ORGANIC LETTERS

2009
Vol. 11, No. 10
2197−2200

CuBr-Catalyzed Oxidative Difluoromethylation of Tertiary Amines with Difluoroenol Silyl Ethers

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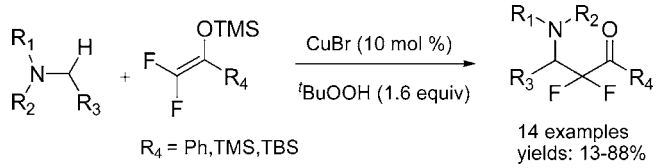
Received March 16, 2009

ABSTRACT



CuBr-catalyzed oxidative difluoromethylation of readily available tertiary amines with difluoroenol silyl ethers was performed under mild conditions to afford *β*-amine-α,α-difluoro ketones.

The introduction of one or a few fluorine atoms into an organic molecule produces profound changes in its chemical, physical, and pharmacological properties.[1] Especially, incorporation of a *gem*-difluoromethylene group (CF_2) into an organic molecule has been used as a strategy for modification of biologically active compounds.[2] This is because the difluoromethylene group can not only enhance its neighboring group acidity but also significantly improve its biological stability when an oxygen at a biochemically labile position is replaced with a CF_2 group. For example, the difluoroketone derivative is an indispensable inhibitor of HIV-1 aspartic protease, in which the strong electron-withdrawing effect of the CF_2 group dramatically increases the electrophilicity of its neighboring carbonyl group; as a result the inhibitor can mimic the tetrahedral intermediate that is formed during peptide bond cleavage.[3] Furthermore, the α,α-difluoro-*β*-amino acids have attracted much interest due to their importance in chemical biology.[4] However, the synthetic methods for *β*-amino-α,α-difluoro ketone or acid derivatives are still limited.[5] The most commonly used methods thus far are Reformatsky addition of α-halodifluoro ketones or

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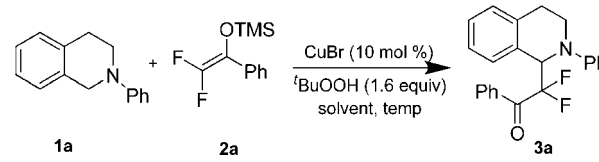
10.1021/ol900541n CCC: $40.75
Published on Web 04/20/2009

bromodifluoroacetate to imines and the reaction of difluoroenol ethers with *N*-acyliminiums or imines under Lewis acid activation.[5a,d−h] Although these are effective methods, they require the use of imines or *N*-acyliminiums prepared from aldehydes and amines. Recently, transition-metal-catalyzed C−H bond functionalization of tertiary amine has attracted great attention in both academia and industry because of its atom- and step-economy, high efficiency, low cost, and minimal environmental impact.[6−10] Generally, direct oxidative transformation of tertiary amine developed by Murahashi et al.,[7] Doyle et al.,[8] Li et al.,[9a−m] and others[9n−p] is performed in two steps:[10] α-H activation of amine to produce iminium ion intermediates and subsequent reaction with nucleophiles. To date, various nucleophiles[6,8] have been used to capture the iminium ions generated in situ by several transition metals.[6−8] We envisioned that the use of difluorinated reagents for catalytic C−H bond functionalization of tertiary amine might be an alternative method to synthesize *β*-amine-α,α-difluoro ketones without pre-functionalization of substrates. To the best of our knowledge, the direct oxidative difluoromethylation of amines has not been reported. Herein, we disclosed the first effective atom- and step-economical synthesis of *β*-amino-α,α-difluoro ketones through addition of difluoroenol silyl ethers to iminium ions generated in situ catalyzed by CuBr under mild conditions.

Inspired by Li's work on CuBr-catalyzed sp^3 C−H bond activation for C−C bond formation,[9a,d] initially we started the synthesis of *β*-amino-α,α-difluoro ketone by coupling of difluoroenol silyl ether **2a**[11] with 1,2,3,4-tetrahydroisoquinoline **1a** in the presence of catalytic amount of CuBr and stoichiometric amount of oxidant *tert*-butyl hydroperoxide (TBHP) under neat conditions at 60 °C. Unfortunately, only trace amount of desired product **3a** was detected by ^{19}F NMR (Table 1, entry 1). Considering the instability of the difluoroenol silyl ether **2a**,[11] the reaction temperature was decreased to room temperature; however, the yield of the product slightly increased to 17% (Table 1, entry 2). To our delight, the efficiency of the reaction was dramatically improved when the reaction was conducted in CH_2Cl_2 and 61% yield of **3a** was obtained (determined by ^{19}F NMR)

