ORGANIC LETTERS

2013
Vol. 15, No. 21
5598–5601

A Straightforward and Highly Diastereoselective Access to Functionalized Monofluorinated Cyclopropanes *via* a Michael Initiated Ring Closure Reaction

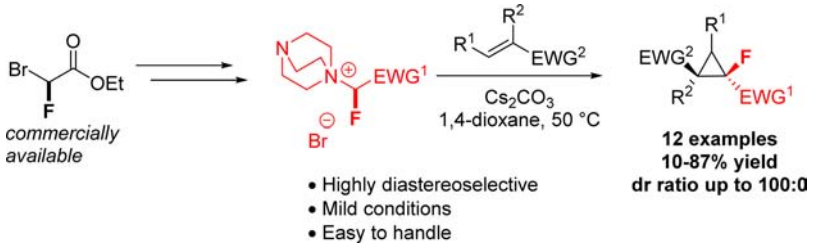
Thibault Ferrary, Emilie David, Gaëlle Milanole, Tatiana Besset, Philippe Jubault,* and Xavier Pannecoucke

Normandie Université, COBRA, UMR 6014 et FR 3038; Université de Rouen; INSA Rouen; CNRS, 1 rue Tesnière, 76821 Mont Saint-Aignan Cedex, France

philippe.jubault@insa-rouen.fr

Received October 2, 2013

ABSTRACT



The synthesis of highly functionalized monofluorinated cyclopropanes based on a Michael Initiated Ring Closure (MIRC) reaction has been developed. The addition of quaternary ammonium salts derived from ethyl bromofluoroacetate on a panel of electron deficient alkenes followed by cyclization gave rise to an efficient access to monofluorinated cyclopropanes with good yields and remarkable diastereoselectivity.

Fluorinated cyclopropanes are key building blocks in biological molecules as well as pharmaceuticals. Therefore, they have tremendous importance in both industry and academic research. Fluorine-containing cyclopropanes appear to be pivotal scaffolds due to their incomparable properties. Indeed, on one hand, the cyclopropane core enables one to bring constraint to molecules.[1] On the other hand, the presence of a fluorine atom[2] often modifies chemical, physical, and biological properties of molecules such as an increase of metabolic stability and lipophilicity.

More particularly, cyclopropanes containing a quaternary fluorinated center bearing a functional group in the *gem* position (e.g., a carboxy moiety) and at least one substituent in the α position are relevant scaffolds in several biologically active compounds[3] and their synthesis is still of high interest (Figure 1). Because of their significant importance, the design of innovative synthetic pathways to construct straightforward, highly valuable fluorinated cyclopropanes has attracted growing interest.[4]

(1) (a) Chen, D.Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041. (c) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051. (d) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (e) Faust, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251. (f) Salaun, J. *Top. Curr. Chem.* **2000**, *207*, 1.

(2) (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Ma, J. A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1.

(3) (a) Pessah, N.; Bialer, M.; Wlodarczyk, B.; Finnell, R. H.; Yagen, B. *J. Med. Chem.* **2009**, *52*, 2233. (b) Chaki, S.; Yoshikawa, R.; Hirota, S.; Shimazaki, T.; Maeda, M.; Kawashima, N.; Yoshimizu, T.; Yasuhara, A.; Sakagami, K.; Okuyama, S.; Nakanishi, S.; Nakazato, A. *Neuropharmacology* **2004**, *46*, 457. (c) Lemonnier, G.; Lion, C.; Quirion, J.-C.; Pin, J.-P.; Goudet, C.; Jubault, P. *Bioorg. Med. Chem.* **2012**, *20*, 4716.

(4) For selected examples, see: (a) Wang, H.; Guptill, D. M.; Varela Alvarez, A.; Musaev, D. G.; Davies, H. M. L. *Chem. Sci.* **2013**, *4*, 2844. (b) Beaulieu, L.-P. B.; Schneider, J. F.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 7819. (c) Oshiro, K.; Morimoto, Y.; Amii, H. *Synthesis* **2010**, 2080. (d) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099. (e) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803. (f) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (g) Hirotaki, K.; Takehiro, Y.; Kamaishi, R.; Yamada, Y.; Hanamoto, T. *Chem. Commun.* **2013**, *49*, 7965. (h) Zheng, J.; Lin, J.-H.; Cai, J.; Xiao, J.-C. *Chem.—Eur. J.* **2013**, DOI: 10.1002/chem.201303248.

