Carbon–Fluorine Bond Activation

International Edition: DOI: 10.1002/anie.201603210
German Edition: DOI: 10.1002/ange.201603210

Asymmetric Desymmetrization via Metal-Free C–F Bond Activation: Synthesis of 3,5-Diaryl-5-fluoromethyloxazolidin-2-ones with Quaternary Carbon Centers

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Dedicated to Professor Dieter Hoppe on the occasion of his 75th birthday

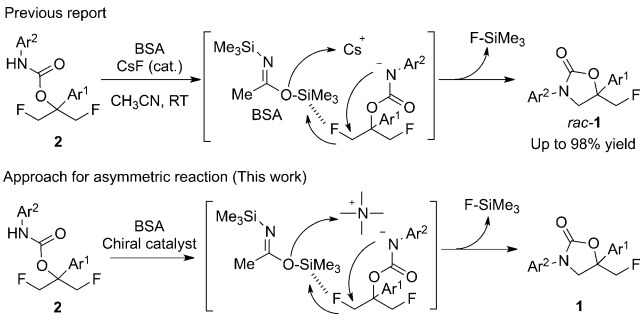
Abstract: *We disclose the first asymmetric activation of a non-activated aliphatic C–F bond in which a conceptually new desymmetrization of 1,3-difluorides by silicon-induced selective C–F bond scission is a key step. The combination of a cinchona alkaloid based chiral ammonium bifluoride catalyst and N,O-bis(trimethylsilyl)acetoamide (BSA) as the silicon reagent enabled the efficient catalytic cycle of asymmetric C_{sp3}–F bond cleavage under mild conditions with high enantioselectivities. The ortho effect of the aryl group at the prostereogenic center is remarkable. This concept was applied for the asymmetric synthesis of promising agrochemical compounds, 3,5-diaryl-5-fluoromethyloxazolidin-2-ones bearing a quaternary carbon center.*

One of the major goals in organofluorine chemistry[1] is the selective formation of new carbon–fluorine bonds to either gain access to fluorinated building blocks[2] or to introduce fluorine into existing complex carbon skeletons at a late stage of synthesis in order to specifically modify the physicochemical properties[3] or the biological activity of compounds intended for the exploration of novel pharmaceuticals and agrochemicals.[4] There are many different methods described in the literature and only very recent developments are mentioned here such as electrophilic monofluorination, electrophilic, nucleophilic, and radical perfluoroalkylation, trifluoromethylthiolation, perfluoroalkylsulfonylation, and difluorocarbene addition.[5]

In recent years a second general approach to access organofluorine compounds was discovered, namely the selective activation of carbon–fluorine bonds in polyfluorinated substrates and their replacement with carbon–hydrogen or carbon–carbon bonds. There are also reports on C–O, C–S, C–N, and C–P bond formation at the expense of C–F bonds.[6,7] However, the cleavage of a C–F bond is one of the most challenging topics in fluorine chemistry as it has the highest dissociation energy (105 kcal mol^{-1}) of all covalent carbon single bonds. Additionally, fluorine is neither a good Lewis base nor a good leaving group.[8] The activation of aliphatic C–F bonds has been less frequently reported than that of aryl fluorides.[6] In most cases the fluorine atom is bound to an activated position such as a benzylic or allylic position, or in α-position to a carbonyl group. Harsh reaction conditions are generally required for C–F bond cleavage and very stable new bonds such as H–F, Si–F, B–F, Al–F, P–F and transition-metal–F bonds have to be formed to make the C–F scission reaction feasible.[6d] Besides high reaction temperatures, lithium reagents, strong Lewis acids, and transition metal reagents are generally needed.[7,9] In addition, activation of benzylic C–F bonds by hydrogen-bonding interactions with isopropanol/water or hexafluoroisopropanol have also been described.[10]

Recently, we reported the cleavage of non-activated aliphatic C–F bonds by utilizing the fluorophilicity of silicon and the formation of strong (ca. 140 kcal mol^{-1}) silicon–fluorine bonds.[11] Using this reaction, 3,5-diaryl-5-fluoromethyloxazolidin-2-ones **1** were synthesized by a conceptually new desymmetrization of non-activated aliphatic 1,3-difluorides with silicon-induced C–F bond activation as a key step under mild reaction conditions with bis(trimethylsilyl)acetamide (BSA) and catalytic CsF (Scheme 1).

