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## Visible light-promoted umpolung coupling of aryl tri-/difluoroethanones with 2-alkenylpyridines

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Tertiary alcohols bearing a trifluoromethyl group are of considerable medicinal interest. Via an umpolung strategy, we herein report the first intermolecular reductive cross-coupling of aryl tri-/difluoroethanones with 2-alkenylpyridines with the aid of a Brønsted acid catalyst upon visible-light irradiation. This metalfree reaction is operationally simple and performed at ambient temperature, allowing to access desired tertiary alcohols with tri-/difluoromethyl groups in moderate to excellent yields. The commercially available and easily handled Hantzsch ester effectively serves as an electron donor, as well as a hydrogen atom source.

A fluorinated mojety is often considered as a "magic" group in pharmaceuticals, agrochemicals and materials.<sup>1</sup> Although the direct construction of C-F bonds and fluorinated C-C bonds with fluorination and fluoroalkylation reagents continues to be the main approach,<sup>2</sup> synthesis with fluorinated building blocks/substrates is also an attractive strategy for the incorporation of fluorinecontaining groups into target molecules.<sup>3</sup> Notably, the fluorine or fluoroalkyl group directly connected with the reactive site could have significant impact on the outcome of the reaction.<sup>3</sup> On the other hand, pyridine with a basic nitrogen centre is ubiquitous in agrochemicals,<sup>4</sup> pharmaceuticals,<sup>5</sup> and ligands in catalysis.<sup>6</sup> As the versatile synthons for the construction of complex molecules with pyridine subunits,<sup>7</sup> alkenylpyridines have electrophilic nature and thus the reductive coupling with another electrophile is rare.<sup>8</sup> Of the few relevant reports, Cu-<sup>8b-c</sup> or Rh-catalysed<sup>8d</sup> reductive C-C coupling of carbonyl or iminyl derivatives to alkenylpyridines at the  $\alpha$ -position of the vinyl moiety was first developed. Furthermore,

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the reaction for  $\beta$ -selective reductive coupling via synergistic Lewis acid/photoredox catalysis has been achieved in a radical process very recently (Scheme 1a).<sup>8a</sup>



b) This study



To produce ketyl radicals, the strongly negative reduction potential of carbonyl compounds<sup>9</sup> ( $E_{1/2}^{red}$  = -1.93 V vs SCE for benzaldehyde and  $E_{1/2}^{red}$  = -2.11 V vs SCE for acetophenone) has to be overcome. Fortunately, the single electron reduction of an electrophilic carbonyl group to generate a polarity-reversed ketyl radical via photoredox catalysis has been developed recently.<sup>10-12</sup> In these protocols, harsh reaction conditions and water-/air-sensitive strong reductants that were often used in the traditional methods are not required.<sup>13</sup> However, these photoredox catalysis reactions are mainly limited to intramolecular rearrangement /addition or radical-radical coupling,<sup>10,11</sup> and there have been only few reports of intermolecular radical addition reactions.<sup>8a,12</sup> Despite these reports, it is important to note that the generation of ketyl radicals requires very expensive Ir- or Ru-photocatalyst. Moreover, tertiary

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alcohols bearing trifluoromethyl group are considerable of medicinal interest.<sup>14</sup> Herein we report a novel intermolecular reductive cross-coupling reaction of aryl tri-/difluoroethanones with 2-alkenylpyridines via a visible light-driven radical process under metal-free conditions (Scheme 1b).

..... a

further tested the influence of light source, finding that 395 nm of LEDs gave the optimal yield of **3a** (entry 15). Finally, we also found that heat at reflux could promote the reaction as well though the chemical yield is much lower than that upon light irradiation (entry 16).

Table 1 Optimization of reaction conditions				
	℃F <sub>3 +</sub>	Hantzsch e Brønsted a LED 2a	ester (2 equiv) acid (20 mol%) olvent s, rt, 12 h	OH CF <sub>3</sub> 3a
Entry	Solvent	Brønsted acid	LEDs	Yield (%) <sup>b</sup>
1	DCE	_	Blue	< 5
2 <sup><i>c</i></sup>	DCE	(PhO) <sub>2</sub> PO <sub>2</sub> H	-	0
3	DCE	(PhO) <sub>2</sub> PO <sub>2</sub> H	Blue	81
4	DCE	CF <sub>3</sub> CO <sub>2</sub> H	Blue	31
5	DCE	CH <sub>3</sub> CO <sub>2</sub> H	Blue	< 10
6	DCE	CH <sub>3</sub> SO <sub>3</sub> H	Blue	47
7	DCE	CF <sub>3</sub> SO <sub>3</sub> H	Blue	51
8	DCM	(PhO) <sub>2</sub> PO <sub>2</sub> H	Blue	86
9	MeCN	(PhO) <sub>2</sub> PO <sub>2</sub> H	Blue	46
10	DMF	(PhO) <sub>2</sub> PO <sub>2</sub> H	Blue	40
11	THF	(PhO) <sub>2</sub> PO <sub>2</sub> H	Blue	77
12	DCE	(PhO) <sub>2</sub> PO <sub>2</sub> H	White	67
13	DCE	(PhO)₂PO₂H	Red	0
$14^d$	DCE	(PhO) <sub>2</sub> PO <sub>2</sub> H	395 nm	90
15	DCM	(PhO) <sub>2</sub> PO <sub>2</sub> H	395 nm	95
16 <sup>e</sup>	DCE	(PhO) <sub>2</sub> PO <sub>2</sub> H	-	23

<sup>&</sup>lt;sup>*a*</sup>**1a** (0.30 mmol), **2a** (0.20 mmol), Hantzsch ester (0.40 mmol), Brønsted acid (20 mol%), solvent (2 mL), LEDs (9 W), room temperature. <sup>*b*</sup>Isolated yield. <sup>c</sup>In the dark. <sup>*d*</sup>395 nm LEDs (6 W). <sup>*c*</sup>Reflux in the dark.