10.1021/ol402837u
Published on Web 10/18/2013

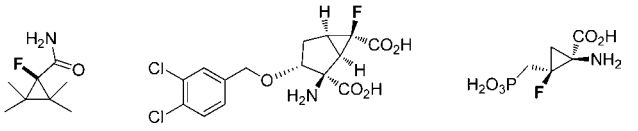
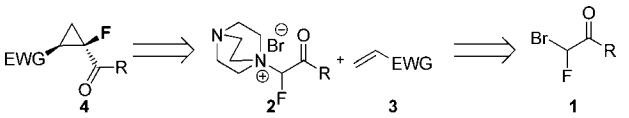


Figure 1. Structure of biologically active molecules containing a functionalized fluorinated cyclopropane.

However, a limited number of methods gave rise to highly functionalized monofluorinated cyclopropanes.[5] Among them, one strategy based on a Michael Initiated Ring Closure (MIRC) reaction has emerged as a powerful and streamlined method.[6] As proof of concept of this approach on nonfluorinated cyclopropanes, the group of Gaunt nicely reported the tertiary amine-catalyzed functionalized cyclopropanes synthesis *via* the nucleophilic addition of ammonium ylides to electron poor alkenes with remarkable stereoselectivity.[7] This example showcases the potential of such a strategy in cyclopropanes synthesis. In 2012, Hu et al. described the fluoromethylenation of α,β-unsaturated Weinreb amides.[8] This method turned out to be a highly enantio- and diastereoselective reaction, leading to fluorinated cyclopropanes bearing essentially (het)aryl and alkyl substituents. In this context, our group has previously developed the Zn/LiCl catalyzed synthesis of monofluorinated cyclopropanes using ethyl dibromofluoroacetate as fluorine source.[3c,9] This approach turned out to be efficient with moderate to good diastereoselectivity toward the *trans* isomer and was then extended to the asymmetric synthesis of enantiomerically pure cyclopropanes *via* a two-step procedure. Nevertheless, the construction of highly functionalized monofluorinated cyclopropanes still remains a great challenge. Herein we report the diastereoselective synthesis of functionalized monofluorinated cyclopropanes from quaternary ammonium salts *via* a MIRC reaction.

Indeed, to pursue our investigations in this field, we thought that the quaternary ammonium salts **2**, obtained after nucleophilic substitution of a tertiary amine on bromofluoroamide derivatives **1**,[10] may act as a good leaving group in a MIRC reaction on electron poor alkenes **3** (Scheme 1), the bromofluoroamide derivatives

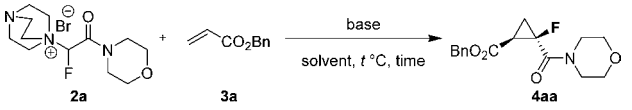
Scheme 1. Retrosynthetic Pathway



1 being easily prepared from the commercially available ethyl bromofluoroacetate.

Our study began with the evaluation of ammonium salt **2a**[11] in the cyclopropane synthesis. The treatment of **2a** with Cs_2CO_3 in the presence of benzyl acrylate **3a** as a coupling partner led to the corresponding cyclopropane **4aa** containing the expected quaternary fluorinated center (Table 1).[10]

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	base	time (h)	yield (%)[b]	dr[c] (*cis*:*trans*)
1	DMF	Cs_2CO_3	14	37	82:18
2	$ClCH_2CH_2Cl$	Cs_2CO_3	14	27	71:29
3	CH_2Cl_2	Cs_2CO_3	14	57	71:29
4	THF	Cs_2CO_3	14	35	83:17
5	CH_3CN	Cs_2CO_3	14	65	73:27
6	1,4-dioxane	Cs_2CO_3	14	40[d]	82:18
7[e]	1,4-dioxane	Cs_2CO_3	14	66	86:14
8	1,4-dioxane	Cs_2CO_3	24	69[f]	81:19
9[g]	**1,4-dioxane**	**Cs_2CO_3**	**24**	**83**	**86:14**
10[g]	1,4-dioxane	CsOAc	24	0	0
11[g]	1,4-dioxane	K_2CO_3	24	0	0
12[g]	1,4-dioxane	DBU	24	0	0
13[h]	1,4-dioxane	Cs_2CO_3	24	65	82:18

[a] Ammonium salt **2a** (0.15 mmol), benzyl acrylate **3a** (1.2 equiv), base (2 equiv), [**2a**] = 0.05 mol·L^{-1} in solvent, 50 °C (oil bath temperature), time. [b] Determined by ^{19}F NMR of the crude reaction mixture using 1-fluoro-2,4-dinitrobenzene as the internal standard. [c] Ratio based on ^{19}F NMR of the crude mixture. [d] 42% of remaining **2a** in the crude. [e] The reaction was carried out at 80 °C. [f] 27% of remaining **2a** in the crude. [g] With 5 equiv of base. [h] With 3 equiv of **3a**. DBU = 1,8-Diazabicyclo-[5.4.0]undec-7-ene.