Table 1. CuBr-Catalyzed Difluoromethylation of 1,2,3,4-Tetrahydroisoquinoline with Difluoroenol Silyl Ether **2a**[a]



1a 2a 3a

entry	**2a**	temp (°C)	solvent	yield (%)[b]
1	1.2	60	neat	8[c]
2	1.2	rt	neat	17
3	1.2	rt	CH_2Cl_2	61
4	1.5	rt	CH_2Cl_2	64
5	2.0	rt	CH_2Cl_2	75
6	2.5	rt	CH_2Cl_2	78
7	3	rt	CH_2Cl_2	98
8	4	rt	CH_2Cl_2	83

[a] Reaction scale: tertiary amine (0.2 mmol, 1 M). [b] Yield was determined by ^{19}F NMR using benzotrifluoride as an internal standard. [c] Reaction was conducted in sealed tube.

(Table 1, entry 3). Increasing the amount of substrate **2a** increased the yield of the product (Table 1, entries 4−7). When the ratio of **1a**/**2a** was 1:3, an excellent yield (98%) was afforded (Table 1, entry 7), and further increasing the ratio of **1a**/**2a** proved to be deleterious to the reaction yield (Table 1, entry 8).

With the optimized reaction conditions in hand (3 equiv of difluoroenol silyl ether, 10 mol % of CuBr, TBHP (1.6 equiv) in CH_2Cl_2), we next examined the scope of the reaction with a variety of substituted 1,2,3,4-tetrahydroisoquinoline derivatives. The results are summarized in Table 2. Substrates with various substitution patterns all provided the expected results in moderate to good yields. Both *N*-aryl- and *N*-alkyl-substituted tetrahydroisoquinolines were effective for the reaction (Table 2, entries 1−6). Electron-poor aryl substitutents afforded better yields than electron-rich substrates. Interestingly, a regioselectivity at the C1 position for difluoromethylation of *N*-benzyl- and *N*-allyl-substituted tetrahydroisoquinolines **1g** and **1h** was observed (regioisomeric couplings of **2a** with benzyl α-methylene or methyl were not observed) (Table 2, entries 7 and 8). The regioselectivity might be due to the stability of the iminium ions intermediate. Importantly, *N*,*N*-dimethylaniline and *N*-benzyldimethylamine were also viable participants in the oxidative difluoromethylation reaction, but the yields of products were low (Tabel 2, entries 9 and 10).

Next, we turned our attention to the use of difluoroenol silyl ethers **4**,[5h] which are synthetic equivalents of α,α-difluoroacylsilanes and can be easily transformed to α,α-difluorocarbonyl compounds such as aldehydes, carboxylic acids, amides, and other derivatives.[12] To our disappointment,

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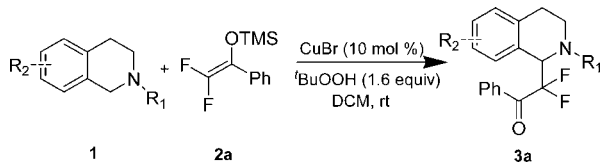
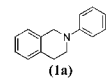
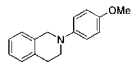
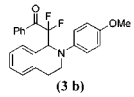
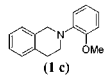
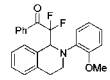
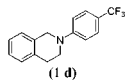
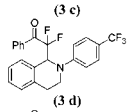
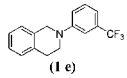
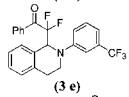
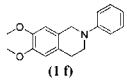
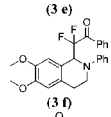
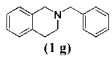
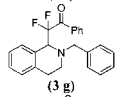
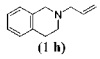
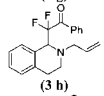
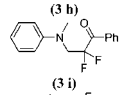
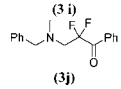
Table 2. CuBr-Catalyzed Difluoromethylation of Tertiary Amines with Difluoroenol Silyl Ether **2a**[a]

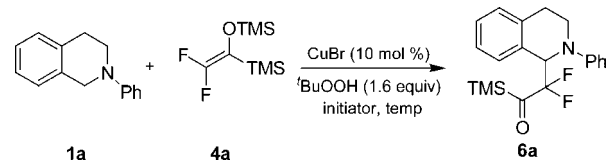


entry	amine	difluoroenol silyl ehter	product	yield (%) [b]
1	 (1a)	 (2a)	 (3 a)	85
2	 (1 b)	(2 a)	 (3 b)	78
3	 (1 c)	(2 a)	 (3 c)	69
4	 (1 d)	(2 a)	 (3 d)	80
5	 (1 e)	(2 a)	 (3 e)	88
6	 (1 f)	(2 a)	 (3 f)	67
7	 (1 g)	(2 a)	 (3 g)	40
8	 (1 h)	(2 a)	 (3 b)	69
9	 (1 i)	(2 a)	 (3 i)	38
10	 (1j)	(2 a)	 (3j)	13

