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Transition-Metal-Free Dehydrosilylative Difluoroamidation of Tetrahydroisoquinolines under Mild Conditions

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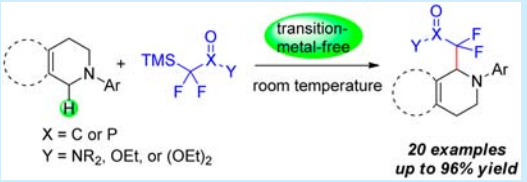
Supporting Information

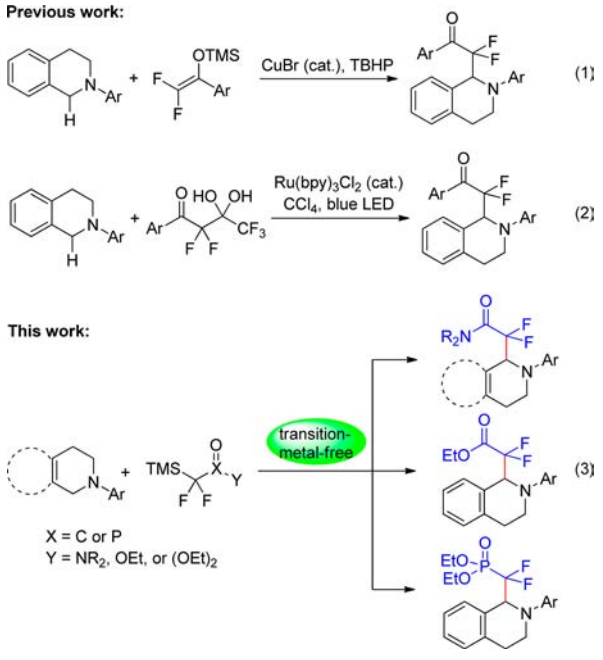
ABSTRACT: Disclosed herein is a dehydrosilylative difluoroamidation of α-Csp^3–H of tetrahydroisoquinolines with α,α-difluoro-α-TMS-acetamides. The process, which occurs at ambient temperature in the absence of any transition metals, provides direct access to a broad range of α,α-difluoroacetamide-substituted tertiary amine derivatives in high yields. Moreover, the method was successfully applied in the Csp^3–H-directed difluorophosphorylation and difluorocarboxylation under the same conditions.



Currently, more and more attention is being focused on fluorinated compounds because of their increasingly significant role in pharmaceuticals, agrochemicals, and materials science.[1] Although general methods exist for the introduction of trifluoromethyl into small organic molecules,[2] efficient and practical strategies for the synthesis of difluoroalkyl-functionalized compounds are relatively limited.[3] In recent years, significant advances have been made in the synthesis of Csp^2-difluoromethyl-containing compounds via transition-metal-catalyzed cross-coupling reactions, leading to a plethora of difluorinated arenes, heteroarenes, and alkenes.[3a,4] However, examples for the coupling between Csp^3 and CF_2 motifs are quite few, especially for the formation of Csp^3–CF_2 via direct C–H bond functionalization.[5]

The currently existing literature describes the preparation of Csp^3–CF_2 via the nucleophilic addition of CF_2 reagents to electrophiles (aldehydes, ketones, imines, alkenes, epoxides, etc.) or electrophilic additions with electrophilic CF_2 reagents.[6−8] Among the handful of achievements, only two examples exist for the coupling between Csp^3 and CF_2 groups via direct C–H bond functionalization.[7,8] In 2009, a copper catalyzed Csp^3-H difluoroalkylation of tetrahydroisoquinolines was developed by Qing and co-workers, leading to a series of β-amino-α,α-difluoro ketones in moderate to good yields (Scheme 1, eq 1).[7] Very recently, this type of compound was obtained via a visible-light-induced oxidative difluoroalkylation by the group of Zhu (eq 2).[8] In spite of these excellent achievements, these Csp^3–H difluoroalkylations were all focused on the synthesis of 1,1-difluoroacetophenone derivatives. In the sharp contrast, a method for the coupling of Csp^3–H with α,α-difluorocarboxylic acid derivatives or α,α-difluorophosphonates has never been documented since it is more difficult to generate the corresponding difluoroenolates from these compounds than from 1,1-difluoroacetophenone derivatives.[9,10] Recently, Hartwig and co-workers disclosed a Pd-catalyzed synthesis of aryl-α,α-difluoroacetamides by using in situ generated silicon enolates of α,α-difluoroacetamides as coupling partners.[10] As part of our continuing effort on the direct functionalization of Csp^3–H systems,[11] we envisioned that the silicon enolate of α,α-difluoroacetamide could be employed for the construction of a Csp^3–CF_2 unit under oxidative conditions. To our delight, all the coupling reactions went smoothly with various difluoroacetamides and tetrahydroisoquinolines in uniformly high yields. These mild and transition-metal-free reaction conditions offer a significant practical advantage. Moreover, using the same strategy,

