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Communication

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Selective Catalytic Formation of Cross-Tetramers from Tetrafluoroethylene, Ethylene, Alkynes, and Aldehydes via Nickelacycles as Key Reaction Intermediates

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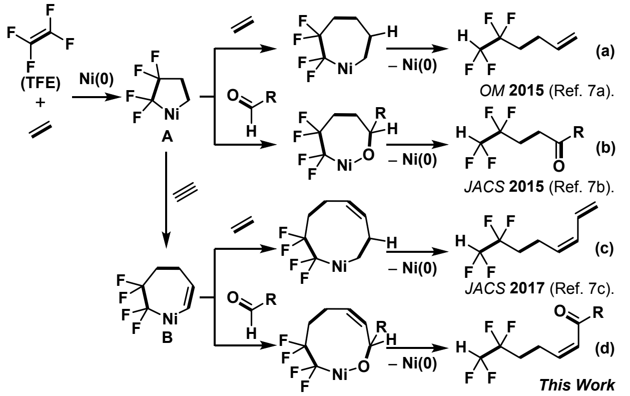
Supporting Information Placeholder

ABSTRACT: In the presence of a catalytic amount of $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) and PCy_3 (Cy = cyclohexyl), the cross-tetramerization of tetrafluoroethylene (TFE), ethylene, alkynes, and aldehydes leads to a variety of fluorine-containing enone derivatives. This reaction is the first example of a highly selective cross-tetramerization between four different unsaturated compounds. Stoichiometric reactions revealed that the present reaction involves partially fluorinated five- and seven-membered nickelacycles as key reaction intermediates.

Oxidative cyclizations with low-valent transition-metal complexes have received increasing attention as a straightforward and environmentally benign route to the construction of C−C bonds between two unsaturated compounds.[1,2] Representative examples are the transition-metal-catalyzed linear trimerization or tetramerization of ethylene to 1-hexene or 1-octene, respectively, via a five-membered metallacycle generated by the oxidative cyclization of two molecules of ethylene.[3] The development of such oligomerizations represents an attractive research target given that α-olefins can be co-polymerized with ethylene to afford polymers with improved properties.[4] On the other hand, transition-metal-catalyzed cross-trimerizations or -tetramerizations of two or more different types of unsaturated compounds allow generating complicated molecular structures in a highly atom-economical manner and a single step. However, the number of hitherto developed selective cross-trimerizations of unsaturated compounds remains low, most likely due to potential side reactions that generate e.g. homo-coupling products.[5] Cross-tetramerizations, especially those using four different unsaturated compounds, have not yet been reported.

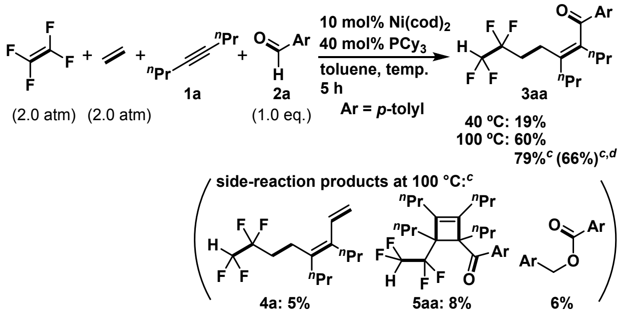
We have been focusing on the usage of tetrafluoroethylene (TFE) as an ideal C2 building block for the introduction of fluorinated functionalized groups, considering that the conventional use of the industrially economical feed stock TFE has been limited mostly to the production of tetrafluoroethylene-based polymers and copolymers with other alkenes.[6–10] We have previously developed chemo- and regio-selective co- or cross-trimerizations of TFE with unsaturated compounds in the presence of a Ni(0) catalyst (Schemes 1a and 1b).[7a,b] More recently, we have discovered an unprecedented Ni(0)-catalyzed cross-tetramerization of TFE, alkynes, and two molecules of ethylene that affords 7,7,8,8-tetrafluoro-1,3-octadiene derivatives (Scheme 1c).[7c] So far, we have rationalized this catalytic reaction in terms of the following reaction sequence: the oxidative cyclization of TFE and ethylene with Ni(0) should yield five-membered nickelacycle **A**, as oxidative cyclizations between electron-rich and -deficient substrates using Ni(0) are in general kinetically much more favorable than those occurring between other substrate combinations.[11] The sequential migratory insertion of an alkyne and a molecule of ethylene into **A** would then lead to a cross-tetramer via seven-membered nickelacycle **B**. The chemoselective generation of **B** from **A** could be caused by the exclusive coordination of the relatively electron-rich and sterically less hindered linear alkynes, especially aliphatic alkynes such as 4-octyne to the Ni(II) center in **A**. Another key feature for the successful development of such cross-tetramerizations is the inability of **B** to undergo not only β-hydride eliminations, but also reductive eliminations that forms new C–C bonds, which is due to the unique inertness of the bonds between transition metals and the perfluoroalkyl ligands.[12] We then envisioned a further expansion of this concept into a chemoselective cross-tetramerization of four different unsaturated compounds, provided that the selective formation of seven-membered nickelacycle **B** can be achieved even in the presence of a fourth unsaturated compound. As aldehydes exhibit a reactivity toward the five-membered nickelacycle **A** that is higher than that of ethylene (Scheme 1b),[7b] a nucleophilic addition of **B** to an aldehyde rather than to ethylene should provide the targeted cross-tetramer (Scheme 1d). Based on this hypothesis, we explored the cross-tetramerization of TFE, ethylene, 4-octyne

