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REGIO- AND STEREOSELECTIVE SYNTHESIS OF *gem*-DIFLUOROCYCLOPROPANES USING 4-BROMO-4,4-DIFLUOROCROTONATE

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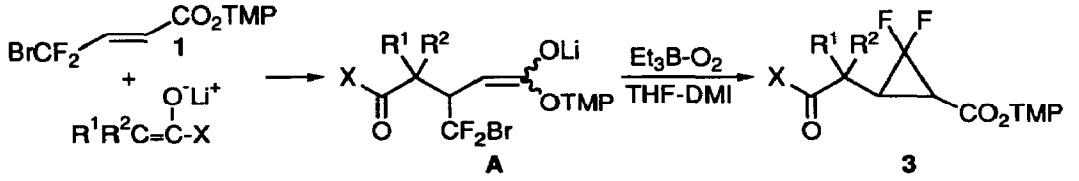
Abstract: *Regio- and stereoselective formation of the functionalized gem-difluorocyclopropane derivative was achieved through the Michael addition of lithium enolate of ester or amide with 4-bromo-4,4-difluorocrotonate I followed by the triethylborane-O_2 mediated intramolecular substitution reaction.*

Cyclopropane derivatives have been recognized as an important class of compounds found in natural and unnatural substances, with particularly significant application in bio- and medicinal chemistry.[1,2] For example, conformationally restricted analogs of glutamic acid having the cyclopropane moiety were studied so as to elucidate the conformations (extended and folded forms) necessary for the receptor subtype specificity,[3] and substrates having the cyclopropane moiety were found to be mechanism dependent inhibitors of certain enzymes.[1a,4] For such chemically modified biologically active compounds, the introduction of fluorine atom(s) onto cyclopropane ring would lead to interesting results in consideration of characteristic features of fluorinated compounds.[5,6] It should thus be needed to develop an efficient method for the preparation of suitably functionalized fluorinated cyclopropanes in a stereoselective manner. In this paper, we report a regio- and stereoselective synthesis of functionalized *gem*-difluorocyclopropane **3** through the sequential Michael addition of lithium enolate of ester or amide with 2,4,6-trimethyphenyl (TMP) ester of 4-bromo-4,4-difluorocrotonate **1**[7,8] and the triethylborane mediated intramolecular substitution reaction (Scheme 1).[9]



Scheme 1

At first, we examined the reaction conditions for the cyclopropanation reaction of **1** with *t*-butyl acetate **2a**. Results are shown in Table 1. Reaction of **1** with lithium enolate of **2a** proceeded at low temperature within a short period to give the Michael addition product **4a**, but the formation of the difluorocyclopropane **3a** was not observed (entry 1). Elongation of reaction period or addition of a polar solvent such as DMI (1,3-dimethyl-2-imidazolidinone) produced a complex mixture (entry 2). These results indicate that activation of the CF_2-Br bond would thus appear essential following the Michael addition of the enolate to **1**. After several attempts, we found that triethylborane(Et_3B)-O_2 and a polar solvent such as DMI were effective additives for this reaction. Thus, after treating **1** with lithium enolate of **2a** in THF at -78°C for 15 min, Et_3B (3 equiv.), O_2 (5 ml bubbled via syringe) and DMI were added and the reaction mixture was stirred at -20°C for 3 h to give the cyclopropane **3a** in 71% yield along with a small amount of the Michael addition product **4a** (entry 5). **3a** was obtained as a single compound and its *trans* stereochemistry was confirmed from the NMR spectrum ($J_{2\text{-}3}$=7.3 Hz)[10] and the regioselectivity in the reaction was assessed by functional selective conversion of *t*-butyl ester group to the alcohol.[11]

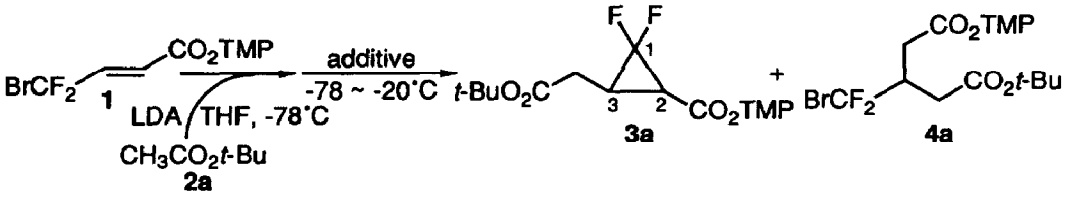


Table 1. Reaction of **1** with *t*-Butyl Acetate **2a**[a]

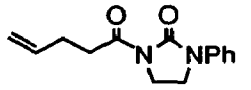
entry	Et_3B (eq)	DMI[b]	yield of **3a** (%)	yield of **4a** (%)
1	none	none	0	70
2	none	10 vol%	0	—[c]
3	0.5	none	26	32
4	3.0	none	17	47
5	3.0	10 vol%	71	7

[a] Reaction was carried out for 15min at -78°C without the additive(s), then for 3h at ca -20°C after addition of additive(s). [b] DMI=1,3-Dimethyl-2-imidazolidinone. [c] Complex mixture. **4a** was detected by TLC and ^{19}F-NMR spectrum of the reaction mixture.