Our examination and optimization of this new photoredox reaction is given in Table 1. At first, we conducted the reaction of 2,2,2-trifluoro-1-phenylethanone **1a** with 2-vinylpyridine **2a** in 1,2-dichloroethane (DCE) by use of Hantzsch ester (HE) as a stoichiometric reductant and diphenylphosphoric acid as a catalyst upon irradiation with household blue LEDs, delightedly giving the desired reductive coupling product **3a** in good yield (entry 3). Control experiments revealed that the Brønsted acid catalyst and visible light were both essential for the success of the reaction (entries 1–2). An evaluation of different Brønsted acids showed that diphenylphosphoric acid was the most effective one (entry 3 vs entries 4–7). It is of note that higher yields of **3a** were obtained when stronger acids were used. Next, a brief screening of organic solvents revealed that DCM was the best one in terms of chemical yield (entry 8). We



Scheme 2 Scope of reductive coupling of aryl trifluoroethanones with 2-alkenylpyridines.

With the optimized conditions in hand, we next aimed to define the scope and limitations of aryl trifluoroethanones in this mild photoredox reaction. As shown in Scheme 2, a broad range of trifluoromethylated products were readily obtained in reasonable yields (3b-s). This protocol could accommodate an array of parasubstituents on the phenyl ring regardless of their electronic properties (3b-i) except the substrate 1aa. Halogen substituents (3b-e), especially bromo and iodo atoms, did not affect the reaction, and the reserved Br and I provide the options for further cross-coupling. In addition, the meta-substituents show little impact on the reaction efficiency (3j-k). However, this transformation appears to be sensitive to ortho steric effects, giving the desired products in lower yields (3I-m) compared to their para counterparts (3c-d) or failing to give any desired products (1ab-1ac). It is noteworthy that the highly electron-rich substrate 1n could furnish the corresponding product 3n in excellent yield. The bicyclic naphthalene was also accommodated with good efficiency (3o). With respect to heteroaromatic substrates, we found that the thienyl moiety (3p) led to much lower yields compared to that of 3a. Moreover, we were pleased to find that methyl and methoxy groups were tolerated on the pyridine ring,

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providing the desired products in good yields (**3q–s**). However, the reaction of alkenes bearing more than one substituent, such as 2-(1-methylalkenyl)pyridine, led to an inseparable complex mixture.



Scheme 3 Scope of reductive coupling of aryl difluoroethanones with 2-vinylpyridine.

Considering the fact that the CF<sub>2</sub>H group is often used as the bioisostere of a carbinol moiety and as a more lipophilic hydrogen bond donor,<sup>15</sup> we further chose aryl difluoroethanones as the coupling partner and the scope was explored (Scheme 3). The reaction proceeded smoothly to achieve the desired difluoromethylated products in satisfactory yields (**5a-f**, 60–72% yield) and this transformation also showed good functional group tolerance though the chemical yields were lower than that of the corresponding trifluoroethanone-alkenylpyridine coupling reaction.



We then extended this protocol to other carbonyl compounds (Scheme 4, eq 1). As might be expected, the reaction of aldehyde **6a** gave the desired reductive cross-coupling product **7a** in reasonable yield. However, for ketones **6b** and **6c**, the reaction proceeded slowly, providing much lower chemical yields of **7b** and **7c**. In addition, we found the formation of **6b** as the reductive defluorination product. To our surprise, only reductive dimerization product **9** was obtained under our optimal reaction conditions (Scheme 4, eq

2) though the reductive cross-coupling with aryl aldehyde was reported  $^{8a}$  when using 4-vinylpyridne as the ketyl radical acceptor.

HE, with strongly negative excited-state oxidation potential  $*E_{ox} = -2.28 \text{ V}$  (vs. SCE), <sup>16</sup> could effect single electron reduction of aryl aldehydes/ketones.<sup>9</sup> It should be noted that the strong inductive effect of the  $\alpha$ -fluoro substituent could substantially increase the negative reduction potentials of aryl ketones. Indeed, the Stern-Volmer experiments showed that trifluoroacetophenone **1a** quenched the photoexcited HE (HE\*) effectively whereas 2-vinylpyridine **2a** did not (Figure S2).<sup>17</sup> In addition, a series of UV-vis absorption experiments were conducted and the data may indicate that no electron donor-acceptor (EDA) aggregate generated between HE and **1a** and/or **2a** (Figure S1).<sup>17</sup> On the other hand, without addition of Brønsted acid, only trace amount of the desired product was detected (Table 1, entry 1), which could be consistent with previous reports of ketyl radical formation by the proton-coupled electron-transfer (PCET) mechanism.<sup>10-</sup>

In summary, we have developed a practical protocol for the intermolecular umpolung reductive cross-coupling of aryl tri-/difluoroethanones with 2-alkenylpyridines under metal-free conditions. This visible-light-induced reaction is operational simple and tolerant of a range of functional groups, furnishing a variety of desired tertiary alcohols bearing vicinal tri-/difluoromethyl groups. The Hantzsch ester serves as an effective electron and proton donor. We also found that the number of the  $\alpha$ -fluorine atoms of the arylethanones could influence the chemical outcome.

## **Conflicts of interest**

There are no conflicts to declare.

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A metal-free, mild, and simple protocol is developed for the synthesis of tertiary alcohols bearing tri-/difluoromethyl groups upon visible-light irradiation.