Scheme 1. Working hypothesis.



(**1a**), and *p*-tolualdehyde (**2a**) in the presence of a Ni(0) catalyst, which exhibited unprecedentedly high selectivity.

Scheme 2. Ni(0)-catalyzed cross-tetramerization of TFE, ethylene, 4-octyne (1a), and *p*-tolualdehyde (2a).[a,b]

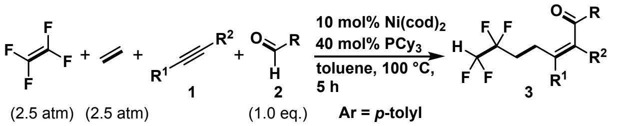


[a] General conditions: **1a** (0.50 mmol), **2a** (0.50 mmol), toluene (1.5 mL). The molar quantities of both gases (c.a. 4.0 mmol at 2.0 atm, room temperature; estimated based on the ideal gas equation) were absolutely larger than those of **1a** and **2a**. [b] The yield of **3aa**, relative to **1a,** was determined by GC analysis using tetradecane as an internal standard. [c] TFE (2.5 atm) and ethylene (2.5 atm) were employed. [d] Isolated yield.

Based on the previously established optimal ligand and ligand/Ni(0) ratio in the cross-tetramerization that leads to the tetrafluoro-1,3-diene derivatives,[7c] a toluene solution of **1a** and **2a** was exposed for 5 h at 40 °C to a gas mixture containing TFE (2.0 atm) and ethylene (2.0 atm) in the presence of $Ni(cod)_2$ and PCy_3 (10 and 40 mol%, respectively). Under these conditions, cross-tetramer **3aa**, a fluorine-containing enone derivative, was formed in 19% yield (Scheme 2). Encouraged by this result, we attempted to optimize the ligands and the ligand/Ni(0) ratio; however, all our attempts confirmed that PCy_3 is indeed the optimal ligand and that the use of 4 equiv of PCy_3 relative to $Ni(cod)_2$ accelerates the catalytic reaction.[13] However, we discovered that the reaction temperature is of paramount importance to this reaction, i.e., increasing the temperature to 100 °C improved the yield of **3aa** to 60%. Moreover, increasing the gas pressure (2.5 atm each) allowed isolating **3aa** in 66% yield (79% GC yield). The crude reaction mixture also contains the three-component cross-tetramer (**4a**; 5%) consisting of TFE, **1a**, and two molecules of ethylene,[7c] the Tishchenko reaction product (6%),[11a] and a cyclobutene derivative (**5aa**; *vide infra*; 8%), whereas another possible α,β-enone derivative via the hydroacylation of **1a** with **2a** is not generated.[14] The thus required purification procedure, which includes column chromatography on silica gel followed by recycling HPLC, is responsible for the relatively low isolated yield of **3aa**. Consequently, the optimal reaction conditions were determined as: 10 mol% $Ni(cod)_2$ and 40 mol% PCy_3 in toluene at 100 °C under an atmosphere of a gas mixture of TFE and ethylene (2.5 atm each).[13] It should be emphasized that an equimolar mixture of the alkyne and aldehyde is sufficient to facilitate the desired cross-tetramerization, which stands in stark contrast to another type of selective four-component cross-tetramerization with TFE, styrene, alkynes, and ethylene.[7c,d] In the catalytic reaction with styrene, the formation of a kinetically less favored five-membered nickelacycle generated by the oxidative cyclization of TFE and styrene with Ni(0) requires the use of an excess of styrene.

