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Efficient Difluoromethylation of sp^3 Carbon Nucleophiles by Bromodifluoromethylation Reagents with Organic Bases

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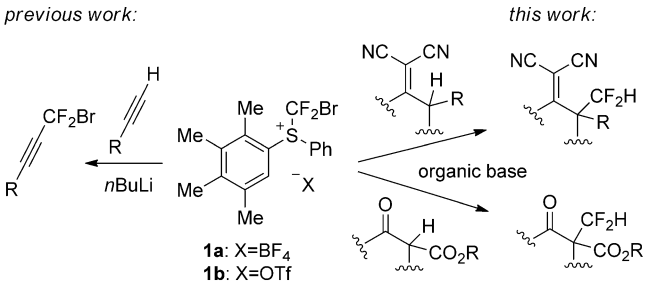
Introduction of a difluoromethyl (CF_2H) unit into organic molecules is of specific interest in medicinal chemistry and chemical biology, as compounds with a CF_2H moiety can act as an isostere to molecules having a methanol (CH_2OH) unit with improved lipophilicity.[1–6] Among several strategies for the synthesis of CF_2H compounds available, a late-stage difluoromethylation using easy-to-handle reagents under mild conditions is principally advantageous for the synthesis of complex molecules.[7,9f] Transferring a CF_2H group from a reagent to a target molecule is key for the reaction, and the reagents are classified according to their nucleophilic, radical, or electrophilic character.[8–10] Electrophilic difluoromethylation through difluorocarbene species has attracted considerable attention, and several methods have been reported.[8a–h,j,l] Although the difluoromethylation of heteroatom-centered nucleophiles such as oxygen, sulfur and nitrogen nucleophiles is well studied,[11,8g,j,l] mild and efficient difluoromethylation methods for carbon-centered nucleophiles are relatively scarce.[8i,k–m,12d] In 2007, Prakash and co-workers developed a new electrophilic difluoromethylating reagent, *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate.[8i] This reagent is effective for the introduction of a CF_2H group into a wide range of heteroatom-centered nucleophiles, but it failed to transfer to carbon nucleophiles. Besides, they point out the drawback of *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate being its slow decomposition over time even at low temperatures.[8m] Lately, Prakash group designed a novel electrophilic difluoromethylating protocol employing in situ prepared *N*,*N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium salt as a robust electrophilic difluoromethylating reagent.[8m] The reagent has exhibited good reactivity toward a broad scope of nucleophiles (N, P, S, and O nucleophiles), but no example was shown for carbon nucleophiles. *N*-Tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine, which was developed as a difluorocarbene precursor by Hu and co-workers in 2009, is effective for transferring a CF_2H group to both heteroatom and carbon nucleophiles.[8l] However, for carbon nucleophiles, only a limited number of phenylacetylene derivatives was examined as substrates for difluoromethylation. As part of our research program towards the enantioselective synthesis of biologically attractive fluoro-organic compounds,[12,13] we required electrophilic difluoromethylation reagents reactive enough for sp^3 carbon nucleophiles, which provide the CF_2H compounds with an asymmetric carbon center. In 2010, Xiao et al. for the first time reported symmetrical *S*-(bromodifluoromethyl)diphenylsulfonium salts.[8q] Recently, we reported the efficient synthesis of a series of unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts **1** which are effective for electrophilic bromodifluoromethylation ($^+CF_2Br$) of terminal alkynes in response to *n*BuLi.[8p] We disclose herein that the same regents **1** can be used as electrophilic difluoromethylation reagents for sp^3 carbon nucleophiles mediated by organic bases (Scheme 1). Allylic difluoromethylation of dicyanoalkylidenes proceeds nicely by **1** in the presence of a P_1 base to give CF_2H products with a quaternary carbon center in high to excellent yields. A wide range of β-ketoesters are also efficiently reacted with **1**, mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)to provide carbon–CF_2H compounds as major products with a small amount of oxygen–CF_2H products in high to excellent yields. In addition to the high yields of the carbon–CF_2H products, the use of reagents **1** having CF_2Br moieties as a CF_2H source is of further advantage, as the CF_2Br-reagents **1** are quite stable due to the lack of an acidic hydrogen atom.[8i,l,m]



Scheme 1. Transferring CF_2Br or CF_2H into carbon centers by **1**.

