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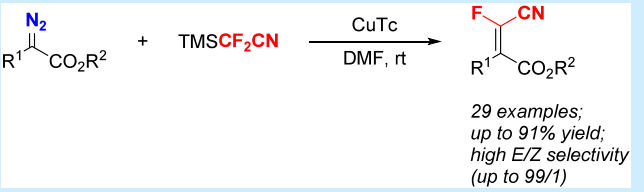
Copper-Mediated Selective Cyanofluoroolefination of Diazo Compounds with $TMSCF_2CN$

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ABSTRACT: Fluorinated alkene-containing molecules are of growing importance in pharmaceutical and agrochemical applications. Herein, we describe a copper-mediated defluorinative coupling of $TMSCF_2CN$ with diazo compounds under mild conditions, providing straightforward access to highly E/Z-selective cyanofluoroalkenes. This method features broad functional group compatibility and is amenable to the late-stage functionalization of complex molecules. Furthermore, the presence of the cyano group offers a versatile handle for further derivatization of the resulting cyanofluoroalkene products.

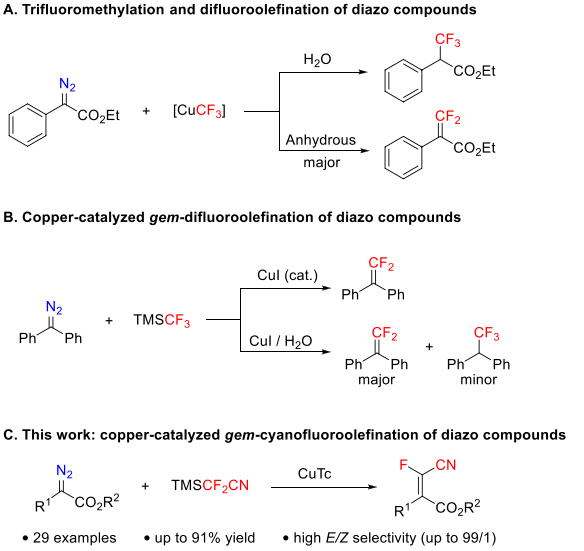


Fluorinated molecules are widely utilized in pharmaceuticals, materials, and agrochemicals, owing to their distinctive physicochemical characteristics including high lipophilicity, enhanced bioavailability, and improved stability.[1] Among the diverse array of fluorine-containing structural units, fluorinated olefins have drawn considerable interest due to their unique features and significant potential in synthetic applications. In particular, monofluoroalkenes have gained prominence in drug design as effective bioisosteres for amide bonds.[2] These compounds are commonly found in biologically active molecules, exemplified by the cytidine nucleotide reductase inhibitor tezacitabine and various fluoroquinolone antibiotic analogues.[3] As a result, the development of synthetic methods for the construction of monofluoroalkenes has become a research topic of growing interest.

2-Fluoroacrylonitriles represent a unique structural framework that underlies a variety of biologically active compounds.[4] The cyano group embedded in this motif can function as a bioisostere of carbonyl, hydroxyl, and some hydrogen-bond accepting groups, as well as a versatile handle for further transformation to amines, carbonyls, and carboxylic acids.[5] Current synthetic strategies for accessing 2-fluoroacrylonitriles include the defluoro-cyanation of *gem*-difluoroalkenes[6] and the Horner−Wadsworth−Emmons (HWE) olefination.[7] Nevertheless, these approaches are often constrained by several drawbacks, such as limited substrate scope, reliance on prefunctionalized olefination precursors, the use of highly toxic cyanating agents (e.g., TMSCN), and insufficient control over stereoselectivity (often leading to undesired stereoisomeric mixtures).

