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Asymmetric Synthesis of Cyclopropanes with a Monofluorinated Quaternary Stereocenter

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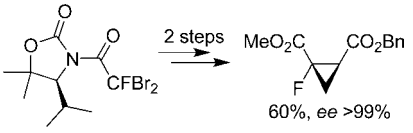
ABSTRACT



New chiral fluorinated reagents (*N*-(dibromofluoroacetyl)oxazolidinones) were easily synthesized and used in an asymmetric cyclopropanation process. The Michael initiated ring closure reaction provided chiral cyclopropanes bearing a fluorinated quaternary stereocenter. Various electron-deficient alkenes can be used to efficiently obtain chiral polysubtituted fluorinated cyclopropanes in good yields. Moderate to very good *cis*/*trans* ratios were obtained with a high level of diastereoselectivity for each isomer.

Presently, the cyclopropyl scaffold and the fluorine atom are both used for the design and the development of new bioactive compounds. The fluorinated cyclopropanes which combine the unique electronic and structural properties of these two entities have already proven to be of high interest for the discovery of efficient therapeutic agents.[1] Only very few examples of asymmetric synthesis of monofluorinated cyclopropanes have been reported to date. Haufe et al. have developed the enantioselective cyclopropanation of α-fluorostyrenes with *ee* values up to 99% and moderate diastereoselectivity.[2] Imura et al. reported the enzymatic resolution[3] of 2-fluorocyclopropanecarboxylates. Terashima et al. used a chiral enamine as a substrate in the Simmons–Smith-like reaction with a fluorinated zinc carbenoid.[4] A good level of facial selectivity was observed, however with moderate *cis*–*trans* selectivity. Most notably, in a recent work by Hu et al., an efficient asymmetric cyclopropanation using a chiral fluorinated sulfoximine was developed.[5] *Ee* values of 93–98% and excellent diastereoselectivity were demonstrated for the cyclopropanes with a tertiary fluorinated carbon from aromatic and aliphatic α,β-unsaturated Weinreb amides. These authors also reported the application of sulfoximine methodology to the synthesis of two cyclopropanes with a quarternary fluorinated stereocenter (1-fluoro-1-methylcyclopropanes). This time, *ee* values of 76% and 86% were observed.

Here we report another approach to the asymmetric synthesis of quarternary fluorinated cyclopropanes based on the use of a new chiral *N*-(dibromofluoroacetyl) oxazolidinone **2**. Resulting 1-fluorocyclopropylcarboxylamides **3** can be readily converted into the corresponding acids and esters thus opening a route to the highly functionalized monofluorinated cyclopropanes[6] in enantiomeric pure form, which have never been, to our knowledge, described.

(1) (a) Yoshida, S.; Rosen, T. C.; Meyer, O. G. J.; Rosen, T. C.; Sloan, M. J.; Ye, S.; Haufe, G.; Kirk, K. L. *Bioorg. Med. Chem.* **2004**, *12*, 2645. (b) Ye, S.; Yoshida, S.; Fröhlich, R.; Haufe, G.; Kirk, K. L. *Bioorg. Med. Chem.* **2005**, *13*, 2489. (c) Hruschka, S.; Rosen, T. C.; Yoshida, S.; Kirk, K. L.; Fröhlich, R.; Wibbeling, B.; Haufe, G. *Bioorg. Med. Chem.* **2008**, *16*, 7148. (d) Nakazato, A.; Kumagai, T.; Sakagami, R.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *J. Med. Chem.* **2000**, *43*, 4893. (e) Nakazato, A.; Sakagami, K.; Yasuhara, A.; Ohta, H.; Yoshikawa, M.; Itoh, M.; Nakamura, M.; Chaki, S. *J. Med. Chem.* **2004**, *47*, 4570. (f) Sakagami, K.; Yasuhara, S.; Chaki, S.; Yoshikawa, R.; Kawakita, Y.; Saito, A.; Taguchi, A.; Nakazato, A. *Bioorg. Med. Chem.* **2008**, *16*, 4359.

