Regioselective C–F Bond Transformations of Silyl Difluoroenolates

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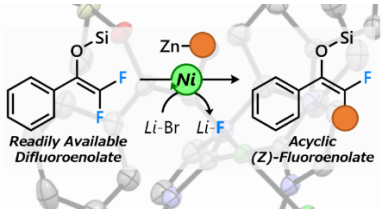
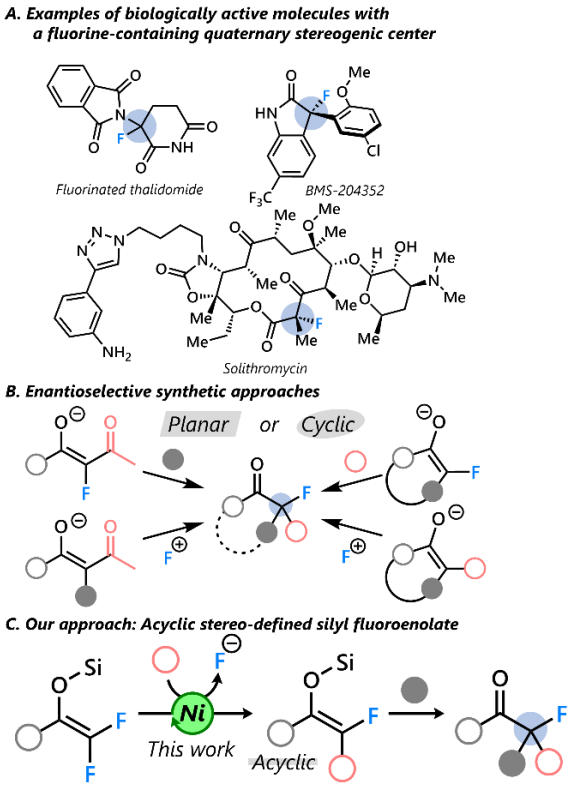


ABSTRACT: Herein, we report the development of a nickel-catalyzed cross-coupling reaction of silyl difluoroenolates with aryl zinc reagents via C–F bond cleavage. Treatment of a stoichiometric amount of Ni(0)/*N*-heterocyclic carbene (NHC) with silyl difluoroenolates in the presence of a lithium salt resulted in C–F bond cleavage to selectively afford the corresponding (*Z*)-alkenyl Ni complexes. Based on the observations, we developed a catalytic cross-coupling reaction that selectively delivers a single geometric isomer of a fluoroenolate.

Organofluorine compounds are attractive synthetic targets in medicinal chemistry.[1] Considering the importance of a C(sp^3)-rich three-dimensional structures for drug candidates, fluorine-containing quaternary stereogenic centers represent an appealing structural motif.[2-4] In fact, a few drug molecules containing this motif have been developed, including the first organofluorine drug molecule, fludrocortisone.[5] In this context, the replacement of an α-hydrogen atom of a carbonyl group with a fluorine atom is a useful strategy to prevent undesired racemization under physiological conditions. A representative example is fluorinated analogues of thalidomide (Scheme 1A).[6,7] The potassium channel modulator BMS-204352 and solithromycin also feature a fluorine-containing quaternary stereogenic center next to the carbonyl group.[8]

The development of efficient synthetic routes to acyclic carbonyl compounds that feature an adjacent fluorine-containing quaternary stereogenic center expands the chemical space of three-dimensional organofluorine molecules. A variety of highly efficient enantioselective electrophilic fluorination reactions[9] and C–C bond forming reactions for fluoroenolate species[10–15] have been disclosed for the fabrication of fluorine-containing quaternary stereogenic centers, although the scope of enolates that provide the product in high enantioselectivity is restricted to cyclic or 1,3-dicarbonyl compounds (Scheme 1B). The lack of successful examples for the acyclic version could possibly be explained in terms of the difficulties associated with controlling the geometric isomerism of the enolate species. Therefore, we anticipated that the emergence of a class of acyclic stereo-defined fluoroenolates would lead to the development of a novel approach to obtain fluorine-containing quaternary stereogenic centers. Silyl fluoroenolates are ideal candidates on account of their easy handling and the track record of their non-fluorinated congeners for stereoselective synthesis.[16] Our literature survey, however, found only a handful of examples of acyclic silyl fluoroenolates.[17-23] Furthermore, the enolate geometries of some of them were not defined or controlled. Herein, we describe the nickel-catalyzed cross-coupling reactions of silyl difluoroenolates with organozinc reagents via C–F bond cleavage (Scheme 1C).[24]

Scheme 1. Research background and conceptual illustration of the objectives of this study



