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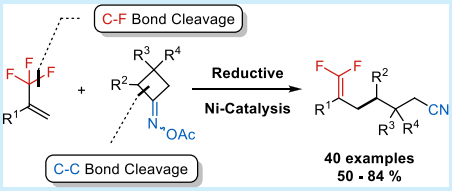
# Synthesis of *gem*-Difluoroalkenes by Merging Ni-Catalyzed C−F and C−C Bond Activation in Cross-Electrophile Coupling

Decai Ding,[†] Yun Lan,[†] Zhiyang Lin,[†] and Chuan Wang*[,†]

[†]Hefei National Laboratory for Physical Science at the Microscale, Department of Chemistry, Center for Excellence in Molecular Synthesis, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 20237, P. R. China

Supporting Information

**ABSTRACT:** By merging C−F and C−C bond activation in the cross-electrophile coupling, we developed an efficient cyanide-free synthesis of diverse functional-group-rich cyano-substituted *gem*-difluoroalkenes using cyclobutanone oxime esters and trifluoromethyl alkenes as precursors. Notably, this Ni-catalyzed reaction is bestowed with broad substrate scope, low catalyst loading, complete regioselectivities, and high tolerance of a wide range of sensitive functional groups. Preliminary mechanistic studies indicate that an iminyl radical-initiated C−C bond cleavage is involved in the reaction pathway.

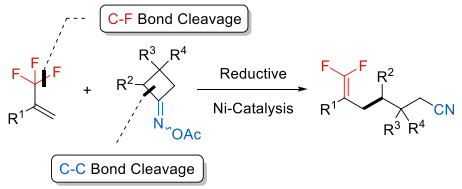





In recent years, cross-electrophile coupling reactions have emerged as a powerful method in organic synthesis toward C−C bond formation.[1] In comparison with the classic traditional cross-coupling reactions using stoichiometric organometallics, cross-electrophile coupling is bestowed with better step economy and higher functional group tolerance. The tremendous advances in this realm focus on the cleavage of relatively weak chemical bonds, such as C−I, C−Br, activated C−Cl, and C−O bonds,[2] whereas the activation of stronger bonds, either C−F[3] or C−C bonds,[4] is rarely involved in this field, let alone their combination.

The synthesis of organofluorine compounds is one of the most important research subjects in pharmaceutical and agrochemical developments.[5] Being the bioisostere of metabolically vulnerable carbonyl compounds, *gem*-difluoroalkenes are of particular interest in drug discovery due to their higher stability in metabolism.[6] Consequently, a number of biologically active compounds containing a *gem*-difluoroalkene moiety have been reported.[7] Furthermore, *gem*-difluoroalkenes are also versatile building blocks for the synthesis of fluorine-containing moieties, such as monofluoromethylene, difluorocyclopropane, and difluoromethyl group.[8] Therefore, organic chemists have made great efforts in the last decades to develop simpler and more efficient methods for the synthesis of structurally diverse *gem*-difluoroalkenes. Conventionally, two successful strategies have been established to access this structural motif. The first approach relies on the functional group conversion, in which carbonyl or diazo compounds were transformed into a difluoromethylene moiety.[9,10] Furthermore, in a convergent strategy, organometallics or strong-base-mediated nucleophilic addition to trifluoromethyl alkenes, followed by $\beta$−F elimination provides an alternative path to *gem*-difluoroalkenes.[11] Recently, both photocatalysis[12] and Ni catalysis[3b−d,13] find applications in the synthesis of *gem*-difluoroalkenes under mild reaction conditions. The C−C bond cleavage of cycloketone oxime esters was successfully employed in a series of C−C and C−heteroatom bond-forming reactions, offering a new entry to synthesize nitriles under cyanide-free conditions.[14,15] Herein, we envisage that both C−C[16] and C−F[17] bond activation could be merged in a Ni-catalyzed cross-electrophile coupling reaction with trifluoromethyl alkenes and strained cyclobutanone oxime esters as precursors, providing an efficient cyanide-free synthesis of diverse cyano-substituted *gem*-difluoroalkenes as products (Scheme 1).