(2) (a) Meyer, O. G. J.; Frohlich, R.; Haufe, G. *Synthesis* **2000**, 1479. (b) Hruschka, S.; Frohlich, R.; Kirsch, P.; Haufe, G. *Eur. J. Org. Chem.* **2007**, 141.

(3) Imura, A.; Itoh, M.; Miyadera, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3047.

(4) Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron Lett.* **1992**, *33*, 3487.

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

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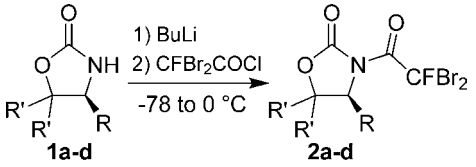
Based on our previous studies on cyclopropanation using ethyl dibromofluoroacetate,[7] we decided to explore the stereodiscriminating ability of a series of chiral auxiliaries bound to a common dibromofluoroacetyl core. Starting chiral reagents **2a**–**d** were prepared in moderate to good yield via the acylation of the commercially available oxazolidinones **1** with $CFBr_2COCl$ (Scheme 1).

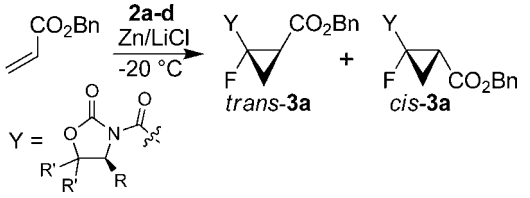
Scheme 1. Preparation of Oxazolidinones **2**



Results of the model reaction with benzyl acrylate and Zn/LiCl[8] are given in Table 1. Increasing the size of a side group clearly leads to better *de* values for both *cis*- and *trans*-isomers with a concurrent decrease in *cis*–*trans* selectivity. Given the high *de* values and better stability demonstrated by **2c**, we decided to use this reagent for further cyclopropanation studies.

In addition to an established method of cyclopropanation based on Zn/LiCl, we examined several other metalating reagents (Table 2). Despite high *cis*–*trans* ratios, all of them demonstrated poorer yields and much lower diastereoselectivity in terms of the absolute configuration of the fluorinated stereocenter. To our delight, the combination of zinc and lithium chloride provided again the best results (yield and diastereoselection).

Table 1. Stereochemistry of the Model Reaction of Benzyl Acrylate with **2a**–**d**



2	*cis*/*trans*[a]	de[a] (cis)	de[a] (trans)
a	3:97	52	68
b	16:84	84	86
c	21:79	84	93
d	27:73	86	88

[a] Determined by ^{19}F NMR of the crude product.

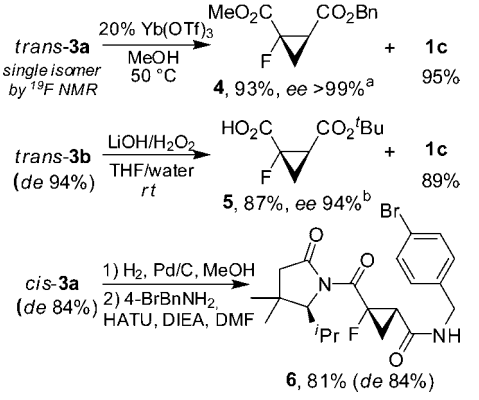
Table 2. Cyclopropanation of Benzyl Acrylate with **2c** and Various Metalating Reagents

reagent	yield,[a] %	*cis*/*trans*[a]	*de*[a] (trans)
^tBuLi	23	4:96	74
iPrMgCl	64	7:93	18
iPrMgCl/LiCl	43	5:95	46
Et_2Zn	<5	–	–
Zn/LiCl	79[b]	21:79	93

[a] Determined by ^{19}F NMR with trifluoroacetophenone as an internal standard. [b] Isolated yield.

Thus, with this optimized procedure in hand, the scope of the cyclopropanation with this new chiral reagent **2c** is given in the Table 3. Reaction takes place with diverse monosubstituted Michael acceptors bearing an ester (entries 1,2), sulfone (entry 3), phosphonate (entry 4), or nitrile (entry 5) as an electron-withdrawing group leading to the expected fluorinated cyclopropanes in good to very

Scheme 2. Transformations of Cyclopropanes **3**



[a] Determined by chiral HPLC. [b] For determination of ee, the acid **5** was converted to the corresponding methyl ester with 65% yield. See Supporting Information for details.