Initially, we attempted an electrophilic bromodifluoromethylation of dicyanoalkylidene **2a** with **1a** under similar reaction conditions as previously described for trifluoromethylation.[13a,c] Namely, **2a** was treated with **1a** in the presence of P_1 in acetonitrile at −43 °C for 1 h. Interestingly, CF_2H compound **3a** was predominantly obtained in 45%, instead of predictable CF_2Br compound **4a** (Table 1, Entry 1). This result spurred us to use **1a** as an electrophilic CF_2H-transfering reagent. We next investigated the effects of base for difluoromethylation of **2a**. Base P_2 gave a similar yield of 43% (Entry 2), but the yield decreased to 11% using DBU (Entry 3). No reaction took place with an inorganic base (i.e., K_2CO_3; Entry 4). Increasing the amount of **1a** to 1.5 equivalents did not improve the yield of **3a** (46%;

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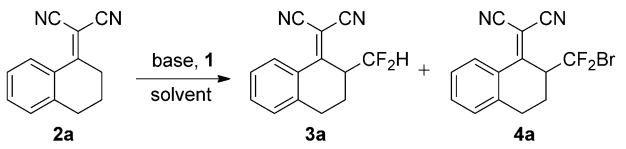
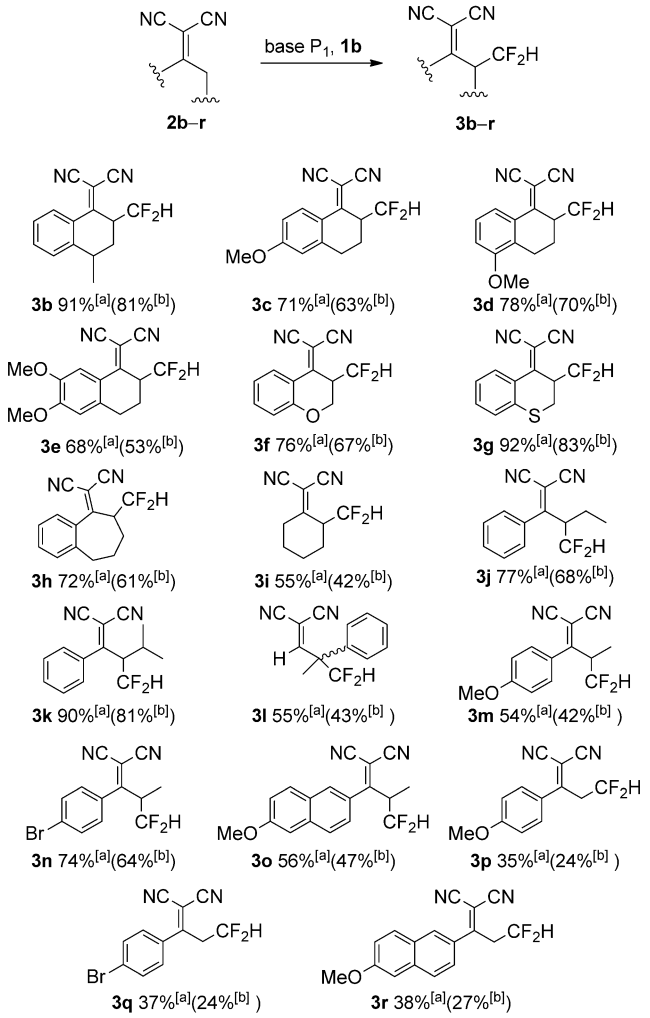
Table 1. Difluoromethylation of dicyanoalkylidene **2a**.[a]



Entry	1	Base[b]	2a/1/Base [equiv]	Solvent	T [°C]	Yield 3a/4a [%]
1	**1a**	P_1	1.0/1.1/2.0	CH_3CN	−42	45/<5
2	**1a**	P_2	1.0/1.1/2.0	CH_3CN	−42	44/<5
3	**1a**	DBU	1.0/1.1/2.0	CH_3CN	−42	11/0
4	**1a**	K_2CO_3	1.0/1.1/2.0	CH_3CN	−42	NR
5	**1a**	P_1	1.0/1.5/2.0	CH_3CN	−42	46/7
6	**1a**	P_1	2.0/1.0/2.0	CH_3CN	−42	67/10
7	**1b**	P_1	2.0/1.0/2.0	CH_3CN	−42	77/9
8	**1b**	P_1	2.0/1.0/2.0	CH_2Cl_2	−75	81/0
9	**1b**	P_1	2.0/1.0/1.2	CH_2Cl_2	−75	66/0