Previously, our group developed a series of fluoroalkylation/olefination reactions employing preformed or *in situ* generated fluoroalkylcopper reagents. In one instance, we achieved a copper-mediated trifluoromethylation using water as a promoter.[8] Mechanistic studies indicated that under anhydrous conditions, the key intermediate (formed via migratory insertion of the trifluoromethyl group into a copper-carbene species) underwent β-fluorine elimination, leading to the formation of a *gem*-difluoroalkene (Scheme 1A). Subsequently, we extended this strategy to a copper-catalyzed *gem*-

Scheme 1. Synthetic Methods Involving Fluoroalkenes with Diazo Compounds



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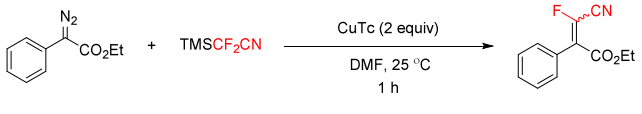
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difluoroolefination of more reactive diaryl diazomethanes.[9] Interestingly, even in the presence of a significant amount of water, the defluorinated *gem*-difluoroalkene remained the major product (Scheme 1B). Furthermore, when pregenerated "$CuCF_2CF_3$" was reacted with diaryl diazomethane, the defluorinated 1-fluoro-1-trifluoromethyl alkene was obtained as the exclusive product.[9]

Moreover, our group has developed a series of controllable fluoroalkyl carbon-chain elongation (CFCE) strategies that enable the incorporation of long-chain fluoroalkyl groups into molecules starting from C1 synthons.[10] The key step in these transformations involves the migratory insertion of fluoroalkyl species into an *in situ* generated copper−difluorocarbene intermediate.[10] Building on our long-time interest in metal-carbene involved fluoroalkylation and fluoroolefination of diazo compounds,[11] we now report a direct cyanodifluoromethylation−defluorination approach for the synthesis of 2-fluoroacrylonitriles using 2,2-difluoro-2-(trimethylsilyl)-acetonitrile ($TMSCF_2CN$) reagent (Scheme 1C).

We began our investigation using diazo compound **1a** as the model substrate and $TMSCF_2CN$ (**2a**) as the fluoroalkylating agent (Table 1).[9] Inspired by previous reports,[8] we initially

Table 1. Optimization of Reaction Conditions



1a **2a** (2 equiv) **3a**

Entry[a]	Deviations from standard conditions	Yield (%)[b]	E/Z
1	none	80	93/7
2	10 h	73	92/8
3	24 h	65	92/8
4	**2a** (1 equiv), CuTc (2 equiv)	74	90/10
5	0 °C	73	91/9
6	**2a** (1 equiv), CuTc (0.1 equiv)	31	89/11
7	**2a** (1 equiv), CuTc (0.5 equiv), 10 h	67	90/10
8	THF as solvent	ND	/
9	DMAc as solvent	83	83/17
10	NMP as solvent	72	87/13

[a]Standard conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.6 mmol, 2.0 equiv) and CuTc (0.6 mmol, 2 equiv) in DMF (4 mL) at 25 °C under N_2 for 1 h. [b]Yields and stereoisomeric ratios were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. ND = not determined.

employed CuI as the copper salt, KF as the initiator, and NMP as the solvent. After generating the fluoroalkylcopper species, diazo compound **1a** was introduced along with H_2O as an additional proton source. Under these conditions, only the defluorinated product **3a** was obtained, and no protonated product was observed—a result that differs significantly from the corresponding trifluoromethylation reaction[8] but aligns with the outcome observed using $CuCF_2CF_3$. This finding suggests that the rate of defluorination to form the olefin intermediate is substantially faster than that of protonation.