Scheme 1. Csp^3-H Difluoroalkylation Reactions



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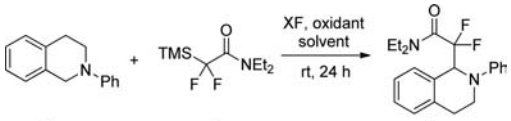
Csp^3–H α,α-difluorophosphorylation and α,α-difluorocarboxylation were also achieved in good yields (eq 3).

We initiated our studies by testing the feasibility of the oxidative coupling of 2-phenyltetrahydroisoquinoline **1a** and the trimethylsilyl enolate of the amide **2a** in the presence of 1.2 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in THF. Fortunately, the reaction proceeded smoothly and gave the desired product **3a** in moderate yield (73%, Table 1, entry 1). Considering the limited solubility of KF in organic solvents, CsF was subjected to the reaction instead. To our delight, a significant increase in the efficiency of the reaction was observed and **3a** was delivered in an excellent yield (96%, entry 2). The frequently used oxidants were also employed for the reaction between **1a** and **2a**. However, only $PhI(OCOCF_3)_2$ showed a comparable effect; others were less effective or completely ineffective (entries 3–7). When air was introduced as the oxidant, no desired product was detected either (entry 8). The screening of solvents revealed that THF is the best media for this transformation (entries 9–11). Lastly, the amount of CsF could be reduced to 1.5 equiv without any influence on yield of the product, while a catalytic amount of CsF was not sufficient to give a good yield of the **3a** (entries 12–13). Reducing **2a** to 1.2 equiv decreased the production of **3a** significantly (entry 14).

Table 1. Optimization of Reaction Conditions[a]



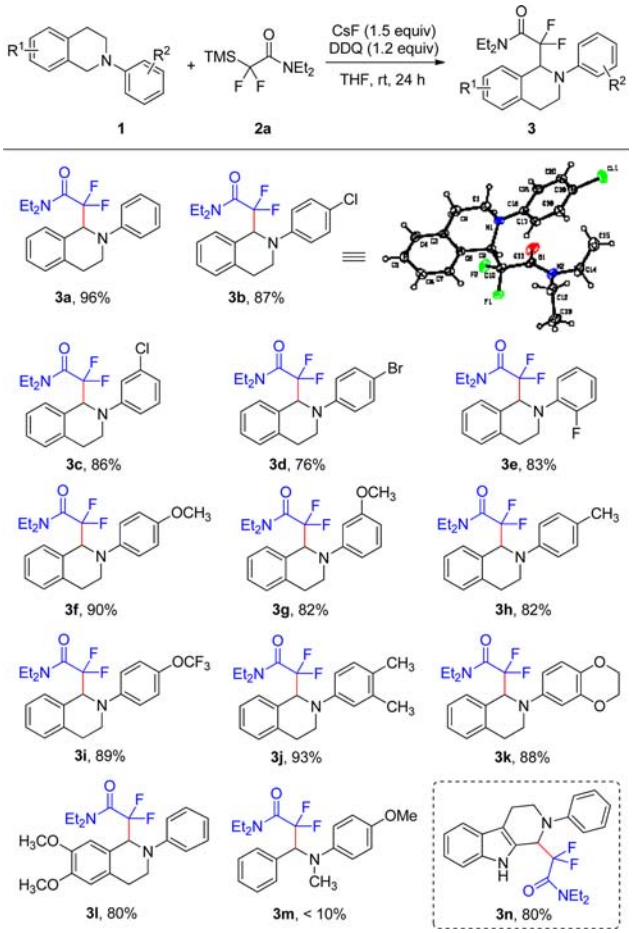
1a 2a 3a

entry	XF	oxidant	solvent	yield[b] (%)
1	KF	DDQ	THF	73
2	CsF	DDQ	THF	96
3	CsF	$TEMPO^+BF_4^-$	THF	61
4	CsF	$PhI(O_2CCF_3)_2$	THF	96
5	CsF	TBHP	THF	trace
6	CsF	$(PhCO_2)_2$	THF	66
7	CsF	$PhI(OAc)_2$	THF	trace
8	CsF	air	THF	0
9	CsF	DDQ	toluene	55
10	CsF	DDQ	CH_2Cl_2	91
11	CsF	DDQ	MeCN	93
12[c]	CsF	DDQ	THF	96
13[d]	CsF	DDQ	THF	11
14[e]	CsF	DDQ	THF	88