With the optimal reaction conditions in hand, we investigated the scope and the limitations of this Ni-catalyzed cross-tetramerization with respect to the alkyne substrates (Scheme 3a). The use of symmetrical aliphatic alkynes, such as **1a**, 3-hexyne (**1b**), 5-decyne (**1c**), and 6-undecyne (**1d**), furnished the desired cross-tetramers (**3aa-3da**), while unsymmetrical alkynes (**1e** and **1f**) yielded a mixture of regioisomers (**3ea** and **3fa**) with poor selectivity. The use of 1-phenyl-1-hexyne (**1g**) afforded the desired product (**3ga**) with moderate regioselectivity, albeit that the yield was low. When tolan (**1h**) was used, the desired cross-tetramer (**3ha**) was not obtained due to the occurrence of trimerization of **1h** and the Tishchenko reaction of **2a** prior to the gas pressurization.[15] An attempt at employing (η^2-$CF_2{=}CF_2)Ni(PCy_3)_2$ (**6**)[8d] as a catalyst precursor in this cross-tetramerization of TFE, ethylene, **1h**, and **2a** was conducted in anticipation of suppressing the advance consumption of **1h** and **2a**, however, the target product **3ha** was not obtained.

Scheme 3. Ni(0)-catalyzed cross-tetramerization of TFE, ethylene, alkynes (1), and aldehydes (2).[a,b]



a) Scope of alkynes (aldehyde = 2a (R = *p*-tolyl))

3ba ($R^1 = R^2 =$ Et): 54%
3ca ($R^1 = R^2 = {}^n$Bu): 63%
3da ($R^1 = R^2 = {}^nC_5H_{11}$): 53%
3ea ($R^1 = {}^n$Pr, R^2 = Me): 40% [56/44][c]
3fa ($R^1 = {}^nC_7H_{15}$, R^2 = Et): 54% [52/48]
3ga ($R^1 = {}^n$Bu, R^2 = Ph): (37%) [67/33]
3ha ($R^1 = R^2$ = Ph): (0%)

b) Scope of aldehydes (alkyne = 1a ($R^1 = R^2 = {}^n$Pr))

3ab (R = Ph): 41%
3ac (R = *m*-tolyl): 48%
3ad (R = *o*-tolyl): (13%)
3ae (R = *3,5*-$Me_2C_6H_3$): 62%
3af (R = *3,5*-${}^tBu_2C_6H_3$): 83%
3ag (R = *3,5*-$(MeO)_2C_6H_3$): 20%
3ah (R = *4*-anisyl): 57%
3ai (R = *4*-$NMe_2C_6H_4$): 33%
3aj (R = *4*-FC_6H_4): 47%
3ak (R = *4*-$MeCO_2C_6H_4$): 71%[d]
3al (R = *4*-$CF_3C_6H_4$): 38%
3am (R = *4*-$BpinC_6H_4$): 58%
3an (R = *3*-vinylC_6H_4): 27%
3ao (R = *4*-$(EtOEt)_2CHC_6H_4$): 42%
3ap (R = *4*-PhC_6H_4): 48%
3aq (R = *1*-naphthyl): (7%)
3ar (R = *2*-naphthyl): 42%
3as (R = *2*-fluorenyl): 52%
3at (R = *2*-thienyl): 80%
3au (R = *2*-benzothienyl): 81%
3av (R = *3*-benzothienyl): 22%[e]
3aw (R = *2*-furyl): 76%
3ax (R = *2*-benzofuryl): 29%
3ay (R = *3*-dibenzo[*b,d*]furyl): 56%
3az (R = *1*-methyl-2-pyrrolyl): 35%[f]
3aa' (R = *trans*-cynnamyl): 54%