[a] Reactions were performed using **1** (1.0 equiv), **2a** (3 equiv), TBHP (1.6 equiv), and CuBr (0.1 equiv) in CH_2Cl_2 (1 M) at rt. [b] Isolated yield after chromatography.

under the previous optimized conditions, the reaction led only to the recovery of **4a** (Table 3, entry 1). We reasoned that, comparing to difluoroenol silyl ether **2a**, difluorinated reagents **4a** is a weak electrophile and an initiator might be required to promote the reaction. Accordingly, a catalytic amount of KF was investigated; however, only a trace

Table 3. CuBr-Catalyzed Difluoromethylation of 1,2,3,4-Tetrahydroisoquinoline with Difluoroenol Silyl Ethers **4**[a]



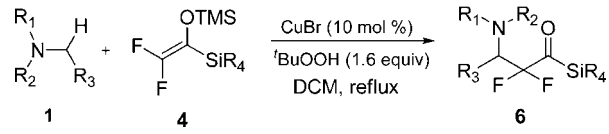
entry	initiator	temp (°C)	result (%)[b]
1	none	rt	no reaction
2	KF (cat.)	rt	trace
3	TBAF (cat.)	rt	25
4	TBAF (cat.)	reflux	89

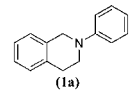
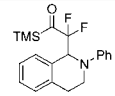
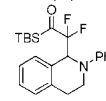
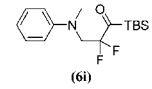
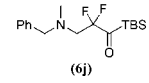
[a] Reactions were performed using **1a** (1.0 equiv), **4** (2.5 equiv), TBHP (1.6 equiv), and CuBr (0.1 equiv) in CH_2Cl_2 (1 M). [b] Yields were determined by ^{19}F NMR using benzotrifluoride as an internal standard.

amount of the desired product was observed (Table 3, entry 2). Because of the poor solubility of KF in CH_2Cl_2, an alternative fluoride ion source, tetra-*n*-butylammonium fluoride (TBAF), was tested. Gratifyingly, the yield was improved to 25% (determined by ^{19}F NMR) (Table 3, entry 3). An excellent yield (89% detected by ^{19}F NMR) was obtained when the reaction mixture was further heated to reflux (Table 3, entry 4).

Compound **4b** was also an effective substrate for this transformation (Table 4, entry 2), and *N*,*N*-dimethylaniline and *N*-benzyldimethylamine were also used as substrates

Table 4. CuBr-Catalyzed Difluoromethylation of Tertiary Amines with Difluoroenol Silyl Ethers **4**[a]



entry	amine	difluoroenol silyl ehter	product	yield (%) [b]
1	 (1a)	 (4a)	 (6a)	71
2	1a	 (4b)	 (6b)	80
3	 (1i)	4b	 (6i)	68
4	 (1j)	4b	 (6j)	26

[a] Reactions were performed using **1** (1.0 equiv), **4** (2.5 equiv), TBHP (1.6 equiv), and CuBr (0.1 equiv) in CH_2Cl_2 (1 M) under reflux. [b] Isolated yield after chromatography.

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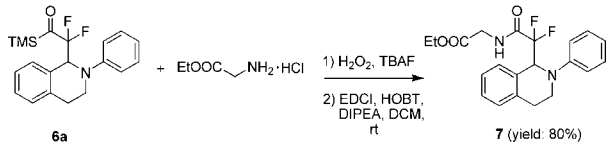
(Table 4, entries 3 and 4). It should be mentioned that the transformation of resulting α,α-difluoroacylsilanes **6a** to dipeptide **7** could be easily performed (Scheme 1).[5h] Since

Scheme 1. Transformation of **6a** to Compound **7**



tetrahydroisoquinolines and difluoromethylene-containing structures are important in pharmaceutical chemistry, this method would open a new way to design and discovery new peptides based on bioactive compounds.

In summary, an effective copper(I)-catalyzed oxidative difluoromethylation of tertiary amine with difluoroenol silyl ethers under mild conditions was developed. This new method provides a simple way to synthesize β-amine-α,α-difluoro ketones from readily available amines. The scope of the present reaction, as well as the application of the resulting difluoromethyleneated building blocks to design and synthesis of bioactive molecules, is under active investigation in our laboratory.

Acknowledgment. National Natural Science Foundation of China, and Shanghai Municipal Scientific Committee are greatly acknowledged for funding this work.

Supporting Information Available: Detailed experimental procedures and analytical data for all new compound. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900541N