# DIAD-mediated metal-free cross dehydrogenative coupling between tertiary amines and $\alpha$ -fluorinated sulfones<sup>†</sup>

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A DIAD-mediated metal-free cross dehydrogenative coupling involving aliphatic tertiary amines and  $\alpha$ -fluorinated sulfones leading to  $\beta$ -fluorinated amines was developed. This protocol represents the first direct fluoroalkylation of C–H bonds with hydrofluorocarbon derivatives (R<sub>F</sub>–H).

Fluorinated amines, especially β-fluorinated amines, have received much attention in bioorganic and medicinal chemistry research due to the profound change of the basicity of the amine functionality imparted by fluorine substitution, which has dramatic and beneficial influences on the bioavailability of a target molecule.<sup>1,2</sup> Among various methods for synthesizing fluorinated amines, nucleophilic fluoroalkylation of C=N bonds in imines, nitrones, hydrazones, iminium ions, and azomethine ylides has been most intensively studied<sup>3,4</sup> because of the easy availability of many nucleophilic fluoroalkylation reagents.<sup>5</sup> Although direct C-H bond fluoroalkylation has emerged as a potentially useful method for late-stage modification of bioactive molecules,<sup>6</sup> most research studies focused on the fluoroalkylation of C-H bonds<sup>7</sup> in  $\pi$ -systems such as arenes, alkenes, and alkynes<sup>8</sup> and the sp<sup>3</sup>-C-H bond adjacent to electron-withdrawing groups such as carbonyl group<sup>9</sup> (Scheme 1, eqn (1)).<sup>7-9</sup> The direct fluoroalkylation of the sp<sup>3</sup>-C-H bond in substrates such as amines is rare.<sup>10</sup> In 2009, Qing et al. reported CuBr-catalyzed oxidative gemdifluoroalkylation of tertiary amines with difluoroenol silyl



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ethers,<sup>10a</sup> and subsequently they reported the oxidative trifluoromethylation of tetrahydroisoquinoline derivatives promoted by benzoyl peroxide.<sup>10b</sup> And the modified oxidative trifluoromethylation of tertiary amines includes CuI-catalyzed oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)<sup>10c</sup> and visible light-induced reaction catalyzed by Rose Bengal.<sup>10d,e</sup> However, these reactions used silane reagents as fluoroalkyl sources. On the other hand, the cross dehydrogenative coupling (CDC) reaction has evolved as an effective strategy for constructing new C-C bonds because of the high step- and atom-economy.<sup>11</sup> To our knowledge, there has been no report on the CDC reaction between α-C-H bonds of tertiary amines and C-H bonds adjacent to the fluorine in hydrofluorocarbons and their derivatives (R<sub>F</sub>-H) (Scheme 1, eqn (2)). In this communication, we report our preliminary results on the CDC reaction between tertiary amines and α-fluorinated sulfones for the synthesis of β-fluorinated amines under metal-free conditions.

 $\alpha$ -Fluorinated sulfones, featured by the activation of the sulfonyl groups and their versatile transformations under mild conditions, have been widely applied for introducing difluoromethylene, difluoromethyl, and fluoromethyl moieties into various molecules.<sup>5b-d</sup> Considering that carbon acids with electron-withdrawing groups are usually used as one of the CDC partners,<sup>11</sup> we envisioned that di- and monofluoromethyl sulfones may undergo oxidative coupling reactions with tertiary amines (Table 1).

At the onset of our study, we chose amine 1a and fluorobis(phenylsulfonyl)methane  $(2a)^{12}$  as the model compound to search for suitable conditions for the coupling reaction. A screening of the peroxides showed that tert-butyl peroxybenzoate (TBPB) can promote the reaction in DCM solvent. Other solvents such as tBuOH, THF, and DMF were ineffective for the reaction. Although it was found that the addition of an inorganic base such as K<sub>2</sub>CO<sub>3</sub> could promote the reaction significantly, 1a and TBPB had to be used in large excess (>6 equiv.). In 2009, Li et al. reported a copper-catalyzed, diethyl azodicarboxylate (DEAD)-mediated regioselective alkynylation of tertiary amines, in which DEAD was proposed to act as the oxidant to form the iminium cation intermediate and CuI assisted the transfer of alkynyl groups from alkynes to the iminium cation.<sup>13</sup> Inspired by this transformation, we examined our reaction using a more stable

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 Table 1
 Fluoromethylation of amine 1a under various conditions<sup>a</sup>