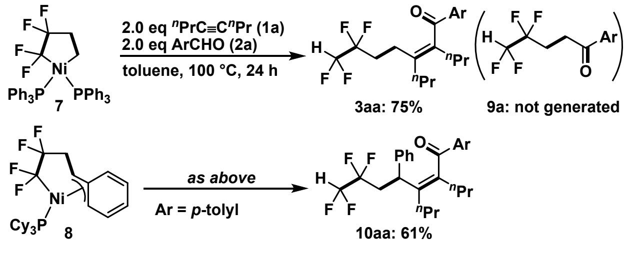
[a] General conditions: $Ni(cod)_2$ (0.05 mmol), PCy_3 (0.20 mmol), alkynes (**1**; 0.50 mmol), aldehyde (**2**; 0.50 mmol), TFE (2.5 atm), ethylene (2.5 atm), and toluene (1.5 mL). [b] Isolated yield. The GC yield is given in parentheses. The ratio of regioisomers is given in square brackets. [c] 20 mol% $Ni(cod)_2$ and 80 mol% PCy_3. [d] 20 mol% $Ni(cod)_2$, 80 mol% PCy_3, and **2k** (0.75 mmol; 1.5 eq.). [e] 20 mol% $Ni(cod)_2$, 80 mol% PCy_3, and **2v** (1.00 mmol; 2.0 eq.), 24 h. [f] 20 mol% $Ni(cod)_2$ and 80 mol% PCy_3, 24 h. The product was a mixture of *E/Z* isomers (54/46).

Subsequently, we explored the substrate scope with respect to various aldehydes (Scheme 3b). Benzaldehyde (**2b**) and *m*-tolualdehyde (**2c**) furnished the corresponding cross-tetramers (**3ab** and **3ac**) in 41% and 48% yields, respectively, while *o*-tolualdehyde (**2d**) afforded a diminished yield, which is probably due to its increased steric demand. In the reactions with 3,5-disubstituted benzaldehydes, 3,5-dimethylbenzaldehyde (**2e**) and 3,5-di-*tert*-butylbenzaldehyde (**2f**) yielded the corresponding cross-tetramers (**3ae** or **3af**) in 62% and 83% yield, respectively, whereas 3,5-dimethoxybenzaldehyde (**2g**) hampered the cross-tetramerization. 4-Anisaldehyde (**2h**), 4-dimethylaminobenzaldehyde (**2i**), 4-fluorobenzaldehyde (**2j**), and methyl 4-formylbenzoate (**2k**) afforded the corresponding cross-tetramers (**3ah-3ak**) in 57%, 33%, 47%, and 71% yield, respectively. However, using 4-trifluoromethylbenzaldehyde (**2l**) yielded the desired cross-tetramerization product (**3al**) in 38% yield together with a considerable amount of **4a** (55% GC yield in the crude mixture). Using *p*-boronate-substituted benzaldehyde **2m** furnished the corresponding cross-tetramer (**3am**) in 58% yield, and the boronate moiety could be used in subsequent cross-coupling reactions to synthesize highly functionalized derivatives. In addition, reactions employing 3-vinylbenzaldehyde (**2n**), 4-(diethoxymethyl)benzaldehyde (**2o**), and 4-phenylbenzaldehyde (**2p**) also afforded the corresponding cross-tetramers (**3an**–**3ap**). The use of 1-naphthaldehyde (**2q**) hampered the reaction due to steric congestion, whereas reactions using 2-naphthaldehyde (**2r**) and 2-fluorenecarboxaldehyde (**2s**) afforded the corresponding cross-tetramers (**3ar** and **3as**) in moderate yields. The use of 2-naphthaldehyde-d_1 (**2r-*d***; 99% D) yielded the corresponding cross-tetramer (**3ar-*d***; 99% D) with a $-CF_2CF_2D$ motif in 45% yield. In this catalytic system, thienyl aldehydes (**2t-2v**) and furyl aldehydes (**2w-2y**) are also applicable. Among these, 2-thiophenecarboxaldehyde **2t** and benzo[*b*]thiophene-2-carboxaldehyde **2u** yielded the cross-tetramers (**3at** and **3au**) in excellent yield (**3at**: 80% isolated and 98% GC yield; **3au**: 81% isolated and 98% GC yield). On the other hand, the reaction using 1-methyl-2-pyrrolecarboxaldehyde (**2z**) was slow and only a small amount of the targeted product (**3az**) was isolated from the crude reaction mixture. Moreover, the use of 2-pyridinecarboxaldehyde did not yield the desired cross-tetramer. Aliphatic aldehydes, such as octanal, cannot be used in this catalytic reaction due to the formation of **4a**. Conversely, *trans*-cinnamaldehyde (**2a'**) engages in the reaction, leading to the desired cross-tetramer (**3aa'**) in 54% yield.[15] It should be noted that, in the reactions that afford the target product **3** in relatively low yield, the starting materials of **1a** and **2** were fully consumed as a result of the undesired formation of **4a**, **5**, and the Tishchenko reaction product.