When the reaction was performed in DMF, the MIRC reaction proceeded smoothly and **4aa** was obtained in 37% yield with a promising diastereoisomeric ratio (*cis*:*trans*) of 82:18. To optimize the efficiency of the process, several solvents were tested (Table 1, entries 1−6). Although acetonitrile gave us very encouraging results (65%, *cis*:*trans* = 73:27, entry 5), we decided to pursue the optimization with

(5) (a) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem.—Eur. J.* **2012**, *18*, 14904 and references therein. (b) Saito, A.; Ito, H.; Taguchi, T. *Tetrahedron* **2001**, *57*, 7487.

(6) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937 and references therein.

(7) (a) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 828. (b) Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *116*, 4741.

(8) Shen, X.; Zhang, W.; Zhang, L.; Luo, T.; Wan, X.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6966.

(9) (a) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 5130. (b) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270. (c) Milanole, G.; Couve-Bonnaire, S.; Bonfanti, J.-F.; Jubault, P.; Pannecoucke, X. *J. Org. Chem.* **2013**, *78*, 212.

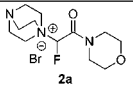
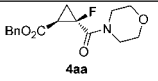
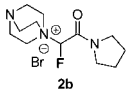
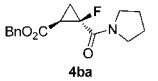
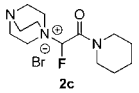
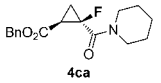
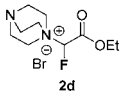
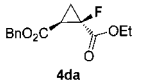
(10) For more details, see Supporting Information.

(11) The ammonium salts **2** were readily prepared in a one step procedure from their corresponding brominated amide precursors **1**; see Supporting Information. Note that when **1a** (precursor of **2a**) was directly engaged in the reaction conditions, only degradation was observed. This control experiment clearly indicated that the ammonium group was crucial for this transformation.

1,4-dioxane (40%, *cis*:*trans* = 82:18, entry 6), since 42% of residual starting material was observed in ^{19}F NMR of the crude reaction and the expected product was obtained with higher diastereoselectivity. The increased reaction temperature did not have a beneficial impact on the transformation. Indeed, even though the yield was slightly improved (66%), more degradation was observed (entry 7). This observation suggested that the right balance between reactivity toward cyclopropane synthesis and side reaction pathways was already obtained at 50 °C. More importantly we found that the reaction time (entry 8) and the relative amount of base (entry 9) were crucial for the efficiency and the diastereoselectivity of the reaction. Our best result (83%, *cis*:*trans* ratio of 86:14, entry 9) was obtained after 24 h of reaction in the presence of 5 equiv of base. Surprisingly, the replacement of Cs_2CO_3 by other bases (entries 10−12) led to complete failure of the reaction, and the use of an excess of **3a** (entry 13) did not bring any improvement.

Encouraged by these results, we investigated the effect of the EWG group on the quaternary ammonium salt **2** on reactivity and selectivity. Good diastereoselectivity was observed for different amide salts (Table 2, entries 1−3), although yields remained rather poor; **2a** was the most efficient substrate concerning both reactivity and selectivity (entry 1, 80% isolated yield, dr = 86:14). In contrast, the salt **2d** derived from the commercially available ethyl bromofluoroacetate turned out to be poorly efficient (entry 4, 31%, dr = 49:51). The low yield was probably due to a competing hydrolysis reaction that had to be circumvented to provide a chemoselective outcome of the reaction.