**Scheme 1. Synthesis of Cyano-Substituted *gem*-Difluoroalkenes by Merging C−F and C−C Bond Cleavage in the Ni-Catalyzed Cross-Electrophile Coupling**




For optimization of the reaction conditions of this Ni-catalyzed reaction, we used acetyl-substituted $\alpha$-trifluoromethylstyrene **1a** and $\alpha$-benzyl cyclobutanone *O*-acetyl oxime **2a** as standard substrates (Table 1). Initially, we tested a series of ligands using $NiCl_2$·glyme as the catalyst and Zn as the reductant in DMF at room temperature. When bipyridine and terpyridine ligands **L1**−**3** were employed, the reaction afforded the cross-coupled product **3a** in low to moderate yields (entries 1−3). Notably, the cleavage of the C−C bond occurred on the more-substituted site with complete regiocontrol. In the case of the phenanthroline-based ligand **L4**, no desired product was formed (entry 4). Next, several Ni salts were investigated as catalysts, providing no better yield

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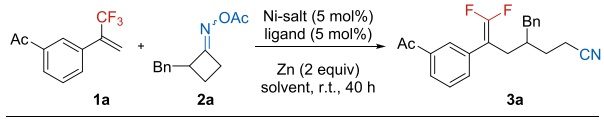
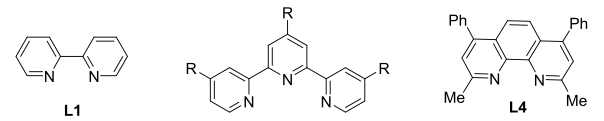
**Table 1. Optimization of the Reaction Conditions for the Ni-Catalzyed Cross-Coupling Reaction**[a]




**L2** R= H; **L3** R= *t*Bu.

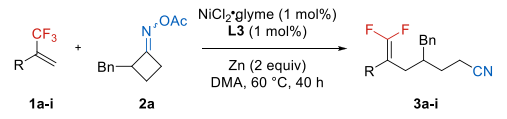
| entry | metal−salt | ligand | solvent | yield (%)[b] |
|---|---|---|---|---|
| 1 | $NiCl_2$·glyme | **L1** | DMF | 13 |
| 2 | $NiCl_2$·glyme | **L2** | DMF | 22 |
| 3 | $NiCl_2$·glyme | **L3** | DMF | 49 |
| 4 | $NiCl_2$·glyme | **L4** | DMF | 0 |
| 5 | $Ni(COD)_2$ | **L3** | DMF | 18 |
| 6 | $NiBr_2$ | **L3** | DMF | 40 |
| 7 | $Ni(acac)_2$ | **L3** | DMF | trace |
| 8 | $NiCl_2$·glyme | **L3** | MeCN | 25 |
| 9 | $NiCl_2$·glyme | **L3** | THF | 16 |
| 10 | $NiCl_2$·glyme | **L3** | DMA | 56 |
| 11[c] | $NiCl_2$·glyme | **L3** | DMA | 0 |
| 12[d] | $NiCl_2$·glyme | **L3** | DMA | trace |
| 13[e] | $NiCl_2$·glyme | **L3** | DMA | 73 |
| **14**[e,f] | **$NiCl_2$·glyme** | **L3** | **DMA** | **82** |
| 15[g] | $NiCl_2$·glyme | **L3** | **DMA** | 58 |

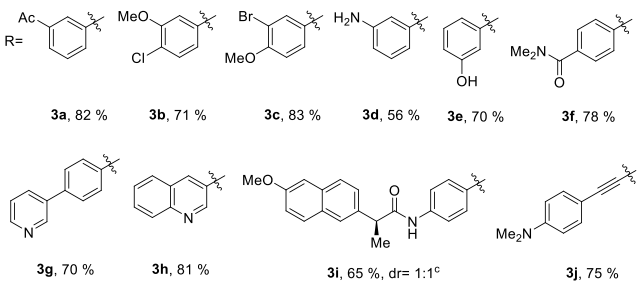
[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of acetyl-substituted $\alpha$-trifluoromethylstyrene **1a** with 2 equiv $\alpha$-benzyl cyclobutanone *O*-acetyl oxime **2a**, 5 mol % nickel-salt, 5 mol % ligand, and 2 equiv Zn as the reductant in 2 mL of solvent at room temperature for 40 h. [b]Yields of the isolated product. [c]Mn was used as the reductant instead of Zn. [d]Reaction was performed at 0 °C. [e]Reaction was performed at 60 °C. [f]Reaction was performed with 1 mol % catalyst and 1 mol % ligand. [g]Reaction was performed with 1 equiv $\alpha$-benzyl cyclobutanone *O*-acetyl oxime **2a**.