After evaluating various copper salts (see the Supporting Information for more details), we selected CuTc as the copper source, which efficiently generates the fluoroalkylcopper species from $TMSCF_2CN$ in high yield without the need for an additional initiator. Pleasingly, conducting the reaction in DMF at room temperature for 1 h afforded the desired product **3a** in 80% yield with high *E*/*Z* stereoselectivity (*E*/*Z* = 93/7; see Table 1, entry 1). Upon extending the reaction time, the yield decreased to 73% after 10 h and 65% after 24 h (entries 2 and 3), indicating the instability of fluorinated alkene **3a** under the reaction conditions. Subsequently, reducing the loading of **2a** to 1 equiv led to a slight decrease in yield (entry 4). Temperature screening revealed that lowering the reaction temperature had little effect on either the yield or the stereoselectivity (entry 5). A decreased copper salt loading resulted in a diminished yield, indicating that while the reaction can proceed under catalytic conditions, it does so with lower efficiency (entries 6 and 7). Solvent screening revealed that the less polar solvent THF failed to deliver the desired product **3a**, whereas more polar solvents afforded the target compound in good to high yields (72−83%, entries 8−10), albeit with a slight decrease in stereoselectivity.

With the optimized conditions in hand (Table 1, entry 1), we evaluated the scope of diazo compounds for this cyanofluoroolefination reaction (Scheme 2). Switching the ester group from ethyl to methyl, isopropyl, or *tert*-butyl resulted in no significant changes in either yield or selectivity, indicating that the reaction is insensitive to the steric bulkiness of the ester group adjacent to the carbenic carbon (**3a**−**3d** and **3j**−**3l**). In contrast, *ortho* substitution on the aromatic ring imposed a slightly higher steric effect (**3e** and **3f**), which is consistent with previously reported trifluoromethylation.[9] Notably, aryl α-diazo esters bearing moderately electron-donating groups on the aromatic ring exhibited higher efficiency than their highly electron-rich and electron-deficient counterparts (**3e**−**3m**). The reaction was compatible with the halogen substituents (F, Cl, Br) on the arene ring, affording the desired products in moderate to good yields (**3o**−**3w**). Naphthyl- and thienyl-substituted diazo esters were both amenable to the reaction, providing the corresponding products in moderate yields comparable to those of their phenyl analogues (**3x** and **3y**). Slightly decreased yields were observed for aryl α-diazo esters bearing bulky substituents at the ortho position of the aromatic ring (**3z** and **3aa**). Further investigation revealed that more complex ester groups had little influence on the yield (**3ab** and **3ac**).

