Reaction conditions: 4-methylacentaniline (**1a**) (0.2 mmol), NFSI (0.4 mmol), oxidant (0.4 mmol) in solvent (2.0 mL) stirring under air for 8 h.
[b] Isolated yields.
[c] 25% starting material recovered.
[d] With 1.5 eq NFSI.

equiv) was carried out for condition optimization (Table 1). After solvent screening, it was found that the reaction proceeded at room temperature in THF in the presence of 2 equivalents of $PhI(OCOPh)_2$ to generate the desired benzylic C–H amination product in 37% yield (entry 6). To our delight, the product yield was greatly improved (65%) by changing the solvent to 2-methyltetrafuran (2-Me-THF) (entry 7). With trace amount of *ortho*-amination product be detected, 25% starting material could be recovered. Hypervalent iodine reagents such as $PhI(OAc)_2$ and $PhI(OPiv)_2$ were also examined but exhibited lower efficiency than $PhI(OCOPh)_2$ (entries 8 and 9). The reaction didn't proceed at all with other oxidants such as TBHP and $K_2S_2O_8$ or without any oxidant (entries 10–12). Subsequent exploration in reactant ratios showed that decreasing or increasing the amount of $PhI(OCOPh)_2$ couldn't provide better results (entries 13 and 14). Reducing the amount of NFSI caused a lower product yield (entry 15). The reaction temperature was then examined and the results showed higher temperature (40 °C or 65 °C) was not beneficial to the product yield (entries 16 and 17). Therefore, the optimal reaction conditions were determined as shown in entry 7.

Under the optimized reaction conditions, a series of 4-methylanilide had been investigated and the results were showed in Table 2. This method was applicable to various alkyl amides such as propionyl (**2b**), butyryl (**2c**), phenylpropionyl (**2d**), isobutyryl (**2e**), cyclopropanecarboxyl (**2f**) and cyclohexanecarboxyl (**2g**) amides for this reaction, affording the corresponding benzylic amination products in moderate yields. Benzamide can also be applied but showed lower reactivity than alkyl amides in this transformation, which provide the amination product in 43% yield (**2h**). The 4-methylpropionylaniline gave the desired product in highest yield of 65%. In most cases, unreacted starting material remained after reaction and could be recovered.

To further explore the applicability of our methodology, a variety of multi-substituted 4-methylanilides was then investigated as shown in Table 3. The anilides possessing 2,4-dimethyl (**2i**–**2m**) or 3,4-dimethyl (**2n**–**2r**) substituents all gave the 4-methyl benzylic C–H bond amination products, which were obtained in moderate yields. No amination was observed at *ortho*- or *meta*-methyl group of the anilides except for unreacted starting materials. The regioselectivity was further confirmed by X-ray crystallography of **2n** (Fig. 1).[14]

Several control experiments were carried out to illustrate the reaction mechanism (Scheme 2). In the presence of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT), the benzylic C–H amination was completely prevented. The starting material almost remained intact and no identifiable product was detected either. Otherwise, the reaction gave the desired product in 50% yield in the presence of proton scavenger DMAP. These results suggested that the reaction might proceed through a radical mechanism. To examine the necessity of the amide group, we tested several analogous substrates such as *N*-methyl-*N*-(*p*-tolyl)acetamide (**1s**), *p*-tolyl acetate (**1t**) and *N*, *N*-dimethyl-*p*-toluidine (**1u**) however no reaction occurred. It indicated the essential role of amide group in this process (Scheme 3).

Thus a plausible mechanism for this remote oxidative benzylic C–H amination has been proposed according to these results and previous reports (Scheme 4). 4-Methylanilide (**1**) was first oxidized by the iodine(III) reagent to generate a radical intermediate **A**.[15] Single electron transfer of **A** formed a cation **B** which might isomerize to a dienimine intermediate **C**.[16] On the other hand, the NFSI converted to a nitrogen radical which might be induced by the iodine radical.[17] Then the nitrogen radical reacted with **C** to form intermediate **D**, which interacted with **1** to generate the product **2**.

Finally, we handled the desulfonylation reaction of the sulfonamide product. The dibenzenesulfonyl group could be easily removed by conc. H_2SO_4 with high efficiency (Scheme 5). It will provide a novel and facile route for the preparation of benzylic amines.

3. Conclusions

In summary, we have developed a metal-free remote oxidative benzylic C–H amination of 4-methylanilides with NFSI mediated by iodine(III) reagent. This method avoided the used of transition metals and proceeded under mild and neutral conditions, providing the highly regioselective benzylic amination products even with multi-substituted 4-methylanilides. A radical reaction pathway was proposed by preliminary mechanistic studies. It provided an novel and facile methodology for the construction of $C(sp^3)$–N bonds. Intensive study and further application of this protocol is currently under way in our lab.