(entries 5−7). Moreover, a brief solvent screening was undertaken, and an improved result was obtained in the case of DMA as the solvent (entries 8−10). Replacing Zn by Mn as the reducing agent resulted in a complete shutdown of the studied reaction (entry 11). Furthermore, the temperature impact on this Ni-catalyzed reaction was explored. At 0 °C, the reaction became very sluggish, affording only a trace of product (entry 12). In contrast, increasing the reaction temperature to 60 °C gave rise to a significantly improved efficiency (entry 13). Finally, the yield of the studied reaction was improved to a high level, when the catalyst loading was lowered to 1 mol % (entry 14). Reducing the amount of the oxime ester **2a** to 1 equiv led to a decrease in the yield to 58%.

After establishing the optimal reaction conditions, we started to evaluate the substrate scope of this Ni-catalyzed reductive cross-coupling reaction (Scheme 2). First, we reacted $\alpha$-benzyl cyclobutanone *O*-acetyl oxime (**2a**) with a variety of aryl and heteroaryl-substituted trifluoromethyl alkenes **1a−i**. To our delight, all of the reactions furnished the corresponding cyano-substituted *gem*-difluoroalkenes **3a−i** in moderate to good yield. Notably, these reactions demonstrate good tolerance of diverse functional moieties including ketones (**3a**), halides (**3b** and **3c**), amines (**3d**), hydroxyl group (**3e**), and amides (**3f** and **3i**). Furthermore, alkynyl trifluoromethyl alkene also

**Scheme 2. Evaluation of the Substrate Scope by Variation of the Structure of the Trifluoromethyl Alkenes**[a,b]




[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of $\alpha$-trifluoromethylstyrenes **1** with 2 equiv $\alpha$-benzyl cyclobutanone *O*-acetyl oxime **2a**, 1 mol % $NiCl_2$·glyme, 1 mol % ligand **L3**, and 2 equiv Zn as the reductant in 2 mL of DMA at 60 °C for 40 h. [b]Yields of the isolated products. [c]Determined by $^{13}C$ NMR spectroscopy.

turned out to be suitable for this Ni-catalyzed reaction, affording the product **3j** in a good yield.

Subsequently, we continued to explore the substrate spectrum of this defluorinative reaction by varying the structure of the cyclobutanone oxime esters (Scheme 3). In the case of symmetrical cyclobutanone *O*-acetyl oximes, all of the reactions proceeded smoothly under the optimal conditions, affording the products **3k−t** in moderate to high yield. When unsymmetrical cyclic oxime esters were utilized as precursors, all of the C−C bond cleavages occurred selectively at the more substituted carbon center, furnishing the products **3u−aj** in good to high yield. Remarkably, in the case of the *cis*-bi-, and tri-cyclic oxime esters as substrates, only the formation of trans-configurated products **3x−aj** was observed, suggesting a complete conversion of the stereochemistry of the newly formed stereocenter. Furthermore, a 10 mmol scale reaction was performed, providing the product **3k** in a similar yield, wherein the catalyst loading could be reduced to 0.5 mol %. Unfortunately, the reactions using cyclopentanone- and cyclohexanone-derived oxime esters as precursors failed to yield the ring-opening products.

Next, we tested the application of our methodology in the reactions involving some structurally complex trifluoromethyl alkenes or cyclobutanone oxime esters, which derive from gemfibrozil, estrone, stigmasterol, and vitamin E. To our delight, all of the reactions afforded the desired products in moderate to good yield (Scheme 4).

Furthermore, some derivatizations based on the conversion of the cyano and *gem*-difluoroalkene moieties were carried out (Scheme 5). The hydrolysis of **3k** under basic conditions delivered a carboxylic acid **4** and an amide **5** in good yield, respectively. The diisobutylaluminum hydride (DIBAL-H)-mediated reduction at −78 °C afforded an aldehyde **6** with high efficiency. In addition, the difluoromethylene moiety was successfully converted to a difluoromethyl group via a Pd/C-catalyzed hydrogenation.