$\bigcirc$	N H +	$H \xrightarrow{F} SO_2 Ph$ SO2Ph	Ph Oxic Solvent,	Temp.		,SO₂Ph `SO₂Ph
Entry	Solvent	Oxidant	Base	Temp. [°C]	Reaction time <sup>b</sup> [h]	Yield <sup>c</sup> [%]
1	$CH_2Cl_2$	TBPB	_	r.t.	12	20
2	tBuOH	TBPB	_	50	1	0
3	THF	TBPB	_	r.t.	1	0
4	$CH_2Cl_2$	TBPB	$K_2CO_3$	r.t.	5	50
5	DMF	TBPB	$K_2CO_3$	50	12	0
6	$CH_2Cl_2$	TBHP	$K_2CO_3$	r.t.	12	0
7	THF	DIAD		r.t.	12	64
8	THF	DIAD	_	r.t.	18	73
9	Et <sub>2</sub> O	DIAD	_	r.t.	12	38
10	Dioxane	DIAD	_	r.t.	12	34
11	DMF	DIAD	_	r.t.	12	53
12	DMF	DIAD	_	r.t.	18	70
13	DMF	DIAD	_	50	3	95

<sup>*a*</sup> For entries 1–6, reaction was conducted with **1a** (1.0 mmol), **TBPB** or TBHP (1.1 mmol), **2a** (0.16 mmol) in solvent (3.0 mL) and K<sub>2</sub>CO<sub>3</sub> (1.0 mmol) was added after the addition of **2a**; for entries 7–13, reaction was conducted with **1a** (1.0 mmol), DIAD (1.1 mmol), **2a** (0.5 mmol) in solvent (3.0 mL). <sup>*b*</sup> Reaction time after the addition of **1a**. <sup>*c*</sup> Yield was determined by <sup>19</sup>F NMR. TBPB = *tert*-butyl peroxybenzoate; TBHP = *tert*-butyl hydroperoxide; DIAD = diisopropanyl azodicarboxylate.

azocarboxylate—diisopropanyl azodicarboxylate (DIAD)—as the oxidant to promote the reaction. After stirring the mixture of amine 1a (2.0 equiv.) and DIAD (2.2 equiv.) in neat at rt for 1 h, solvent and sulfone 2a (1.0 equiv.) were added subsequently. The reaction conditions were optimized by screening several

reaction parameters (solvent, temperature, and time). The reaction in THF at room temperature gave the desired product **3a** in a slightly higher yield than that in DMF; however, an unidentified byproduct (<sup>19</sup>F NMR:  $\delta$  –151.7 ppm) was detected in *ca.* 5% yield. When the reaction in DMF was performed at an elevated temperature, the coupling product **3a** was obtained regioselectively in excellent yield. It is noteworthy that the reaction proceeded smoothly without a copper catalyst.

Based on the previously reported DEAD-mediated alkynylation of tertiary amines,<sup>13,14</sup> we proposed a plausible reaction mechanism for the current cross dehydrogenative coupling between **1a** and **2a** (as shown in Scheme 2). Firstly, the nucleophilic addition of amine **1a** to DIAD affords a zwitterionic intermediate **4**,<sup>15</sup> which undergoes intramolecular



Scheme 2 Proposed mechanism for the coupling reaction.

1,4-hydrogen transfer and subsequent fragmentation to afford an ion pair consisting of iminium cation **5** and nitrogen anion **6**. In the presence of **2a**, anion **6** acted as a base and abstracted a proton from **2a** affording the dihydrogenated DIAD (7) and fluorinated sulfone anion **8**. A further addition of anion **8** to iminium cation **5** gave the coupling product **3aa**.

With the optimized reaction conditions identified, various tertiary amines were subjected to the fluoroalkylation reactions with sulfone **2a**, and representative results are shown in Table 2. In addition to the simple aliphatic amines (entries 1–3), the protocol could also be successfully applied in the fluoroalkylation of amines with ether and hydroxyl functional groups (entries 4 and 5). Moreover, all reactions showed very high regioselectivity—only product arising from fluoromethylation of methyl was obtained (entries 1–5). In the case of 2-benzyloxy-substituted amine **1d**, the moderate yield of the coupling product is probably due to the

**Table 2**The scope of DIAD-mediated fluoromethylation of tertiary<br/>amines $^{a}$ 





<sup>*a*</sup> Tertiary amine (1.0 mmol), DIAD (1.1 mmol), sulfone (0.5 mmol), DMF (3.0 mL) (see Experimental section). <sup>*b*</sup> Isolated yield of analytically pure product. <sup>*c*</sup> A solution of Me<sub>3</sub>N (33 wt% in ethanol) was used.