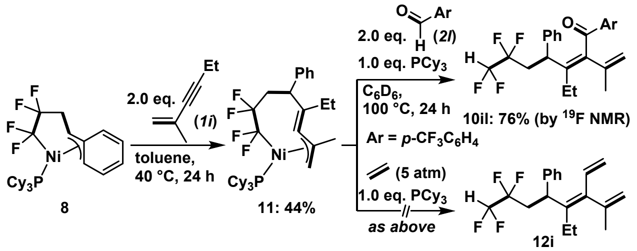
To gain deeper insight into the reaction mechanism as well as the origin of the unique chemoselectivity in this cross-tetramerization, several stoichiometric reactions were carried out. The treatment of either $(CF_2CF_2CH_2CH_2)Ni(PPh_3)_2$ (**7**)[7a] or $(\eta^1{:}\eta^3\text{-}CF_2CF_2CH_2CH\text{-}Ph)Ni(PCy_3)$ (**8**)[7d] with 2 equiv of **1a** and **2a** in toluene at 100 °C for 24 h led to the formation of the corresponding cross-tetramers **3aa** and **10aa** in 75% and 61% yield, respectively (Scheme 4). It should be emphasized that in the former reaction, an expected cross-trimer (**9a**) that consists of TFE, ethylene, and **2a** was not generated, which stands in contrast to our previous observation that the corresponding cross-trimer (**9b**) was obtained from the reaction of **7** with benzaldehyde **2b**.[7b] This result clearly supports the notion that the insertion of the alkyne into the Ni–CH_2 bond of the five-membered nickelacycle is much faster than that of the aldehyde.[16]

We once again conducted a stoichiometric reaction of **8** with 2 equiv of 2-methyl-1-hexen-3-yne (**1i**) in order to trap a potential seven-membered nickelacycle intermediate with an η^3-butadienyl moiety,[17,18] although attempts to isolate the nickelacycles from the reactions of **8** with **1a** or **1h** have failed due to the occurrence of α-fluorine elimination to yield Ni(II) fluoride species.[7c,19] As a result, we managed to isolate the corresponding seven-membered nickelacycle (**11**) in 44% yield, and its molecular structure was unambiguously determined by X-ray diffraction analysis (Scheme 5, Figure 1). Further treatment of **11** with 2 equiv of **2l** in the presence of an equimolar amount of PCy_3 in C_6D_6 at 100 °C for 24 h afforded the corresponding four-component cross-tetramer (**10il**) in 76% yield. In contrast, complex **11** exhibited lower reactivity toward ethylene, i.e., the reaction of **11** with ethylene (5 atm) did not furnish the corresponding cross-tetramer (**12i**). These results are consistent with our working hypothesis (Scheme 1). The formation of the side-reaction product **5aa** was rationalized based on the results of a stoichiometric reaction between **6**, 4 equiv of **1a**, and 2 equiv of **2a**, which afforded **5aa** in 53% isolated yield as a mixture of diastereoisomers (Scheme 6). A plausible mechanism for the formation of **5aa** might involve the initial formation of an acyclic dienone derivative (**13**) via a Ni(0)-mediated cross-tetramerization of TFE, two molecules of **1a**, and **2a**, followed by an oxidative cyclization of **13** with Ni(0) and a reductive elimination.[20]

Scheme 4. Stoichiometric reaction of five-membered nickelacycles 7 and 8 with a mixture of 1a and 2a.