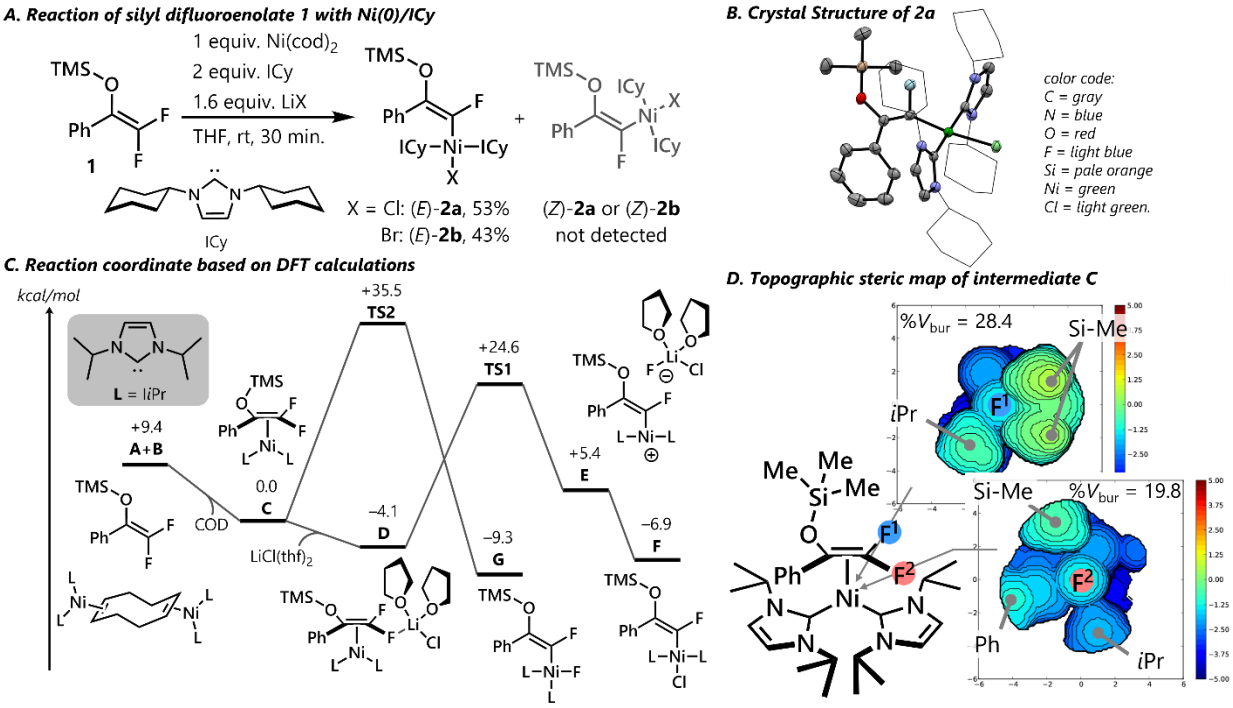


Figure 1. A. Stoichiometric reaction of difluoroenolate **1** with Ni(0)/ICy (TMS = trimethylsilyl). B. Crystal structure of (*E*)-**2a** with thermal ellipsoids at 50% probability; hydrogen atoms and a solvated toluene molecule are omitted for clarity; the cyclohexyl rings of ICy ligands are depicted in wireframe fashion. C. The reaction coordinate based on DFT calculations. D. The topographic steric maps of intermediate **C**.

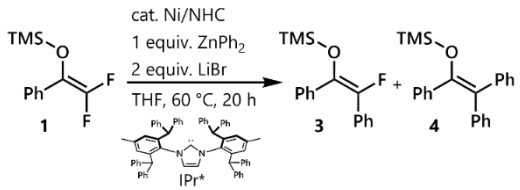
We initiated our study by testing the ability of a Ni(0) complex to cleave a C–F bond in silyl difluoroenolate **1**. We chose *N*-heterocyclic-carbene (NHC) ligands because such systems have already been studied for the cleavage of C(sp^2)–F bonds.[25-35] Accordingly, we mixed Ni(cod)$_2$, ICy, and **1** in C_6D_6, and the reaction was monitored using ^{19}F NMR spectroscopy. We observed the formation of TMSF, indicating that a C–F bond was cleaved, albeit that the fluoride anion was abstracted by the silicon in **1**. Upon examining the literature, we decided to add a lithium salt as a fluoride scavenger to the reaction mixture.[36-38] Thus, we performed the reaction of **1** with Ni(cod)$_2$/ICy in the presence of LiCl or LiBr, which produced a single peak at around −85 ppm in the ^{19}F NMR spectra of the crude reaction mixture, which was assigned to the oxidative addition products (*E*)-**2a** and (*E*)-**2b** (Figure 1A). The structure of (*E*)-**2a** was determined unambiguously using single-crystal X-ray diffraction analysis (Figure 1B).