[a] The yields determined by ^{19}F NMR are based on substrate (Entries 1–5) or reagent (Entries 6–9). [b] P_1: *tert*-butyliminotri(pyrrolidino)phosphorane, P_2: tetramethyl(tris(dimethylamino)phosphoranylidene)phosphorictriamid-Et-imin, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 2. Difluoromethylation of dicyanoalkylidene **2b–r**. *Reagents and conditions*: **2b–r** (2.0 equiv), P_1 (2.0 equiv), **1b** (1.0 equiv), CH_2Cl_2, −75 °C. [a] Determined by ^{19}F NMR using trifluorotoluene as the internal standard. [b] Isolated yields.

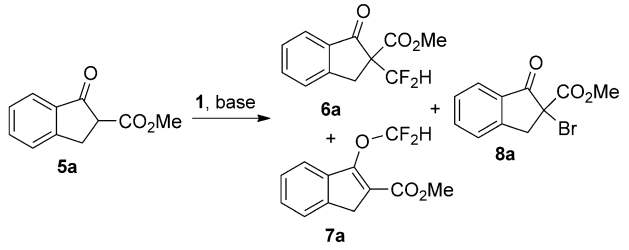
Entry 5). Because **2a** was completely consumed in most cases according to TLC analysis, we next carefully examined the ratio of **2a**, **1a** and P_1. A good yield of 67% was observed at a ratio of 2.0:1.0:2.0 of **2a**/**1a**/P_1 (the yield based on **1a**; Entry 6), and the yield of **3a** was further improved to 77% using triflate **1b** (Entry 7). When the reaction temperature was lowered to −75 °C in dichloromethane, **3a** was obtained in 81% (Entry 8). At a ratio of 2.0/1.0/1.2 of **2a**/**1b**/P_1, 66% of **3a** was obtained (Entry 9). It should be mentioned that no bromination product was isolated in all cases in contrast to the results for the difluoromethylation of β-ketoesters **5** (see below).

With the optimized reaction conditions in hand (**2**/**1b**/P_1 = 2.0:1.0:2.0), we screened a variety of substrates **2** (Scheme 2). All the benzodicyanoalkylidenes afforded the corresponding allylic CF_2H compounds **3b–e** in good to excellent yields, and the hetero-cyclodicyanoalkylidenes **2f** and **2g** were also transferred efficiently into **3f** and **3g** in 76% and 92%, respectively, and nonaromatic substrate **2i** gave allylic CF_2H compound **3i** in 55%. We next investigated the reaction of acyclic dicyanoalkylidenes **2j–r** with **1b**. The desired CF_2H compounds **3j–r** were obtained in moderate to excellent yields.

Difluoromethylation of β-ketoester **5a** with **1** was next evaluated (Table 2). Based on the results for difluoromethylation of **2** with **1**, we first examined the reaction under the conditions of **5a**/**1a**/P1 at a ratio of 2.0:1.0:1.0 in CH_2Cl_2 at −75 °C. A mixture of C–CF_2H product **6a** and O–CF_2H product **7a** was obtained in 51% (**6a**/**7a** = 65:35; Entry 1). Optimization of base was next performed (Entries 2–4) and DBU gave a good result of 70% (**6a**/**7a** = 69:31; Entry 3). Because approximately 20% of **1a** was not consumed according to ^{19}F NMR analysis, the conditions were changed to **5a**/**1a**/DBU at a ratio of 2.2:1.0:1.3, affording **6a** and **7a** in 81% yield (**6a**/**7a** = 65:35; Entry 5). The result was further improved using **1b** instead of **1a** under the same conditions, as a combined yield of 85% was achieved with higher C/O regioselectivity (**6a**/**7a** = 80:20; Entry 6). We also noticed that 82% of α-brominated product **8a** was produced (Entry 6). It is should be mentioned that difluoromethylation of **5a** with *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine developed by Hu gave a mixture of **6a** and **7a** at low yields of 38% with lower C/O regioselectivity (**6a**/**7a** = 63:37; data not shown).[12d] The CF_2H analogue of **1a**, Prackash reagent, also gave a mixture of **6a** and **7a** in good 80% yield but with lower C/O regioselectivity (**6a**/**7a** = 66:34; Entry 7).[8i]