A series of control experiments were carried out to explore the mechanism of this Ni-catalyzed reaction (Scheme 6). First, a stoichiometric reaction of $Ni(COD)_2$ with the trifluor-



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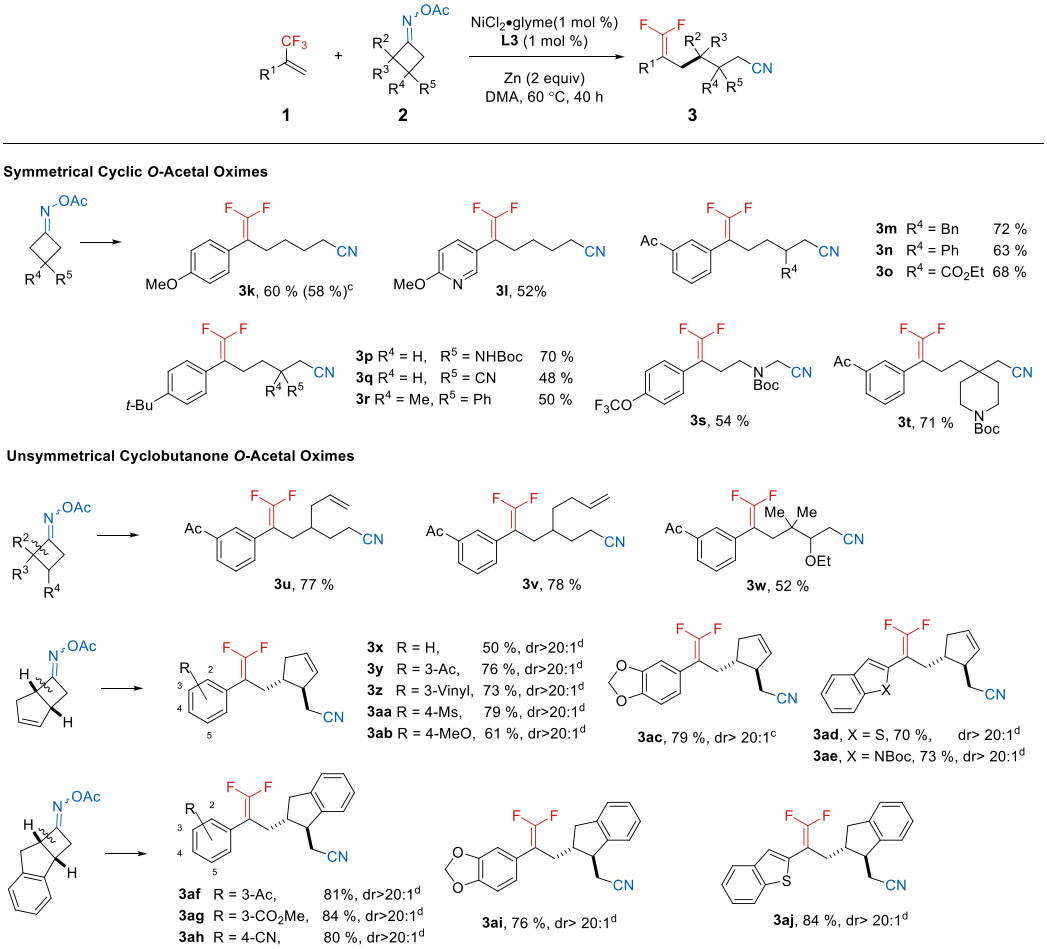
**Scheme 3. Evaluation of the Substrate Scope by Variation of the Structure of the Cycloketone *O*-Acetyl Oximes**[18 a,b]




[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of trifluoromethyl alkenes **1** with 2 equiv cyclobutanone *O*-acetyl oximes **2**, 1 mol % $NiCl_2$·glyme, 1 mol % ligand **L3**, and 2 equiv Zn as the reductant in 2 mL of DMA at 60 °C for 40 h. [b]Yields of the isolated products. [c]Reaction was performed on a 10 mmol scale using 0.5 mmol % catalyst loading. [d]Determined by $^{13}C$ NMR spectroscopy.