To understand the selectivity of the stoichiometric C–F bond-cleavage reaction, we performed a series of DFT calculations at the M06/6-311++G(d,p)//B3LYP-D3/6-31g(d) level in which I*i*Pr (**L**) was employed as a truncated model for ICy in order to reduce computational costs (Figure 1C). The results revealed that the reaction of difluoroenolate **A** and Ni$_2$(I*i*Pr)$_4$(cod) (**B**), which is generated from Ni(cod)$_2$ and **L**, to form the η^2-complex **C** is a thermally favored process. The subsequent coordination of LiCl(thf)$_2$ to give complex **D** is also thermally favored. The transition state **TS1** for fluoride elimination assisted by the Li cation was calculated to produce complex **E** with an energetic barrier of 28.7 kcal/mol. The abstraction of chloride by the cationic nickel center furnishes the oxidative-addition product **F**. The oxidative addition of the C–F bond without the support of a lithium salt via **TS2** was calculated to require 35.5 kcal/mol, which is significantly higher than the barrier for **TS1**. These calculations are in agreement with the experimentally observed requirement for a lithium salt for the oxidative addition to proceed smoothly. We propose that the critical factor determining the *E*/*Z* selectivity of the oxidative addition is the different degrees of steric congestion around the two fluorine atoms. We prepared topographic steric maps using SambVca 2.1[39,40] to visualize the steric environment around the fluorine atoms located *cis* and *trans* to the siloxy group, which are labeled as F^1 and F^2, respectively (Figure 1D). The topographic steric map with F^1–Ni oriented along the *z*-axis indicated that F^1 is shielded by three methyl groups, two of which are attached to the TMS group and one of which belongs to the isopropyl group of **L**. In contrast, F^2 is located in a plane surrounded by a phenyl group and two methyl groups of TMS and **L**. Hence, it seems feasible to assume that the lithium cation coordinates exclusively to the less-congested F^2, which results in a selective cleavage of that C–F bond that produces the *E* isomer.

The results of the stoichiometric reactions encouraged us to develop a catalytic reaction using aryl zinc reagents.[41] For that purpose, we prepared diphenylzinc via the transmetallation of the corresponding Grignard reagent with ZnBr$_2$. Then, **1** was treated with diphenylzinc in the presence of 10 mol% Ni(cod)$_2$, 20 mol% ICy, and 2 equivalents of LiBr in THF at 60 °C. Unfortunately, the reaction quantitatively furnished the disubstituted product **4** instead of the desired fluoroenolate (**3**) (Table 1, entry 1). The formation of **4** indicates that the cleavage of the second C–F bond in **3** is favored over the dissociation of **3** from the nickel center. Based on this concept, we performed the screening of bulkier NHC ligands (see Supporting Information). Ultimately,

we used IPr*[42] to obtain **3** in 82% yield (entry 2). Control experiments revealed that the addition of both Ni and IPr* is crucial to obtain **3** in high yield, albeit the addition of $Ni(cod)_2$ alone gave the coupling product in poor yield (entries 3–5). We next investigated the effect of salts on the yield of the cross-coupling reaction. When we ran the reaction without lithium salt, we obtained the desired product in moderate yield (entry 6). In contrast, the reaction using isolated $ZnPh_2$ (under Li- and Mg-free conditions) delivered the desired product in low yield (entry 7). In this case, ~15% TMSF was observed in the ^{19}F NMR spectrum of the crude reaction mixture. Taken together, these results indicate that Mg salts could also promote the reaction in a way similar to that of Li salts, while the silyl enolate itself can also act as a fluoride scavenger in the absence of such salts. We found that less expensive and air-stable $Ni(acac)_2$ also acts as a catalyst and slightly suppresses the generation of by-product **4** (entry 8). The catalyst and LiBr loadings could be reduced to 1 mol% and 1 equiv., respectively (entry 9).