To explore the scope of difluoromethylating β-ketoester **5** with **1b** under optimum reaction conditions, we carried out experiments with a variety of substrates **5**, including indanone carboxylates, tetralone carboxylates, and other β-ketoesters (Table 3). Methyl indanone carboxylates **5b–f** with a variety of substituents in the aromatic ring proceeded well at providing their corresponding CF_2H compounds **6b–f** and **7b–f** in good to excellent yields with high C/O regioselectivity (70:30 to 84:16; Entries 1–5). Substrates with an electron-withdrawing group in the aromatic ring gave higher yields than those with-

Table 2. Difluoromethylation of β-ketoester **5a**.[a]

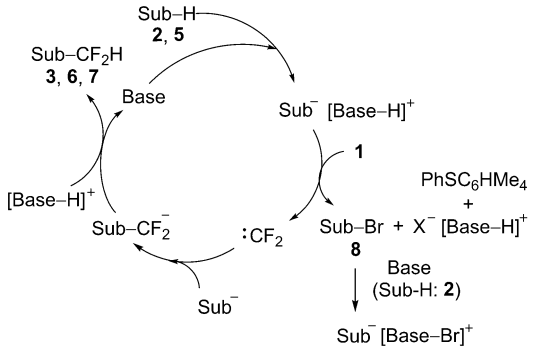


Entry	1	Base[b]	5a/Base [equiv]	Yield 6a and 7a [%][c]	Ratio 6a/7a	Yield 8a [%][d]
1	**1a**	P_1	2.0/1.0	51	65/35	–
2	**1a**	P_2	2.0/1.0	47	72/28	–
3	**1a**	DBU	2.0/1.0	70	69/31	–
4	**1a**	Cs_2CO_3	2.0/1.0	NR	–	NR
5	**1a**	DBU	2.2/1.3	81	65/35	–
6	**1b**	DBU	2.2/1.3	85	80/20	82
7	**1c**[e]	DBU	2.2/1.3	80	66/34	–

[a] *Reagents and conditions*: **5a**, **1a**–c (1.0 equiv), base, CH_2Cl_2, −75 °C. [b] P_1: *tert*-butyliminotri(pyrrolidino)phosphorane, P_2: tetramethyl-(tris(dimethylamino)phosphoranylidene)phosphorictria-mid-Et-imin, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [c] Yields were determined using ^{19}F NMR based on **1**. [d] Isolated yield. [e] **1c**: Prakash reagent[8i] (CF_2H analogue of **1a**) was used under the same reaction conditions for comparison.

out substituents or those with an electron-donating group in the aromatic ring (Entries 4 and 5). Ethyl, benzyl, *tert*-butyl, *iso*-propyl and allyl indanone carboxylates **5g–l** also proceed smoothly in good to excellent yields of CF_2H products **6g–l** and **7g–l** (Entries 6–11). Although tetralone carboxylates **5m** and **5n** were less reactive with **1b** to provide corresponding CF_2H products **6m**/**7m** and **6n**/**7n** in moderate yields (49% and 47%, respectively; Entries 12 and 13), high C/O regioselectivities were achieved (88:12 and 87:13, respectively; Entries 12 and 13). Benzyl 2-oxocyclopentanecarboxylate **5o** gave **6o** and **7o** in 63% at a 79:21 ratio (Entry 14). Acyclic β-ketoester **5p** also proceeded well to provide corresponding CF_2H compounds **6p** and **7p** (Entry 15). It was noteworthy that brominated compounds **8** were isolated with excellent yields in all cases except for **8o** and **8p**.

Based on the experimental results, we propose a plausible mechanism for difluoromethylation with **1** taking into account information from the literature[8l,m] (Scheme 3). Initially, substrate Sub–H (**2**, **5**) was treated with a base (P_1 or DBU) to provide $Sub^-[Base–H]^+$. Generated Sub^- attracts the bromine atom in **1** to give brominated product Sub–Br (**8**) and difluorocarbene ($:CF_2$) with $PhSC_6HMe_4$ and $X^-[Base–H]^+$. Difluorocarbene ($:CF_2$) reacts with additional Sub to give difluoromethylated products **3, 6** and **7** with base. In the case of difluoromethylation of dicyanoalkylidenes **2**, no bromination product such as **8** was detected and two equivalents of base were required. These facts can be explained, as bromination products of **2** (Sub–Br) are further reacted with base to give salts $Sub^-[Base–Br]^+$.