omethyl alkene **1a** and the oxime ester **2a** in the absence of a reducing agent was carried out, providing the coupling product **3a** in a moderate yield (Scheme 6A). This result indicates that the Zn powder can serve as a terminal reductant in this reaction. In our previous work, it was discovered that Ni(0) species does not react with acyclic oxime esters.[19] Thus we wonder if strained cyclic oxime esters are also inert in the presence of Ni(0) complex. To verify this, we performed the stoichiometric reaction between $Ni(COD)_2$ and the oxime ester **2a** (Scheme 6B). In contrast, a full consumption of **2a** was observed, and the ring opening product 5-phenylpentanenitrile was afforded in a moderate yield after the reaction was quenched with water. It is known that transition-metal-promoted ring opening of cycloketone oxime esters can proceed via either two-electron *β*-carbon elimination[15a,b] or iminyl radical-initiated ring opening.[15c−o] To find out the actual pathway of the studied reaction, we conducted the stoichiometric reaction of the cyclic ketone ester **2n** and $Ni(COD)_2$ with TEMPO as a radical scavenger (Scheme 6C). In this case, the TEMPO adduct **8** was obtained in a moderate yield, suggesting the formation of a carbon-centered radical in the reaction mixture, which is generated through the iminyl radical-initiated C−C bond cleavage. The aforementioned results imply that the Ni(0) species is probably responsible for the ring opening of cyclobutanone *O*-acetyl oximes. However, we cannot exclude the possibility that an in situ generated Ni(I) complex is the actual species inducing the radical-type ring opening because the Ni(I) species is known to produce alkyl radicals through interaction with alkyl halides.[20]

Next, a sequential stoichiometric reaction was conducted by adding the trifluoromethyl alkene **1b** to the premixed oxime ester **2b**, ligand **L3**, and $Ni(COD)_2$ in DMA. However, the cross-coupled product **3k** was not formed in this case (Scheme 3D). The rapid H-radical abstraction of the carbon-centered radical prior to the addition of **1b** might account for this result. Subsequently, we continued to explore the interaction between the catalyst and the trifluoromethyl alkenes. According to our previous work,[3b,c] Ni(0) species can likely form a complex with trifluoromethyl alkenes using pyridine-based ligands, whereas Ichikawa et al. discovered the formation of nickelacyclopropane in the reaction between $Ni(COD)_2$ and a trifluoromethyl alkene using a phosphine ligand.[13,21] Moreover, we wonder how trifluoromethyl alkenes interact with the Ni(I) species, which is probably also available in the reaction mixture under the reductive conditions. Thus we performed the stoichiometric reaction employing trifluoromethylalkene **1b** and $NiCl_2$·glyme with Zn as the reductant (Scheme 6E). In this case, the hydrogenated product **9** was furnished in a moderate yield, implying the formation of a nickelacyclopropane through the interaction between an in situ generated Ni(I) species and the



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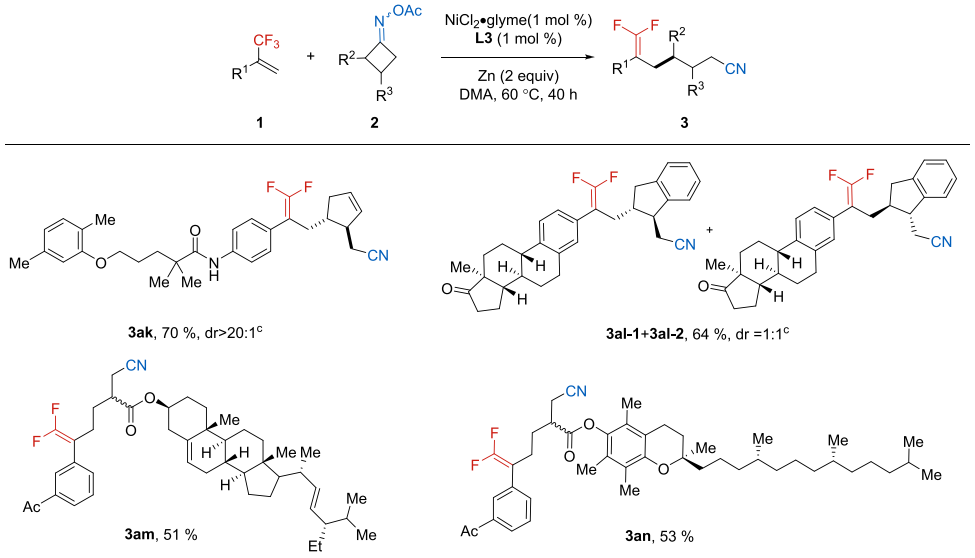
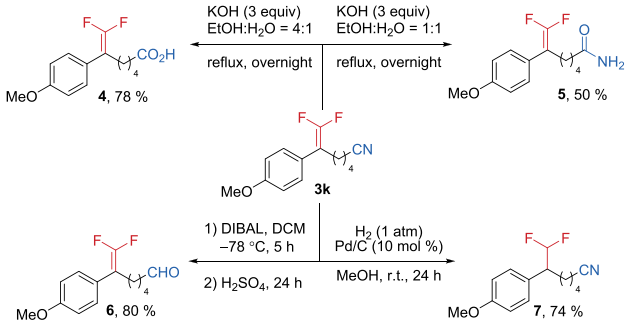
**Scheme 4. Cross-Coupling Reaction Involving Structurally Complex Trifluoromethyl Alkenes or Cyclobutanone Oxime Esters**[a,b]