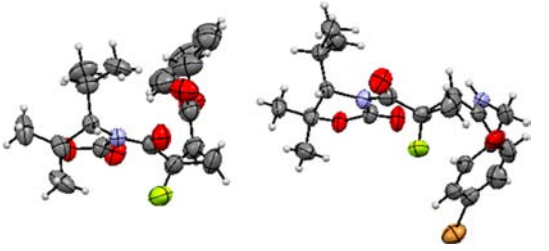


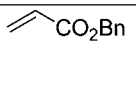
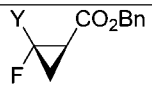
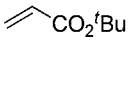
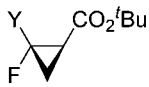
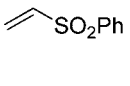
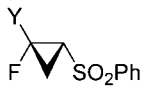
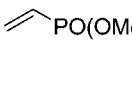
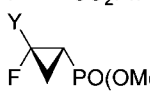
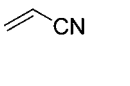
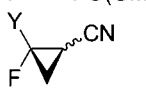
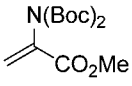
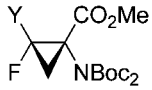
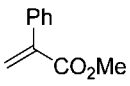
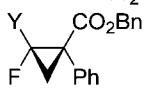
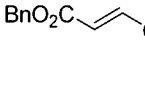
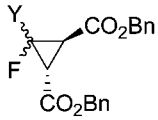
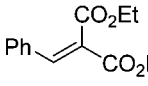
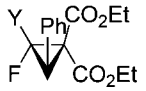
Figure 1. X-ray structures of *trans*-**3a** and **6**.

(6) For several examples of relevant transformations, see: Lemonnier, G.; Lion, C.; Quirion, J.-C.; Pin, J.-P.; Goudet, C.; Jubault, P. *Bioorg. Med. Chem.* **2012**, *20*, 4716.

(7) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270.

(8) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

Table 3. Scope of the Cyclopropanation Reaction with a Chiral Oxazolidinone **2c**

entry	alkene	major product[a]	3	overall yield[b]	*cis*:*trans*[c]	*de*[c] (yield[b]) *cis*	*de*[c] (yield[b]) *trans*
1			**a**	79	21:79	84 (14)	93 (65[d])
2			**b**	69	16:84	76 (8)	94 (61)
3			**c**	79	78:22	88 (62[d])	92 (17[d])
4			**d**	62	85:15	>94 (55[d])	80 (7)
5			**e**[e]	70[f]	50:50	94 (36[d])	>94 (34[d])
6			**f**	78	73:27	80 (56[d])	84
7			**g**	74	45:55	>90 (33[d])	>92 (41)
8			**h**[h]	79	5:95[g]	-	64
9			**i**[i]	66	36:64	>94 (24[d])	>94 (42[d])

[a] Absolute configuration of the cyclopropanes is based on the stereochemical model given in Scheme 3 (for definition of Y see Table 1). [b] Isolated yield of both isomers. [c] Determined by ^{19}F NMR of the crude product. [d] Single isomer by ^{19}F NMR of the isolated product. [e] Equimolar mixture of isomers is formed. [f] 1.5 equiv of acrylonitrile was used. [g] Absolute configuration cannot be deduced from our stereochemical model (Scheme 3). [h] Cis–trans ratio refers to the stereochemistry of ester groups. [i] After 1 h at −20 °C the reaction mixture was stirred at *rt* overnight.

good overall yields. Di- and trisubstituted alkenes also react with good overall yields and generally the same level of diastereoselectivity (entries 6–9). In most cases the diastereomerically pure fluorinated cyclopropanes can be easily separated by column chromatography.