To extend this chemistry, we set our next goal as "asymmetric desymmetrization" via C–F bond activation. Our approach toward the enantioselective reaction relies on the replacement of CsF by chiral ammonium fluorides. Enantioselective reactions via C–F bond activation are quite rare. To the best of our knowledge, only two reports



Scheme 1. Background of this research and approach to asymmetric desymmetrization.

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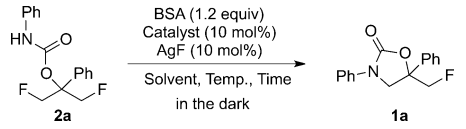
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201603210.

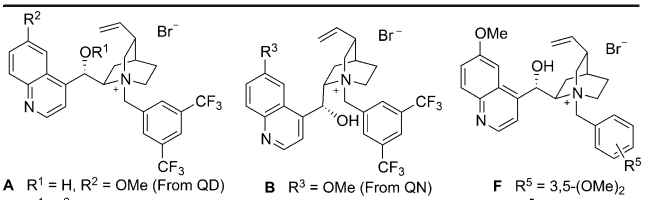
have been published so far, both from our group.[12] Although we achieved enantioselective C–F bond cleavage, only allylic fluorides, compounds with activated aliphatic C_{sp3}–F bonds, have been accepted as substrates. Herein, we succeeded in the asymmetric synthesis of 3,5-diaryl-5-fluoromethyloxazolidin-2-ones **1** having a quaternary carbon center with high enantioselectivities via cleavage of much more challenging non-activated aliphatic C_{sp3}–F bonds (Scheme 1). The use of a chiral ammonium bifluoride catalyst and the effect of the *ortho*-substituted aryl group (*ortho* effect) at the prostereogenic center are crucial to the success of the reaction.

In initial work the reaction conditions for the asymmetric reaction were optimized (Table 1). Chiral ammonium fluorides are known to be unstable salts.[13] Therefore, we chose the method of in situ generation of the salts from silver fluoride and chiral ammonium bromide.[13a] Four chiral

Table 1: Optimization of conditions for the asymmetric reaction .



Entry	Precat.	Solvent	Temp.	Time [h]	Yield [%]	*ee* [%]
1	**A** (QD)	CH_2Cl_2	RT	1	97	37
2	**B** (QN)	CH_2Cl_2	RT	4	78	8
3	**C** (CN)	CH_2Cl_2	RT	4	82	0
4	**D** (CD)	CH_2Cl_2	RT	4	74	0
5	**A**	CH_2Cl_2	0 °C	16	59	35
6	**E**	CH_2Cl_2	RT	15	95	0
7	**A**	toluene	RT	24	27	13
8	**A**	CH_2Cl_2/ toluene (1:2)	RT	48	96	13
9	**F**	CH_2Cl_2	RT	24	88	8
10	**G**	CH_2Cl_2	RT	24	12	68

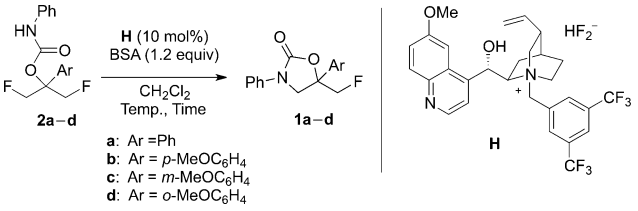


A R^1 = H, R^2 = OMe (From QD)
C R^1, R^2 = H (From CN)
E R^1 = Me, R^2 = OMe (From QD)
B R^3 = OMe (From QN)
D R^3 = H (From CD)
F R^5 = 3,5-$(OMe)_2$
G R^5 = 3,5-$(NO_2)_2$