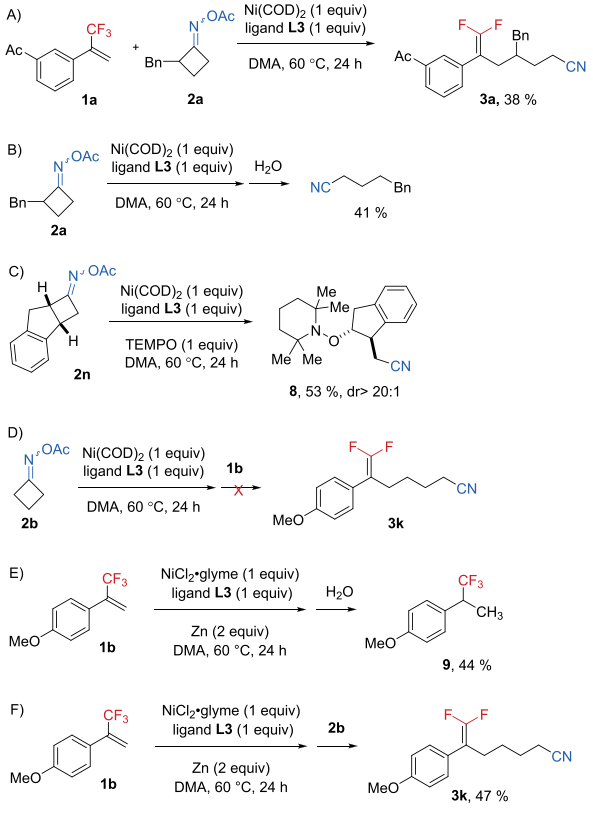



[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of trifluoromethyl alkenes **1** with 2 equiv cyclobutanone *O*-acetyl oximes **2**, 1 mol % $NiCl_2$·glyme, 1 mol % ligand **L3**, and 2 equiv Zn as the reductant in 2 mL of DMA at 60 °C for 40 h. [b]Yields of the isolated products. [c]Determined by $^{13}C$ NMR spectroscopy.

**Scheme 5. Derivatizations of a Ni-Catalyzed Defluorinative Cross-Coupling Product**




**Scheme 6. Control Experiments**




trifluoromethyl alkene **1b**. When the oxime ester **2b** was added to the mixture instead of water, the desired product **3k** was provided in a moderate yield, revealing that a catalytic cycle with the interaction between trifluoromethyl alkenes and Ni catalyst as the initial step is feasible.