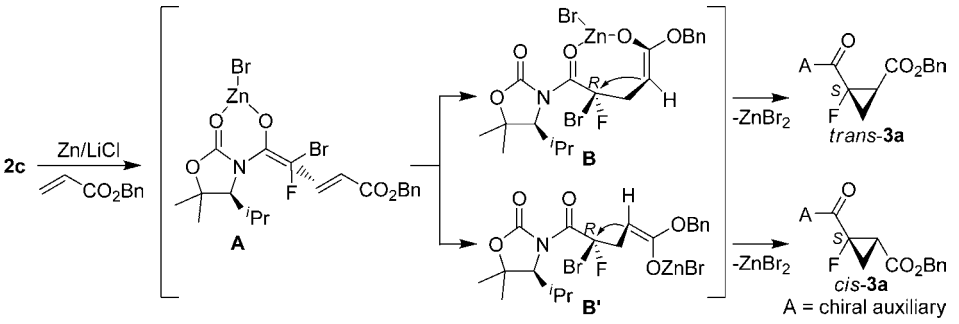
Cleavage of the chiral auxiliary in acrylate-derived cyclopropanes *trans*-**3a** and *trans*-**3b** was carried out under either acidic or basic conditions leading to the ester **4** and the acid **5**, respectively (Scheme 2). In both cases it proceeded smoothly with no epimerization of the cyclopropane and very good recovery of the chiral auxiliary.[9] Alternatively, the benzyl ester group, from *cis*-**3a**, can be selectively cleaved by hydrogenolysis. It was then further transformed into the amide derivative in order to simplify the analysis procedure.

Presently, cyclopropanation demonstrates relatively high diastereoselectivity but, at the same time, highly variable *cis*–*trans* ratios for different types of substrates. In order to elucidate the origin of this complex stereochemistry we determined the absolute configurations of the two major isomers (*cis* and *trans*) of **3a** by single-crystal X-ray analysis (Figure 1). While *trans*-**3a** can be easily crystallized from the crude product, *cis*-**3a** had to be converted into the *N*-4-bromobenzylamide **6** in order to obtain crystals of sufficient quality for X-ray analysis. Both isomers share the same absolute configuration (*S*) of the fluorinated stereocenter and differ in the position of the ester group for *trans*-**3a** (amide group for **6**).

Formation of a pair of epimeric products during the MIRC-type cyclopropanation is consistent with highly stereoselective 1,4-addition followed by a less selective cyclization leading to a mixture of *cis*- and *trans*-isomers (Scheme 3). Although we do not know the exact structure of the unstable organozinc intermediate **A**, it possibly reacts as a chelated enolate as depicted in Scheme 3. In such an intermediate the (*Z*)-configuration of a double bond should be preferred based on the steric effect of the voluminous bromine atom. This model can also explain the observed lowering of *cis*–*trans* selectivity with the increase of bulkiness of the chiral auxiliary (see Table 1). The *cis*–*trans* selectivity of the cyclopropanation of unsaturated esters may be controlled by chelation in intermediate **B**, leading to the preferential formation

(9) See Supporting Information for the synthesis of racemic fluorinated cyclopropanes and ee determination.

Scheme 3. Stereochemical Model Based on the X-ray Data for *trans*-**3a** and **6**



of a *trans*-isomer. This is in contrast with the *cis*-selective formation of the sulfone- and phosphonate-derived products **3c,d**. The difference may account for a steric effect of heavy heteroatoms or a change in the mechanism, e.g. participation of a C-metalated analog of the intermediate **B**. Further studies on the structure and reactivity of sulfur- and phosphorus-stabilized organozinc compounds are needed in order to develop a consistent stereochemical model. The stereochemistry of fumarate-derived cyclopropane **3h** is dominated by the 1,2-repulsion of ester groups which results in the preferential formation of a pair of isomers in which the two ester groups adopt a *trans* relationship.

In conclusion, a straightforward two-step procedure for the asymmetric synthesis of highly functionalized enantiomerically pure monofluorocyclopropanes was developed. A stereochemical model of cyclopropanation is proposed based on the X-ray analysis of major products. Further developments especially devoted to the incorporation of this type of fluorinated scaffolds in more complex structures are currently under investigation in our laboratory.

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Supporting Information Available. 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.