Table 1. Screening the reaction conditions for the cross-coupling of 1 with $ZnPh_2$[a]



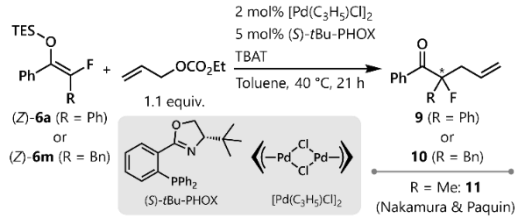
Entry	Conditions	Yield[b] 3	Yield[b] 4
1	10 mol% $Ni(cod)_2$, 20 mol% ICy,	trace	>99%
2	10 mol% $Ni(cod)_2$, 10 mol% IPr*	82%	5%
3	-	n.d.	n.d.
4	10 mol% $Ni(cod)_2$	3%	16%
5[c]	10 mol% IPr*	n.d.	n.d.
6[c]	10 mol% $Ni(cod)_2$, 10 mol% IPr*	68%	10%
7[d]	10 mol% $Ni(cod)_2$, 10 mol% IPr*	17%	18%
8	10 mol% $Ni(acac)_2$, 10 mol% IPr*,	88%	trace
9[e]	1 mol% $Ni(acac)_2$, 1 mol% IPr*	94%	trace

[a]$ZnPh_2$ was prepared by mixing 2 equiv. of PhMgBr and 1 equiv. of $ZnBr_2$. [b]Yields were determined via ^{19}F NMR analysis of the crude reaction mixture using trifluoromethyl cyclohexane as an internal standard; n.d. = not detected. [c]Without LiBr. [d]Using isolated $ZnPh_2$ (purified by sublimation). [e]With 1 equiv. of LiBr.

Isolation of **3** using column chromatography on silica gel was hampered by protonation (Scheme S2). We thus investigated the corresponding triethylsilyl (TES) ether **5a**, which would be less prone to protonation than the TMS ether. The catalytic reaction proceeded in the same manner as for the TMS ether (98% NMR yield) and the desired silyl fluoroenolate (**6a**) was isolated in 89% yield after chromatographic purification. The geometry of isolated **6a** was determined to be *Z* using ^1H–^{19}F heteronuclear Overhauser effect spectroscopy (HOESY; Scheme S3). We confirmed that the reaction also proceeded on the gram scale to give 2.1 g of the desired product (78% yield). With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction (Figure 2A). Aryl, alkyl, alkoxy, aniline, and fluorine substituents were tolerated under the optimal conditions to give the corresponding products (**6b–6k**). However, the reaction using an organozinc reagent containing the electron-withdrawing CF_3 group resulted in low yield (**6l**). We found that benzylation (**6m–6q**) and methylation (**6r**) also proceeded in moderate to good yield. Some silyl difluoroenolates containing oxygen, nitrogen, and fluorine were also applicable for this reaction (**6s–6x**).

We also tested other *gem*-difluoroalkenes to explore the potential versatility of our defluorinative coupling. When we performed the reaction using 1-(2,2-difluorovinyl)naphthalene (**7a**), we observed the formation of (*Z*)-**8a**, which is a typical product of defluorinative coupling reactions of *gem*-difluoroalkenes (Figure 2B, left).[44] In our case, the major product was 1-(2,2-diphenylvinyl)naphthalene (49%). In contrast, the reaction of **7b** having a methyl group furnished (*E*)-**8b** in excellent yield (Figure 2B, right). This result represents a rare example of highly stereoselective C–F bond coupling with a disubstituted *gem*-difluoroalkene *without* a directing group.[41]

Table 2. Asymmetric Tsuji–Trost reaction of (*Z*)-6 using the ligand (*S*)-*t*Bu-PHOX



Entry	Substrate and product	TBAT	Yield (%)[a]	*ee* (%)[b]
1	**6a**, **9**	33 mol%	86	<5
2	**6a**, **9**	-	15	11
3	**6m**, **10**	33 mol%	33	79
4	**6m**, **10**	100 mol%	73	68

[a]Isolated yields are shown. [b]Enantiomer ratio was determined using supercritical fluid chromatography (SFC).

The preliminary results of the asymmetric Tsuji–Trost reaction[45,46] using our acyclic silyl fluoroenolates are summarized in Table 2. We first tested the reaction of (*Z*)-**6a** and allyl ethyl carbonate in the presence of catalytic amounts of $[Pd(C_3H_5)Cl]_2$ and (*S*)-*t*Bu-PHOX (entry 1). We added tetrabutylammonium triphenyldifluorosilicate (TBAT) to activate the silyl group according to Paquin's report.[47] Disappointingly, the desired product (**9**) was racemic. When we omitted the addition of TBAT to prevent the rapid *E*/*Z* isomerization of **6a** (Scheme S2), **9** was obtained in 11% *ee*, although the yield was only 15% (entry 2). Gratifyingly, the reaction of (*Z*)-**6m**, which did not isomerize in the presence of TBAT, furnished ketone **10** in 33% yield and 79% *ee* (entry 3). When we attempted a reaction using a stoichiometric amount of TBAT, we obtained **10** in 73% yield with 68% *ee* (entry 4). The benzyl group is important for good enantioselectivity, since the related reactions using a ketoester or allyl carbonate have been reported to furnish **11** in 51% *ee*[48] and 36% *ee*[49], respectively.