On the basis of the experimental results and previous reports, we proposed two plausible mechanisms for this Ni-catalyzed reaction (Scheme 7). The main difference between them lies in the way the radicals add to the olefinic unit in the C−C bond-forming step, which can proceed either off or on the Ni catalyst. The first catalytic cycle is initiated by the interaction of a Ni(0) species **I** with cyclobutanone oxime ester **2** (Scheme 4A). The generated iminyl radical **II** undergoes the ring-opening reaction, providing a C-centered radical **III**. The subsequent radical addition of **III** to trifluoromethyl alkene **1** without the participation of a Ni catalyst affords a relatively electron-deficient *α*-trifluoromethyl carbon-radical **IV**, which tends to perform the radical addition to the Ni(I) species **V**. Next, the *β*-fluoro elimination on the resultant Ni(II) intermediate **VI** provides the *gem*-difluoroalkene **3** as the product and a Ni(II) species **VII**, which is reduced by Zn to regenerate the Ni(0) species **I** for the next catalytic cycle. The seminal work of Zhou and Molander revealed that alkyl radicals are able to perform the addition to trifluoromethyl alkenes in polar aprotic solvent in the absence of Ni, which supports the mechanism mentioned above.[12] Alternatively, the reaction can start with the complexation of trifluoromethyl alkene **1** with the Ni(0) species **I** (Scheme 4B). The afforded Ni(0) complex **VIII** interacts with cyclobutanone oxime ester



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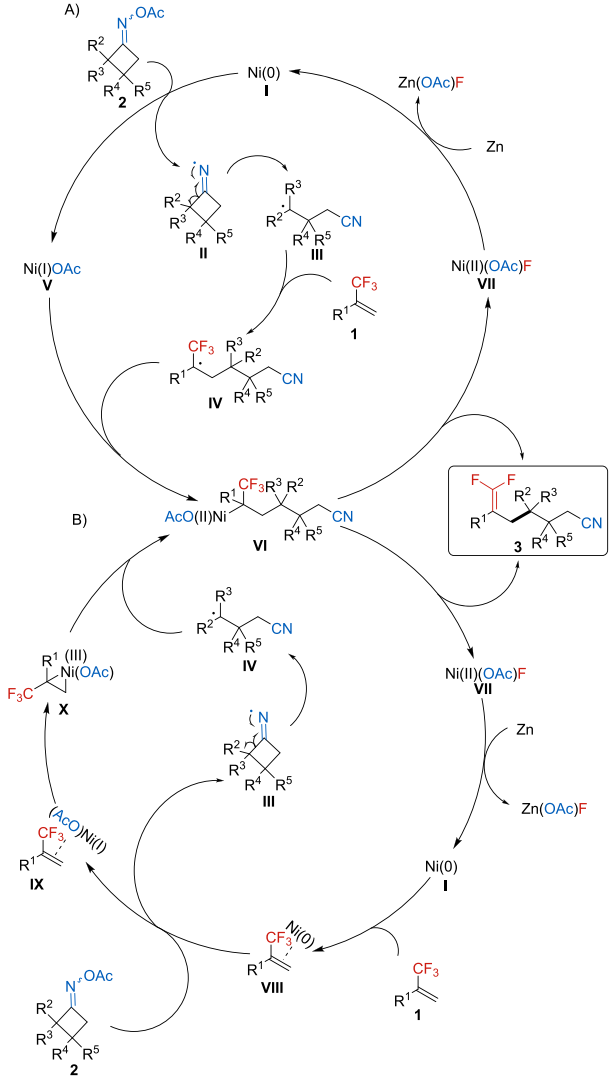
**Scheme 7. Proposed Mechanisms of the Ni-Catalyzed Reaction**




**2** to initiate the radical-mediated C−C bond cleavage. Meanwhile, the produced Ni(I) complex **IX** undergoes the oxidative addition to form a nickelacyclopropane **X**. The subsequent reductive ring opening of **X** leads to the formation of the Ni(II) intermediate **VI**. The following *β*-fluoro elimination furnishes the coupling product **3**. In the final step, Zn-mediated terminal reduction of **VII** regenerates the Ni(0) species **I**.

In summary, a Ni-catalyzed cross-electrophile coupling of cycloketone oxime esters with trifluoromethyl alkenes has been accomplished through merging C−F and C−C bond activation. This new method offers efficient access to prepare various cyano-substituted *gem*-difluoroalkenes under cyanide-free conditions, featuring a broad substrate scope, low catalyst loading, complete regiocontrol, and high tolerance of a wide range of sensitive functional moieties. Two different versions of the reaction mechanism were proposed based on experimental results and previous reports, and Ni-mediated generation of iminyl radicals leading to the subsequent C−C bond cleavage is involved in both cases.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00692.

Representative experimental procedures and necessary characterization data for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: chuanw@ustc.edu.cn.

### ORCID

Chuan Wang: 0000-0002-9219-1785


### Notes

The authors declare no competing financial interest.

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