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), XF (2 equiv), and oxidant (1.2 equiv) in 2 mL of solvent at room temperature for 24 h, unless otherwise specified. [b]Isolated yield. [c]1.5 equiv CsF of was used. [d]0.2 equiv of CsF was used. [e]1.2 equiv of **2a** and 1.2 equiv of CsF were used.

To demonstrate the substrate scope, a variety of tetrahydroisoquinolines were subjected to this dehydrosilylative difluoroamidation under the optimized conditions (Scheme 2). Generally, the electronic character and the position of the substituent on the *N*-substituted ring slightly affected the activity of the tertiary amine substrates, and the desired products were obtained in good to excellent yields (**3a**–**k**). The methoxy group on the tetrahydroisoquinoline ring showed a small negative effect on the reaction and produced **3l** in 80% yield. Disappointingly, *N*-benzyl-4-methoxy-*N*-methylaniline was inert to this transformation, and only a trace of the product (**3m**) was detected. It should be noted that under the stated conditions difluoroamidation of a more complex substrate, namely indolopiperidine tetrahydro-β-carboline, was also achieved with good yield (**3n**). The structure of the products was also determined by X-ray diffraction of **3b** (see the Supporting Information).

Scheme 2. Difluoroamidation Reactions with Various Tetrahydroisoquinolines[a,b]



[a]All of the reactions were carried out on a 0.2 mmol scale with 1 (0.2 mmol), 2a (0.3 mmol), CsF (0.3 mmol), DDQ (0.24 mmol), and at room temperature for 24 h. [b]Isolated yields.

We next focused our attention on the oxidative coupling reaction of tertiary amine **1a** with various α,α-difluoro-α-(trimethylsilyl)acetamides **2** (Scheme 3). We found that difluoromethylacetamides bearing a six-membered ring gave higher yields than those containing a five-membered ring (**3p**/**3q** vs **3o**). The methylbenzylamide substrate was also tolerated in the reaction and gave the corresponding product in 80% yield (**3r**).

Following our successful development of the Csp^3–H difluoroamidation reaction, we further extended the protocol to the Csp^3–H difluorophosphorylation and difluorocarboxylation reactions. By using α,α-difluoro-α-(trimethylsilyl)-phosphonate or α,α-difluoro-α-(trimethylsilyl)ethyl acetate, Csp^3–H difluoroalkylations were accomplished in good yields under the conditions in Scheme 2 (Scheme 4, eq 1 and 2). Moreover, the reaction could be conducted on a gram scale without affecting the reactivity of the process (eq 3).

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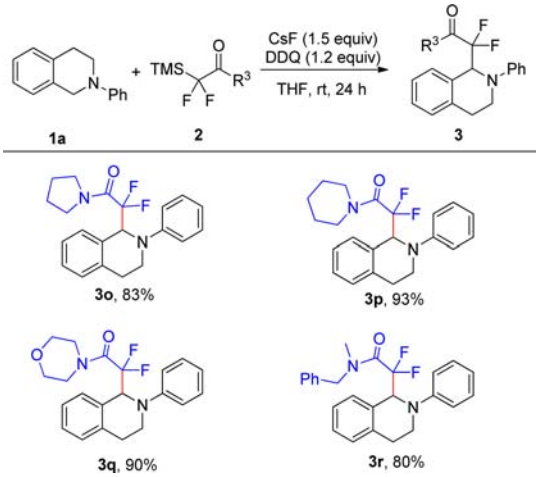
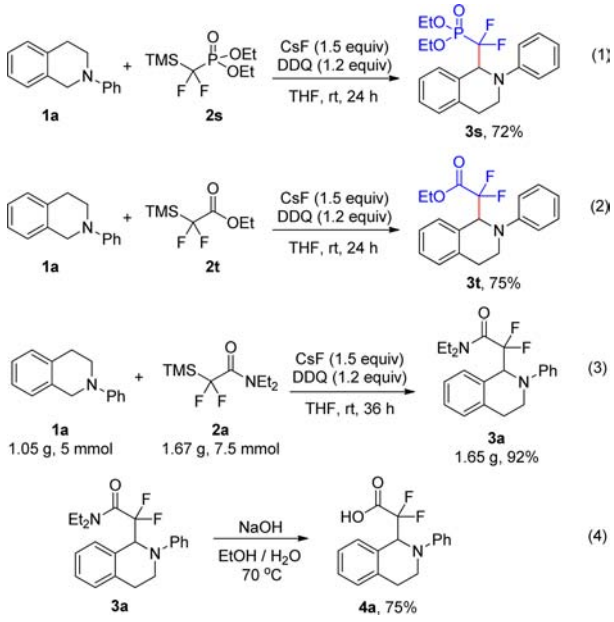
Scheme 3. Difluoroamidation Reactions with Various α,α-Difluoro-α- (trimethyl)silylacetamides[a,b]