ammonium bromides derived from quinidine (QD), quinine (QN), cinchonine (CN), and cinchonidine (CD) were used as catalyst precursors (entries 1–4). The reaction at room temperature in the presence of quinidinium fluoride formed in situ from **A** afforded the target product **1a** with 97% yield and 37% *ee* in 1 h (entry 1), while catalysts formed from **B**, **C**, and **D** gave lower yields (74–82%) and lower or no enantioselectivity (0–8% *ee*, entries 2–4). Therefore, we continued our investigations with the catalyst derived from **A**. At 0 °C a reaction time of 16 h was required and both yield and enantioselectivity decreased (59%, 35% *ee*, entry 5). Methylation of the OH group of **A** (precatalyst **E**) resulted in high product yield but no chiral induction at room temperature (entry 6). Thus, the hydroxy group in the catalyst structure is essential for high *ee* values. In previous work we often used toluene and CH_2Cl_2/toluene mixtures for asymmetric reactions with organocatalysts,[14] but in this case the enantioselectivity dropped (entries 7 and 8). Next the effect of the substituents on the benzylic moiety of catalyst was studied. Electron-donating groups like methoxy in **F** afforded the product with low asymmetric induction (entry 9). On the other hand, the catalyst **G** with strong electron-withdrawing nitro groups gave the target product with acceptable 68% *ee*, but in a complex mixture (12% yield, entry 10). These results indicate that the nature of the chiral ammonium catalyst is crucial for asymmetric induction.

However, the chiral ammonium bromide/AgF system presented us with three problems: 1) in situ generated chiral ammonium fluoride from **A** is unstable; 2) AgF is almost insoluble in CH_2Cl_2 at low temperatures; and 3) the reaction has to be performed in the dark to avoid reduction of silver cation. To overcome these drawbacks, we focused on a chiral ammonium bifluoride catalyst reported by the groups of Corey and Maruoka.[15] Bifluoride catalysts have been reported to be more stable, so that this catalyst was expected to be a promising alternative in our asymmetric reaction (Table 2). Surprisingly, this catalyst accelerated the reaction

Table 2: Asymmetric reaction with chiral quinidinium bifluoride.



a: Ar =Ph
b: Ar = *p*-$MeOC_6H_4$
c: Ar = *m*-$MeOC_6H_4$
d: Ar = *o*-$MeOC_6H_4$

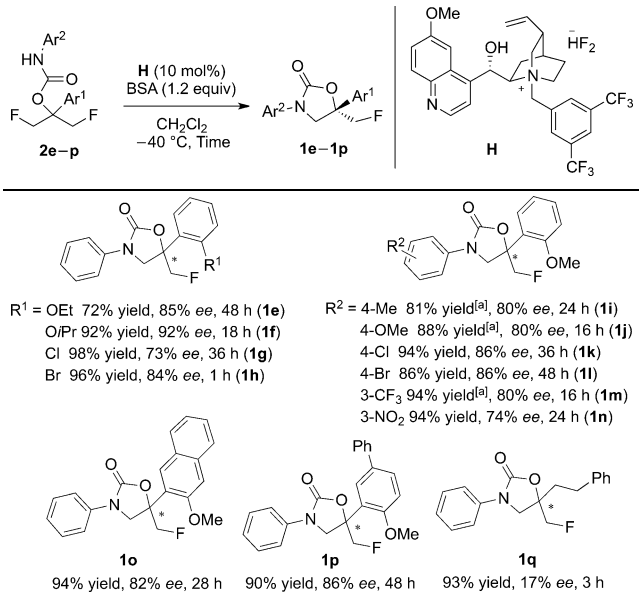
Entry	**2**	Temp. [°C]	Time [h]	**1**	Yield [%]	*ee* [%]
1	**2a**	RT	10 min	**1a**	99	24
2	**2a**	0	10 min	**1a**	98	30
3	**2a**	−20	1	**1a**	88	37
4	**2a**	−40	45	**1a**	81	48
5	**2b**	−40	12	**1b**	95	45
6	**2c**	−40	12	**1c**	90	48
7	**2d**	−40	48	**1d**	94	84

rate and the transformation was completed in only 10 min at room temperature to give the product **1a** in quantitative yield with 24% *ee* (entry 1). The rate acceleration effect observed is presumably due to the higher solubility and stability of ammonium bifluoride in organic solvents. Encouraged by this result, we lowered the reaction temperature successively. At −40 °C the enantiomeric excess was 48%, although the reaction required 45 h reach completion (entry 4). In order to improve the enantioselectivity of this unprecedented asymmetric desymmetrization of bis-monofluoride **2a**, we investigated the effect of substituents on the aryl ring at the quaternary center (entries 5–7). 2-Aryl-1,3-difluoropropan-2-(*N*-phenylcarbamates) **2b** and **2c**, which have a methoxy group at the *para* and *meta* position of Ar, respectively, showed higher reactivity and yield with almost unaffected enantioselectivity (entries 5 and 6, 90–95% yields, 45–48% *ee*). Fortunately, the *ortho* substituent of **2d** caused

a dramatic increase of the enantioselectivity (84% *ee*) and excellent yield of 94% (entry 7).