Scheme 3. Proposed reaction mechanism.

In conclusion, we have developed a new protocol for electrophilic difluoromethylation of sp^3 carbon nucleophiles by shelf-stable CF_2Br reagent **1** through the in situ generation of difluorocarbene induced by an organic base. A wide range of dicyanoalkylidenes **2** and β-ketoesters **5** proceed efficiently to give corresponding C–CF_2H products **3** and **6** in good to excellent yields under mild conditions. Enantioselective difluoromethylation of sp^3 carbon nucleophiles by **1** is under investigation.

Experimental Section

General procedure for electrophilic difluoromethylation of dicyanoalkylidenes: To a stirred solution of dicyanoalkylidenes (0.20 mmol) in dry CH_2Cl_2 (2 mL), a corresponding base (0.20 mmol) was added at −20 °C under an inert atmosphere. After stirring for 20 min at −20 °C, the resulting reaction mixture was further cooled to −75 °C, and reagent **1** (0.10 mmol) was added to the reaction mixture in one portion at the same temperature. The resulting mixture was maintained for 1 h at −75 °C, then warmed to RT naturally. The reaction mixture was concentrated in vacuo, and the residue was subject to column chromatography on silica gel to afford the pure products.

General procedure for electrophilic difluoromethylation of β-ketoesters: To a stirred solution of β-ketoesters (0.22 mmol) in dry CH_2Cl_2 (2 mL), a corresponding base (0.13 mmol) was added at −75 °C under an inert atmosphere. After stirring for 30 min at −75 °C, reagent **1** (0.10 mmol) was added to the reaction mixture in one portion at the same temperature. The resulting mixture was maintained for 1 h at −75 °C, then warmed to RT naturally. The reaction mixture was concentrated in vacuo and the residue was subject to column chromatography on silica gel to afford the pure products.

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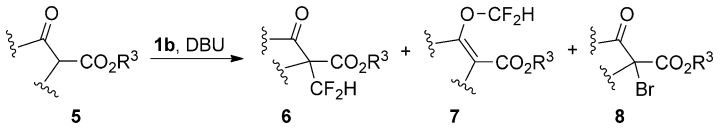
Table 3. Difluoromethylation of β-ketoester **5b–p**.[a]



5 **6** **7** **8**

Entry	β-Ketoester **5**					Yield **6** and **7** [%][b]	Ratio **6**/**7**[c]	Yield **8** [%][d]
		R^1	R^2	R^3	*n*			
1	**5b**	Me	H	Me	1	88 (75)	75:25	95
2	**5c**	OMe	H	Me	1	89 (78)	75:25	90
3	**5d**	OMe	OMe	Me	1	89 (80)	84:16	91
4[e]	**5e**	H	Br	Me	1	quant. (91)	71:29	92
5[e]	**5f**	H	Cl	Me	1	quant. (88)	70:30	92
6	**5g**	H	H	Bn	1	84 (76)	72:28	93
7	**5h**	H	H	Et	1	84 (76)	75:25	92
8	**5i**	H	H	*t*Bu	1	80 (74)	77:23	96
9	**5j**	H	H	Allyl	1	82 (75)	73:27	95
10[e]	**5k**	H	H	*i*Pr	1	74 (60)	77:23	84
11[e]	**5l**	H	Br	Bn	1	89 (73)	71:29	90
12[f]	**5m**	H	H	Me	2	49 (32)	88:12	74
13[e,f]	**5n**	H	H	Bn	2	47 (27)	87:13	72
14[g]	**5o**	–	–	–	–	63 (47)	79:21	–
15[g,h]	**5p**	–	–	–	–	56 (41)	74:26	-

[a] *Reagents and conditions*: **5b–p** (2.0–2.2 equiv), **1b** (1.0 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 1.0–1.3 equiv), CH_2Cl_2, −75 °C. For detailed reaction conditions, see the Supporting Information. [b] Yields were determined by ^{19}F NMR using trifluorotoluene as the internal standard, and the data in parentheses are isolated yields. [c] Determined using ^{19}F NMR. [d] Isolated yields. [e] Substrate/DBU/CF_2Br = 2.0:1.0:1.0. [f] **7** were not separated because of their low yields. [g] **8** could not be obtained as a pure product. [h] P_1 was used instead of DBU.

Keywords: difluorocabenes · difluoromethylation · electrophilicity · fluorine · regioselectivity

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