[a]All reactions were carried out in a 0.2 mmol scale with 1a (0.2 mmol), 2 (0.3 mmol), CsF (0.3 mmol), DDQ (0.24 mmol), and at room temperature for 24 h. [b]Isolated yields.

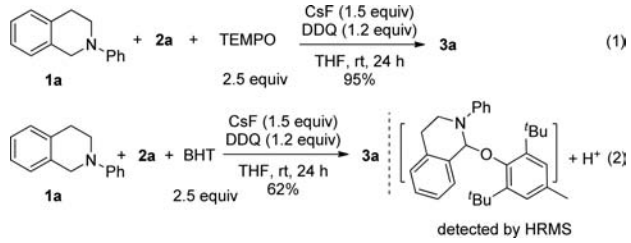
Scheme 4. Difluorophosphorylation and Difluorocarboxylation Reactions



Furthermore, the coupling product **3a** was transformed to the corresponding difluorinated amino acid **4a** in 75% isolated yield by the treatment of sodium hydroxide in a mixed solvent (eq 4).

In order to gain some mechanistic insight into the present reaction, we conducted the radical inhibition experiments (Scheme 5; see the Supporting Information for details). Under the standard conditions, when TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) was added to the system, the yield of the coupling product **3a** was found to be almost the same as that for the model reaction (eq 1). On the contrary, the presence of BHT (2,6-di-*tert*-butyl-4-methylphenol) led to a dramatically lower yield of the desired product (decreased from 96 to 62%). The ESI-HRMS experiment of the reaction mixture indicated the formation of BHT−**1a** adduct (eq 2). These results

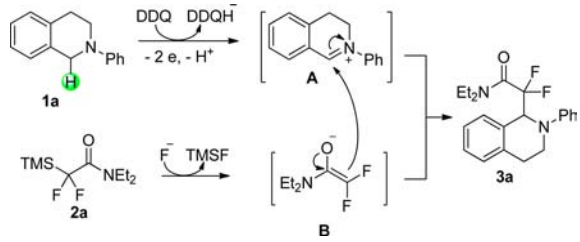
Scheme 5. Radical-Trapping Study



suggested that a rapid radical cation might be involved in the transformation.[12] ^{19}F NMR analysis demonstrated the generation of TMSF since the fluorine signal of TMSF was detected in the mixture of the model reaction as well as the radical inhibition reactions.[13]

On the basis of the above experimental results and past literature reports,[14] a plausible mechanism is proposed in Scheme 6. Following oxidation with DDQ, **1a** forms an

Scheme 6. Proposed Mechanism



iminium cation intermediate **A** through the single-electron transfer and proton abstraction process. At this point, a difluoroenolate **B** is generated in situ by a F^--promoted desilylation of **2a**. The nucleophilic addition of the difluoroenolate to the iminium cation gives the desired product **3a**.

In summary, the first dehydrosilylative difluoroamidation of Csp^3−H has been developed under mild and transition-metal-free conditions. A broad range of tetrahydroisoquinolines bearing α,α-difluoroacetamides were obtained in high yields. Moreover, Csp^3−H α,α-difluorophosphorylation and α,α-difluorocarboxylation were also achieved under the standard conditions. The establishment of this effective and concise strategy could offer new opportunities for the application of difluorinated compounds in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01997.

Experimental details, characterization data, and NMR spectra (PDF)

Crystallographic data for compound **3b** (CIF)

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Notes

The authors declare no competing financial interest.

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