Encouraged by the remarkable *ortho* effect of the methoxy group, this methodology was extended to a variety of substrates with other *ortho*-substituted phenyl rings at the prostereogenic center (Table 3). We found that substrates with any *ortho* substituents gave rise to excellent yields and

Table 3: Substrate scope of the asymmetric desymmetrization reaction.



[a] Reactions were carried out at −20 °C.

high asymmetric induction. Electron-donating *ortho* substituents such as EtO and *i*PrO groups afforded the products **1e** and **1f** with high yields (72–92%) and high enantioselectivities (85–92% *ee*). Electron-withdrawing halogens, that is, Cl and Br, were also efficient *ortho* functional groups to provide **1g** and **1h** in excellent yields (96–98%) with high enantioselectivities (73–84% *ee*). The bulkier *i*PrO and Br led to higher enantioselectivities independent of their electronic nature. Next the effect of substituents on the Ar^2 group of the carbamate was studied (**2i–n**). Again, reactions of substrates with electron-donating Me and MeO groups (**1i** and **1j**), or halogens like Cl and Br in *para* position (**1k** and **1l**), or with powerful electron-withdrawing groups like CF_3 and NO_2 in *meta* position (**1m** and **1n**) gave high yields (81–94%) and high enantioselectivities (74–86% *ee*). We further elaborated the scope of this reaction with substrates having sterically more demanding Ar^1 groups at the prostereogenic center. The substrates with *ortho*-methoxynaphthyl and *ortho*-methoxybiphenyl groups gave the cyclized products **1o** and **1p** with 82% *ee* and 86% *ee*, respectively, with >90% yield. As expected, very low asymmetric induction was observed for aliphatic substrate **1q** (93% yield, 17% *ee*). Thus, the sterically demanding Ar^1 group is required to gain high enantioselectivity.

From difluoride **2h** the *S*-configurated product **1h** was formed selectively (84% *ee*). The structure was proved by X-ray crystallography (CCDC 1471286, Figure 1a). Other compounds **1** are supposed to have *S* configuration as well.

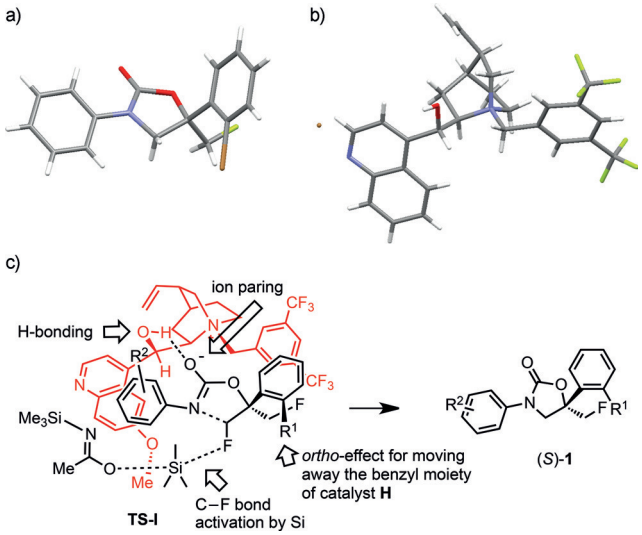
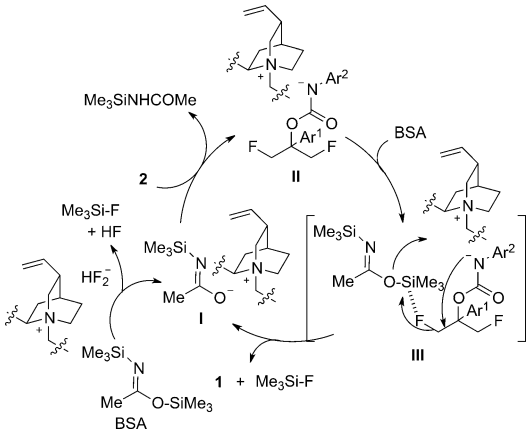


Figure 1. a) X-ray crystallographic structure of (*S*)-5-fluoromethyl-3-phenyl-5-(*o*-bromophenyl)oxazolidin-2-one (**1h**) (CCDC 1471286). b) X-ray crystallographic structure of precatalyst **C** from CCDC 738896.[16] c) Proposed transition-state model **TS-1** for the transformation of **2** to (*S*)-**1**.