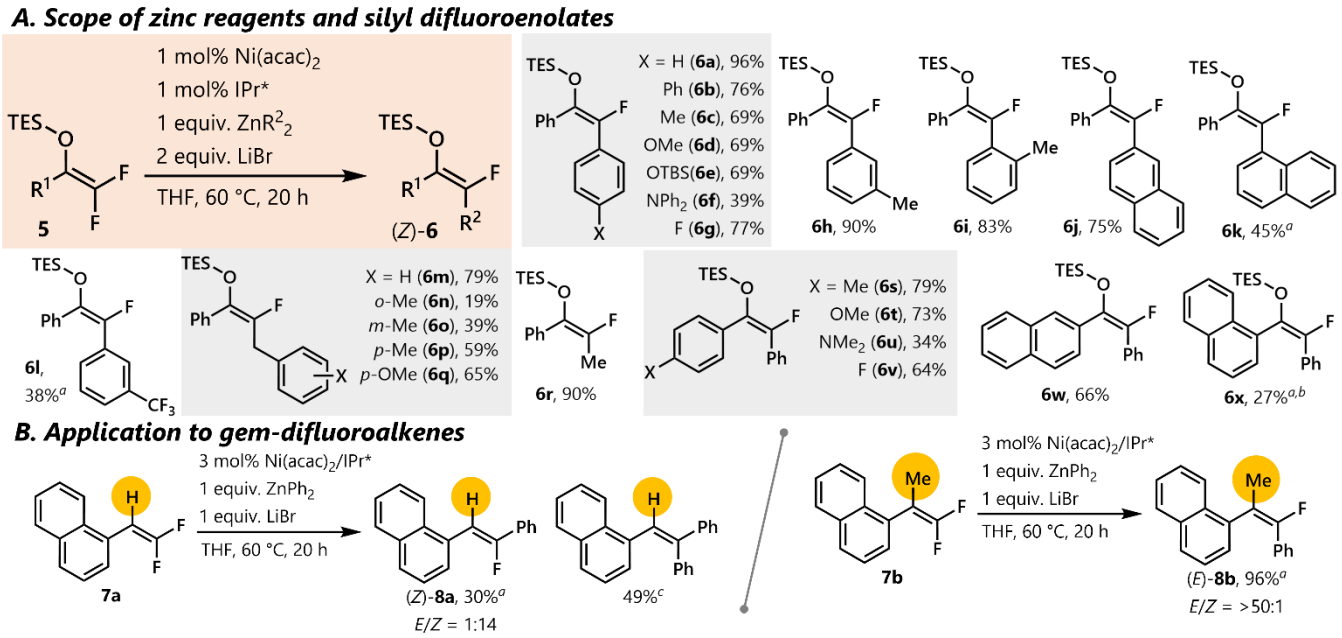


Figure 2. Substrate scope; isolated yields are shown; unless otherwise stated, Z/E > 50:1. [a]NMR yield determined by ^{19}F NMR analysis of the crude reaction mixture. [b]Z/E = 10:1. [c]NMR yield determined by ^{1}H NMR analysis of the crude reaction mixture.

In short, we have discovered a Ni-catalyzed defluorinative coupling of silyl difluoroenolate with organozinc reagents, which was inspired by our stoichiometric C–F bond-cleavage reaction. Further studies, including an expansion of the scope, synthetic application of the silyl fluoroenolates, and detailed mechanistic studies of the catalytic process, are currently in progress.

ASSOCIATED CONTENT

Data Availability Statement: The data underlying this study are available in the published article and its Supporting Information.

Suppporting Information: Experimental details, computational details, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding Sources

This work was financially supported by Grants-in-Aid for Early-Career Scientists (22K14682 and 19K15550), the Mitsubishi Foundation, and the TOBE-MAKI Foundation.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Dr. Naoya Inazumi (Osaka Univ.) is acknowledged for the acquisition of the ^{1}H–^{19}F HOESY spectra. This work is the result of using research equipment shared in a MEXT project for promoting public use of advanced research infrastructures (Program for Supporting the Construction of Core Facilities; grant number JPMXS0441200023). The computational study was carried out using SQUID at the Cybermedia Center at Osaka University.

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