Scheme 5. Isolation of a seven-membered nickelacycle (11) via a stoichiometric reaction between 8 and 1i.



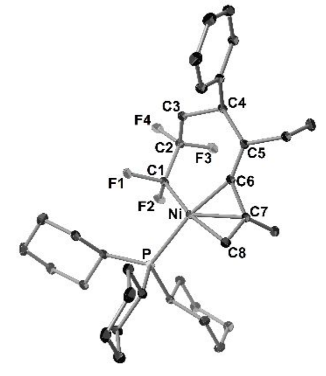
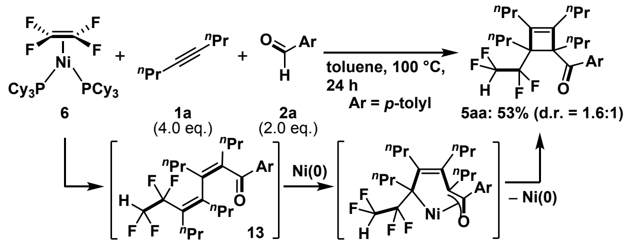


Figure 1. ORTEP representation of **11** with thermal ellipsoids set at the 30% probability level. All hydrogen atoms have been omitted for clarity and only selected atoms are labelled.

Scheme 6. Stoichiometric reaction of (η^2-CF_2CF_2)Ni(PCy_3)$_2$ (6) with a mixture of 1a and 2a.



In conclusion, we have demonstrated that the cross-tetramerization of tetrafluoroethylene, ethylene, alkynes, and aldehydes affords a variety of enone derivatives with fluoroalkyl chains. This is the first example of a highly selective cross-tetramerization using four different unsaturated compounds. The key reaction intermediates are the partially fluorinated five- and seven-membered nickelacycles.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, analytical and spectral data for all new compounds, and a CIF file for **11**. The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(15) For the substrate scope with respect to other substrates in the Ni(0)-catalyzed cross-tetramerization, see the Supporting Information.

(16) Ni(0)-catalyzed cross-tetramerization of TFE, styrene, **1a**, and **2a** was sluggish to afford the desired product **8aa** in 36% yield. See also the Supporting Information in details.

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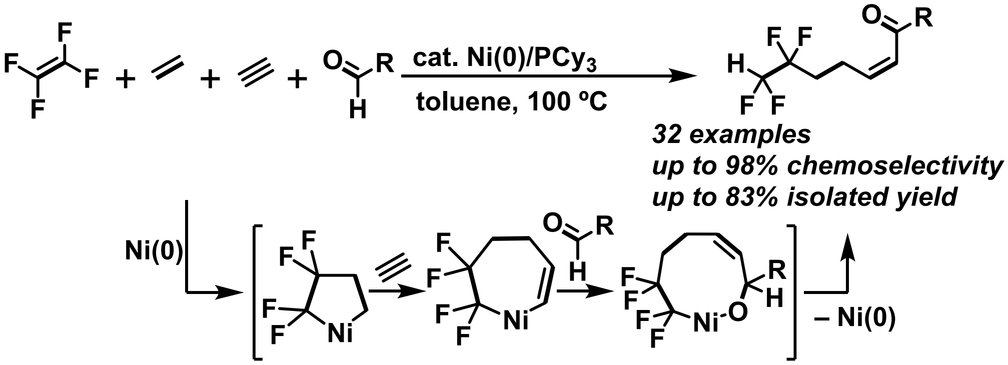
(18) The stoichiometric reaction of **6** with **1i** was also conducted. In addition, attempts at the catalytic cross-tetramerization of TFE, ethylene, **1i**, and **2a** gave a desired cross-tetramer in <1 % yield. See also the supporting information in detail.

(19) We also updated the information regarding the reactivity of the Ni(II) fluoride species,[7c] which are useful for the preparation of fluorinated cyclic compounds. See the Supporting Information in details.

(20) Application of the stoichiometric reaction to a catalytic reaction was conducted. However, even after optimization of reaction conditions, the result was not so fruitful.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