Scheme 2 presents our mechanistic explanation for the asymmetric desymmetrization reaction. Initially, BSA was activated by chiral ammonium bifluoride to provide amide anion **I**, along with the release of Me_3Si–F and HF. Anion **I** then abstracts the carbamate proton from **2** to generate anion



Scheme 2. Plausible reaction mechanism.

II, along with $Me_3SiNHCOMe$. Next the less hindered C–F bond of **II** was activated by interaction with the Si atom of BSA, depicted by transition-state model **III**. This conformation induces an intramolecular cyclization with C–F fission furnishing the chiral oxazolidin-2-one **1** and Me_3Si–F. The amide anion **I**, which is regenerated from **III**, is the active catalyst in this cycle.

To explain the high enantioselectivity achieved in the present reactions, we postulated a transition-state structure

for the formation of (*S*)-**1** controlled by catalyst **H**. The geometry of **H** was generated from our X-ray crystallographic data of catalyst **C** (Figure 1 b)[16] showing that the cinchona alkaloid exists in an open conformation.[17] The absolute configuration of product **1 h** determined by X-ray diffraction (Figure 1 a) was used as a model for the reacting enantiotopic fluoromethyl group of substrates **2**. The free OH group at the prostereogenic carbon center and the OMe group of the quinoline moiety of **H** should play important roles based on the results of the catalyst screening (see entries 1, 3, and 6 in Table 1). Hence, the transition-state structure **TS-I** is proposed. The OH captures the anions of carbamates **2**, by intermolecular hydrogen bonding to the oxygen.[18] Additionally, the carbamate anion is stabilized by ion pairing with ammonium cation. These attractions facilitate the location of the substrate **2** in the space between the left part of the quinuclidine ring and the bulky bis(trifluormethyl)benzyl group on the right. Steric repulsion induced by an *ortho*-substituted aryl group efficiently moves away the benzyl moiety of catalyst **H** and locks **TS-I**. The opposite side of the quinoline moiety of **H** is blocked by its methoxy group, which further confines the substrate molecules within the restricted space of catalyst **H** (Figure 1 c).

In conclusion, we have achieved the first asymmetric desymmetrization of 1,3-difluorides using *N*,*O*-bis(trimethylsilyl)acetamide and catalyzed by a cinchona alkaloid derived ammonium bifluoride salt providing chiral, non-racemic 3,5-diaryl-5-fluoromethyloxazolidin-2-ones in high yields with high enantioselectivities of up to 92 % *ee*. Since the 3,5-diaryl-5-trifluoromethyloxazolidin-2-ones are promising agrochemicals (insecticides, acaricides, ectoparasiticides),[19] monofluorinated analogues are highly desirable. A notoriously difficult non-activated aliphatic C–F bond scission was realized and a metal-free, silicon-mediated selective C–F bond activation was a key step. The combination of a cinchona alkaloid based chiral ammonium bifluoride catalyst and a silicon reagent enabled the efficient, asymmetric cleavage of C_{sp3}–F bonds under mild conditions with high enantioselectivities. The remarkable steric effect of an *ortho*-substituted aryl group at the prostereogenic carbon for asymmetric induction is observed not only for MeO, but also other alkoxy groups, halogens, and bigger aryl groups. This concept of asymmetric C–F bond activation might be applicable for other types of asymmetric synthesis with cyclization. This idea is now under consideration.

Acknowledgments

This research is partially supported by the Platform for Drug Discovery, Informatics and Structural Life Science from The Ministry of Education, Culture, Sports, Science and Technology-Japan (MEXT), and Japan Agency for Medical Research and Development (AMED), the Advanced Catalytic Transformation (ACT-C) from the JST Agency, and the Kobayashi International Foundation. We also acknowledge the help of Chisato Terada at the beginning of this research.

Keywords: asymmetric synthesis · C–F bond activation · desymmetrization · fluorine · organocatalysis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 9432–9436
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Received: April 1, 2016
Published online: June 22, 2016