Table 2. Screening of Ammonium Salts **2**[a]

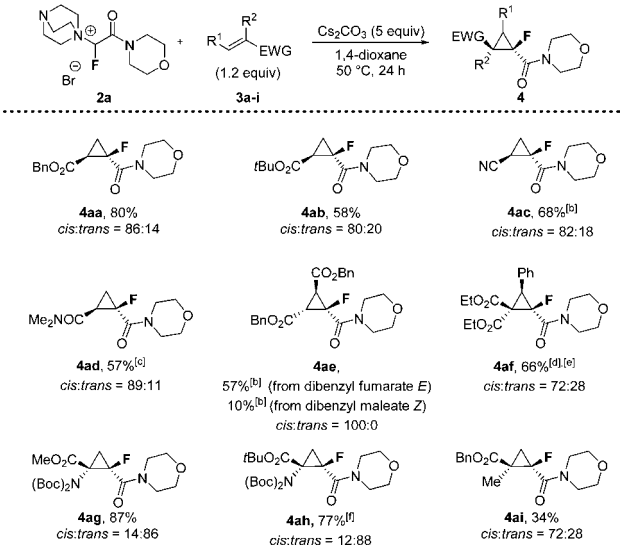
entry	ammonium salt **2**	product **4**	yield (%)[b]	dr[c] (*cis*:*trans*)
1	 **2a**	 **4aa**	80	86:14
2	 **2b**	 **4ba**	44	82:18
3[d]	 **2c**	 **4ca**	30	83:17
4[e]	 **2d**	 **4da**	31	49:51

[a] Ammonium salt **2** (0.6 mmol), benzyl acrylate **3a** (1.2 equiv), Cs_2CO_3 (5 equiv), [**2**] = 0.05 mol·L^{-1} in 1,4-dioxane, 50 °C, 24 h. [b] Isolated yields of both diastereoisomers. [c] Ratio based on ^{19}F NMR of the crude mixture. [d] **4ca** and its isomer were isolated as a mixture with an inseparable impurity (13%). [e] **4da** and its isomer were isolated with traces of an inseparable impurity (4%).

(12) It should be noted that vinylsulfone, 1-dimethoxyphosphorylethene, or 1,2-disubstituted electron-poor olefins such as cinnamaldehyde and chalcone gave only trace amounts of product under standard conditions (see Supporting Information) probably because they mainly underwent side reactions.

The scope of the reaction was then examined, and the desired products were generally isolated with moderate to good yields and high diastereoselectivities. Moreover, the transformation demonstrated large functional group tolerance (Scheme 2).[12] The reaction worked well with a range of terminal alkenes, and fluorinated cyclopropanes bearing a panel of functional groups such as esters (**4aa**, **4ab**), nitrile (**4ac**), and even amide (**4ad**) could be obtained with high selectivity for the *cis* isomer. When using either the dibenzyl fumarate or the dibenzyl maleate, an identical stereochemical outcome was obtained for both isomers. In addition, different 1,1′-disubstituted alkenes turned out to be efficient coupling partners, leading to the major *trans* isomer cyclopropanes (**4ag**, **4ah**, and **4ai**). This inversion of diastereoselectivity has been already observed in our previous studies.[9a,b,13]

Scheme 2. Scope of the Cyclopropanation Reaction[a]



[a] Ammonium salt **2a** (0.59 mmol), **3** (1.2 equiv), Cs_2CO_3 (5 equiv), 1,4-dioxane (11.8 mL), 50 °C, 24 h. Isolated yields of both diastereoisomers. *cis*:*trans* ratio determined on ^{19}F NMR of the crude mixture. The major isomer is depicted. [b] 5 equiv of Michael acceptor **3**. [c] 4 days; **4ad** and its isomer were isolated as a mixture with an inseparable impurity (10%). [d] 3 equiv of Michael acceptor **3g**. [e] 48 h. [f] 30 h.

To confirm the stereoselectivity observed in this case, the major isomer *trans*-**4ag** was crystallized and its structure was confirmed by a single-crystal X-ray analysis (Figure 2). Importantly, trisubstituted olefin (**3f**) could also be employed, showing that the cyclopropanation reaction was not limited to terminal or 1,1-disubstituted alkenes, and the desired product **4af** was isolated in good yield (66%). Noteworthy, the use of electron deficient alkenes is required for this transformation. When styrene derivatives (styrene and *trans*-3-nitrostyrene) were engaged, no cyclopropanation occurred probably due to the lower activity of the

(13) In previous studies (cf. ref 9a, 9b), *trans*-cyclopropanes were mostly obtained with terminal olefins, and an inversion of diastereoselectivity was also observed in the case of 1,1′-disubstituted alkenes leading to the major *cis* isomer.

coupling partners and their instability under the reaction conditions. To highlight the synthetic value of this strategy, the standard reaction was run on 6 mmol scale, and the product **4aa** was obtained in 57% yield (dr = 83:17).