Scheme 4 Possible pathway for the formation of 3ca.

competitive formation of benzyloxy-substituted enamine by  $\beta$ -dehydrogenation from the N,N-dimethyl iminium cation.<sup>15a</sup>

In the case of N,N-dimethylbenzyl amine 1f, the reaction requires elevated temperature and prolonged reaction time, and a mixture of 3fa and 3ca was given as the fluoroalkylated products (Scheme 3). 3ca was supposed to arise from the phenyl transfer in intermediate 9 (Scheme 4, eqn (1)). Although the benzyl C-H bond of 1f is more reactive than the methyl C-H bond, no fluoromethylation of benzyl was observed (Scheme 4, eqn (2)). The absence of benzyl fluoroalkylation is probably due to the high steric sensitivity of the addition reaction of the bulky fluoromethyl anion 8 with iminium cation 12. When N,N-dimethyl-1-(naphthalen-2-yl)methanamine was used instead of 1f, 2-naphthaldehyde could be isolated in 79% yield (based on 2a) after aqueous workup, which supports our explanation.

The reaction was also amenable to other fluorinated sulfones such as 2b and 2c; and their coupling with 1a afforded the desired products in excellent yields (Table 2, entries 6 and 7). It is interesting that when tropine le was used as the tertiary amine, the decarboxylated product 14 was obtained in one pot in 91% yield (Scheme 5). However, it should be mentioned that



Scheme 5 Fluoromethylation of tropine 1e with sulfone 2b.



when other fluorinated sulfones such as PhSO<sub>2</sub>CHF<sub>2</sub> and PhSO<sub>2</sub>CHFSPh were used as R<sub>F</sub>-H sources in the reaction, no desired CDC reaction occurred probably due to the relatively low R<sub>E</sub>–H acidity of these sulfones.

To demonstrate the synthetic utility of the obtained amines 3. the reductive desulfonvlation was conducted with Na-Hg amalgam. As is exemplified in Scheme 6, amine 3aa could be smoothly transformed into β-fluorinated tertiary amine 15 in 82% yield.

In conclusion, we have developed a DIAD-mediated metal-free fluoroalkylation of aliphatic tertiary amines with  $\alpha$ -fluorinated sulfones, which is efficient for the synthesis of  $\beta$ -fluorinated tertiary amines. The protocol represents the first cross dehydrogenative coupling reaction between  $\alpha$ -C-H bonds of tertiary amines and C-H bonds adjacent to the fluorine in hydrofluorocarbon derivatives (R<sub>F</sub>-H). Further research on the direct fluoroalkylation of various C-H bonds with hydrofluorocarbons is underway in our laboratory.

## **Experimental**

SO<sub>2</sub>Ph

SO<sub>2</sub>Ph

SO<sub>2</sub>Ph

SO<sub>2</sub>Ph

3fa 39%

3ca 35%

### Typical procedure for the coupling reaction between tertiary amines and $\alpha$ -fluorinated sulfones

To a 25 mL Schlenk tube with N,N-dimethylcyclohexylamine 1a (150 µL, 1.0 mmol) was dropwise added DIAD (230 µL, 1.1 mmol) in 1-2 minutes at 0 °C. The mixture was stirred in neat for 1 hour at room temperature. Then DMF (3 mL) and fluorobisphenylsulfonylmethane 2a (157 mg, 0.5 mmol) were successively added. The resulting mixture was stirred at 50 °C for 3 hours. After cooling to room temperature, saturated brine (20 mL) was added and the mixture was extracted with ethyl acetate (15 mL  $\times$  3). The combined organic phase was dried with anhydrous MgSO4 and evaporated to almost dryness under reduced pressure. Purification by flash column chromatography on silica gel (200-300 mesh) with petroleum ether-ethyl acetate (5:1) as an eluent gave product 3aa (207 mg, 94% vield). White solid, M.p.: 140-142 °C. IR (KBr): 2935, 2858, 1583, 1447, 1340, 1150, 1080 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  7.96 (d, J = 7.8 Hz, 4H), 7.69 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 7.8 Hz, 4H), 3.62 (d, J = 24.0 Hz, 2H), 2.19–2.28 (m, 1H), 1.93 (s, 3H), 1.44–1.72 (m, 4H), 0.95–1.14 (m, 6H).  $^{19}{\rm F}$  NMR:  $\delta$  –146.3 (t, J = 24.8 Hz, 1F). <sup>13</sup>C NMR:  $\delta$  136.7, 134.8, 130.9, 128.5, 116.8 (d, J = 271.0 Hz), 64.3, 53.6 (d, J = 16.1 Hz), 37.0, 27.6, 26.0,25.9. MS (ESI, m/z): 440.4 ([M + H]<sup>+</sup>). Anal. calcd for C<sub>21</sub>H<sub>26</sub>FNO<sub>4</sub>S<sub>2</sub>: C, 57.38; H, 5.96; N, 3.19; found: C, 57.49; H, 6.02; N, 3.11%.

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