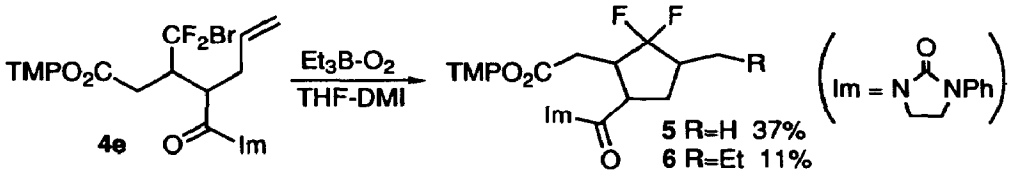
In a similar manner, ester and amide enolates reacted with **1** in the presence of Et_3B-O_2 to give the corresponding difluorocyclopropane **3** (Table 2). A complete regio- and stereoselectivity in the formation of the cyclopropane d_2-**3b** was observed for the deuterated acetate d_3-**2b** (entry 2). With the TMP ester of α,α-disubstituted carboxylic acid **2c**, the *trans*-cyclopropanes **3c** was obtained in a good yield (entry 3).

It has been reported that trialkylborane reacts with oxygen to generate an alkyl radical at low temperature and Et_3B-O_2 system is an effective radical initiator for tinhydride or alkyl iodide and bromide.[12,13] In the present cyclopropane formation, Et_3B-O_2 may possibly initiate the radical cleavage of CF_2-Br bond of the intermediate Michael adduct (**A** in Scheme 1). To examine the cleavage of CF_2-Br bond by Et_3B-O_2 system, a control experiment was conducted by using the Michael adduct **4e**, which possesses a double bond as a radical acceptor. Thus, by treating the Michael adduct **4e** with Et_3B-O_2 in THF-DMI at -20°C for 3 h, the 5-exo

Table 2. Et_3B-O_2 Mediated Cyclopropanation Reaction[a]

entry	2	3 (yield, %)[b]	4[c] (yield, %)[b]
1	CH_3CO_2TMP **2b**	**3b** (47)	**4b** (18)
2	CD_3CO_2TMP **d_3-2b**	**d_2-3b** (48)	**d_2-4b** (17)
3	$(CH_3)_2CHCO_2TMP$ **2c**	**3c** (73)	**4c** (8)
4	$CH_3CON(CH_3)_2$ **2d**	**3d** (51)	**4d** (23)
5	 **2e**	**3e** (75)	**4e** (3)[d]

[a] Reaction conditions; THF, -78°C, 15 min for Michael addition, then Et_3B, O_2 and DMI, ca -20°C, 3h. [b] Isolated yield. [c] Michael addition product. [d] The cyclopentane derivative **5** (see Scheme 2) was also isolated in 2.5% yield.



Scheme 2

cyclized products **5** and **6** were obtained in 37% and 11% yield, respectively, along with the recovery of **4e** in 35% (Scheme 2). Under the sequential Michael addition and cyclopropanation conditions, the *N*-(4-pentenoyl)imidazolidinone **2e** afforded the cyclopropane **3e** in 75% yield along with the 5-exo cyclized product **5** (2.5%) and the Michael adduct **4e** (3.4%), respectively (Table 2, entry 5). These results may suggest that the formation of the cyclopropane **3e** from the intermediate **A** is much faster than the 5-exo cyclization reaction. Investigation of the mechanistic aspects of the present reaction in detail is a future subject.

In conclusion, we have shown that bromodifluorocrotonate **1** is an efficient building block[14] for the preparation of functionalized difluorocyclopropanes through the activation of CF_2-Br bond by Et_3B-O_2 in an intramolecular substitution reaction with lithium enolate.

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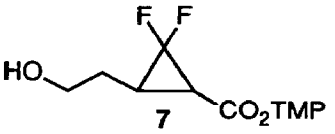
11. Treatment of **3a** with CF_3COOH followed by reduction of carboxylic acid with BH_3-THF gave the alcohol **7** in 82 % yield.



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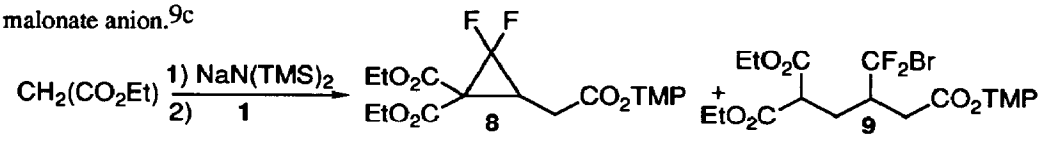
14. Bromodifluorocrotonate **1** showed a high reactivity as a Michael acceptor with active methylene compounds. Reaction of **1** with malonate anion provided the Michael adduct **9** and/or the cyclopropane **8** depending on the reaction conditions: (a) **9**, 71% (THF, rt); (b) **8**, 64% (THF, reflux, 2 h); (c) **8**, 66% (THF-DMI, rt, 24 h). In the case of 4-bromocrotonate, only direct S_N2 displacement occurred with malonate anion.[9c]



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