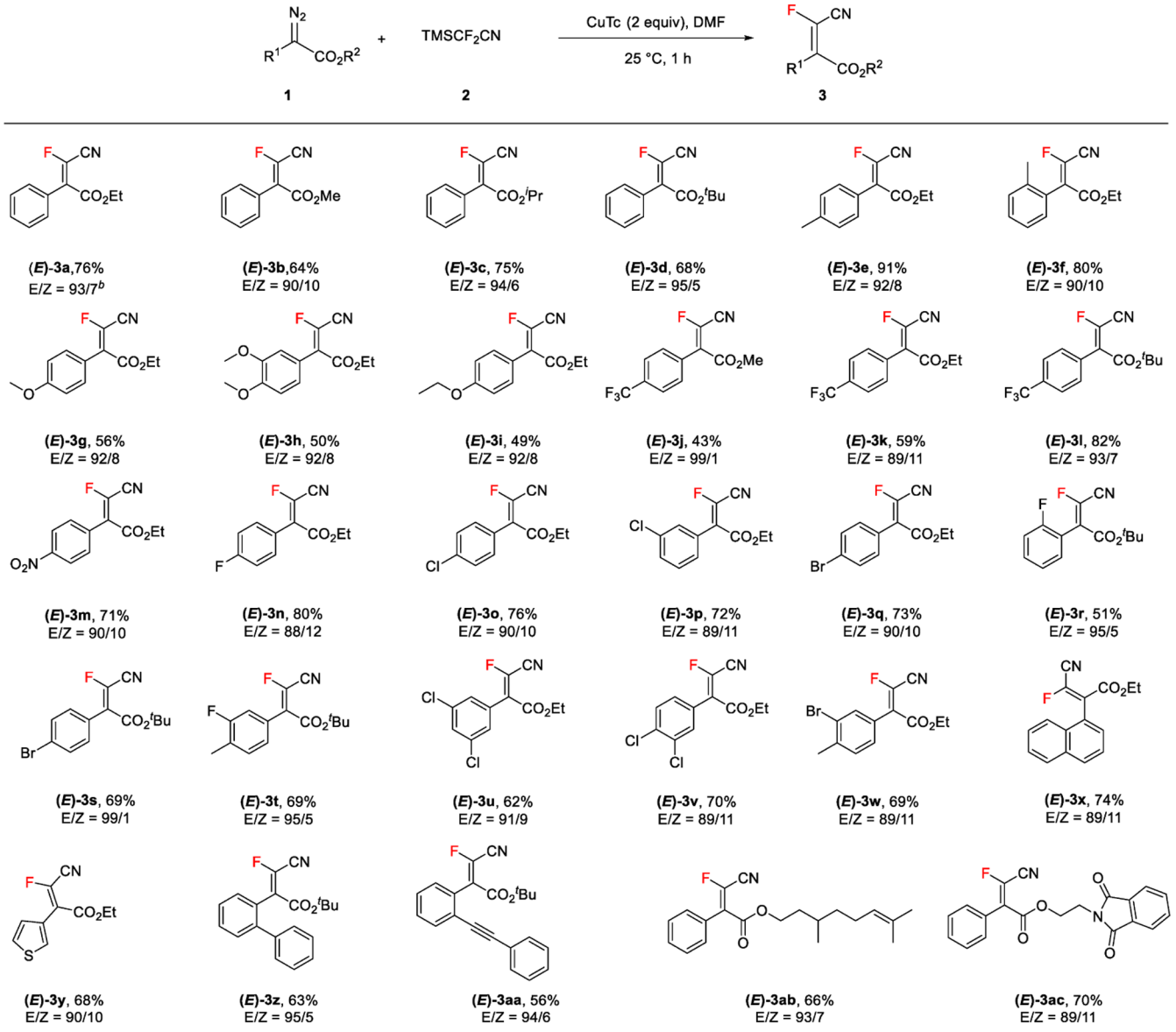
Furthermore, a gram-scale experiment afforded the target product (*E*)-**3e** in 78% isolated yield (1.09 g scale), demonstrating the excellent robustness and practicality of the current strategy. Finally, diverse transformations of product (*E*)-**1e** further validated the synthetic utility of this method. Under sulfuric acid-assisted hydrolysis, compound (*E*)-**1e** reacted with methanol to afford diester **4a** in 33% yield (Scheme 3B). Treatment of (*E*)-**1e** with $NaBH_4$ led to the defluorinated product (*Z*)-**4b**, where fluorine serves as an acrylonitrile protecting group to mask the α-position (Scheme 3C).

To gain deeper insight into the stereoselectivity of this cyanofluoroolefination reaction, density functional theory (DFT) calculations (M06-D3/Def2-TZVPP//B3LYP-D3BJ/6-311+G(d,p)-SDD(Cu) level) were performed to elucidate the reaction mechanism (Scheme 4) (see the Supporting Information for details). Initially the energies of *Z*/*E* isomers were calculated, revealing that the *E* isomer is more stable ($\Delta\Delta G_f$ = +0.7 kcal/mol, Scheme S1). We propose that the E/Z selectivity of the product is not directly governed by thermodynamic factors. We subsequently computed the potential energy surface for the cyanofluoroolefination reaction (Scheme 4). Starting with the migration−insertion step from

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Scheme 2. Substrate Scope of the Monofluoroolefination Reaction[a]



[a]Reaction conditions: **1** (0.3 mmol, 1.0 equiv), **2** (0.6 mmol, 2.0 equiv) and CuTc (0.6 mmol, 2.0 equiv) in DMF (4 mL) at 25 °C under N_2 atmosphere. Unless other mentioned, yields refer to isolated products on a 0.3 mmol scale. The configurations of *E*- and *Z*-isomers were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b]The configurations of *E*- and *Z*-isomers were determined by ^{1}H-^{19}F heteronuclear Overhauser effect spectroscopy (HOESY).