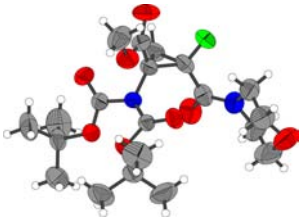
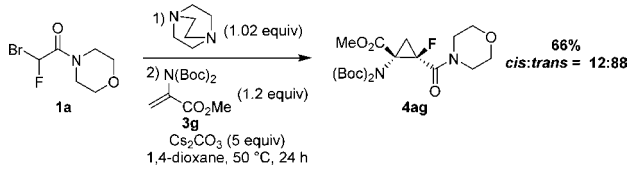


Figure 2. X-ray structure of *trans*-**4ag**.

Furthermore, the practicality of this method was demonstrated by the development of a "one-pot" procedure. When **1a**, DABCO, and **3g** were reacted consecutively, the desired product **4ag** was obtained with a slightly lower yield and similar diastereoselectivity (*cis*:*trans* ratio of 12:88, Scheme 3).[14]

Scheme 3. Stoichiometric "One-Pot" Procedure

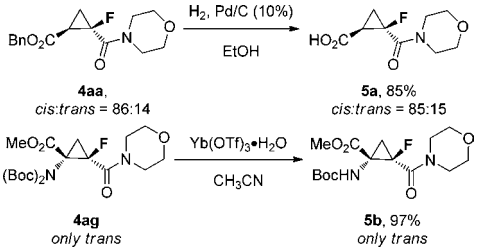


To illustrate the potential of this method further, we succeeded in modifying the functional groups of **4aa** and **4ag** selectively while retaining a high diastereoisomeric ratio (Scheme 4). Indeed, in the case of **4aa**, the ester group can be converted into its corresponding carboxylic acid in high yield (85%). In addition, monodeprotection[9c] of **4ag** tertiary amine with $Yb(OTf)_3$ was possible with total selectivity for all these transformations.

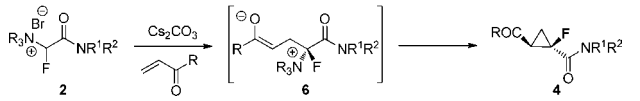
Concerning the mechanism of this transformation, the synthesis of **4ae** might support a stepwise pathway. Therefore, following the mechanistic scenario proposed for nonfluorinated coupling partners,[7] a two-step mechanism of this transformation may be suggested as outlined in Scheme 5: (1) nucleophilic addition of the anionic species (enolate or ylide) generated from **2a** on a Michael acceptor under basic conditions, followed by (2) a nucleophilic cyclization of the enolate **6** affording the corresponding cyclopropane **4**. Theoretical studies are currently ongoing to gain insight into the mechanism of this transformation.

(14) It is important to notice that no complete conversion of the starting material occurred, and a mixture of **1a**/*cis*-**4ag**/*trans*-**4ag** was obtained in a 1/0.9/6.7 ratio.

Scheme 4. Selective Deprotection of Products **4aa** and **4ag**



Scheme 5. Proposed Mechanism



In conclusion, an efficient and mild method for the synthesis of monofluorinated cyclopropanes bearing functional groups on the *gem* and α-positions to the fluorine atom has been developed. For that purpose, the use of straightforward, accessible, and easy to handle ammonium salts **2** derived from ethyl bromofluoroacetate, in a MIRC reaction, was really efficient. A panel of cyclopropanes containing a fluorinated quaternary center was synthesized with high diastereoselectivity. The scope of this transformation was quite broad, and various functional groups were tolerated. Thanks to the practicality of this method and the rather inexpensive reagents, this strategy paved the way for the synthesis of polyfunctionalized cyclopropanes suitable for further transformations and applications. Consequently, it might become a modern and important key synthetic tool for the preparation of fluorinated cyclopropanes and relatively more complex molecules.

Acknowledgment. We thank Elise Navarre (INSA Rouen) and Jonathan Cousin (INSA Rouen) for complementary experiments. This work was supported by MESR (Ministère de l'Enseignement Supérieur et de la Recherche), the Région Haute-Normandie (CRUNCH program), CNRS, University of Rouen, and INSA of Rouen. This work was also supported by ERDF funding through the Interreg Project A-I Chem Channel Program, the project BIOFLUORG 32819, and LABEX SynORG.

Supporting Information Available. Detailed experimental procedures, spectral data for the new compounds, crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.