IM-A, we found that rotation about the C−Cu bond requires only +1.0 kcal/mol, whereas the migratory insertion itself has a much higher barrier. These kinetic parameters are consistent with a Curtin−Hammett-type analysis, in which the stereochemical outcome is determined by the relative transition-state energies; accordingly, the product derived from **TS-A** is predicted to be kinetically favored. We then extended this analysis to **IM-B**, where the rotation barrier about the C−C bond is significantly higher (+12.0 kcal/mol) than that observed for **IM-A** (+1.0 kcal/mol). This pronounced increase can be rationalized by the negative hyperconjugation effect[12,13] (for details, see Scheme S4 in the Supporting Information), which enhances the C−C π-bond character and thus hinders rotation.

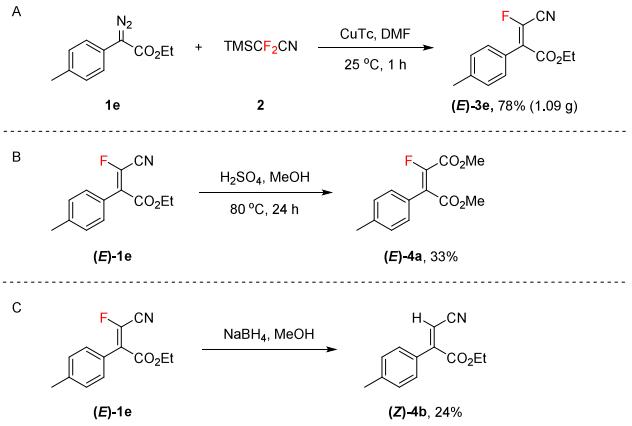
In 2019, Hoveyda and co-workers reported a mechanistic study of a copper-catalyzed Cu−F β-elimination reaction.[14] In this work, the *syn*-Cu−F β-elimination experienced a higher barrier than the Lewis acid-promoted *anti*-Cu−F β-elimination. Inspired by these results, the two energy barriers of the Cu−F β-elimination of **IM-B** were compared (Scheme 4). When CuTc acted as the Lewis acid, the *anti*-elimination pathway is found to be exergonic and effectively barrierless ($\Delta G‡ = -3.7$ kcal/mol), whereas the *syn*-elimination requires a barrier of +20.4 kcal/mol. The CuTc-assisted anti-elimination is therefore significantly more favorable than its syn counterpart. In addition, the C−F bond trans to copper is elongated by the negative hyperconjugation effect, which renders it more susceptible to Lewis acid-assisted cleavage.

Based on previous reports,[8,10] our experimental results and DFT calculations, a plausible mechanism for the copper-mediated cyanofluoroolefination of diazo compounds is proposed (Scheme 5). Initially, CuTc assists the trans-

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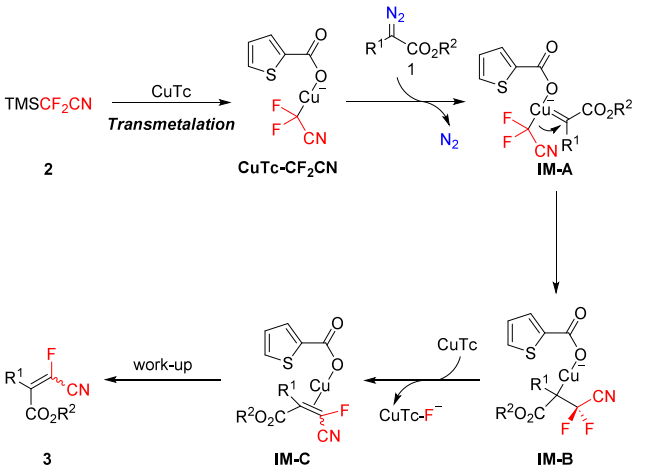
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Scheme 3. Gram-Scale Reaction and Synthetic Applications



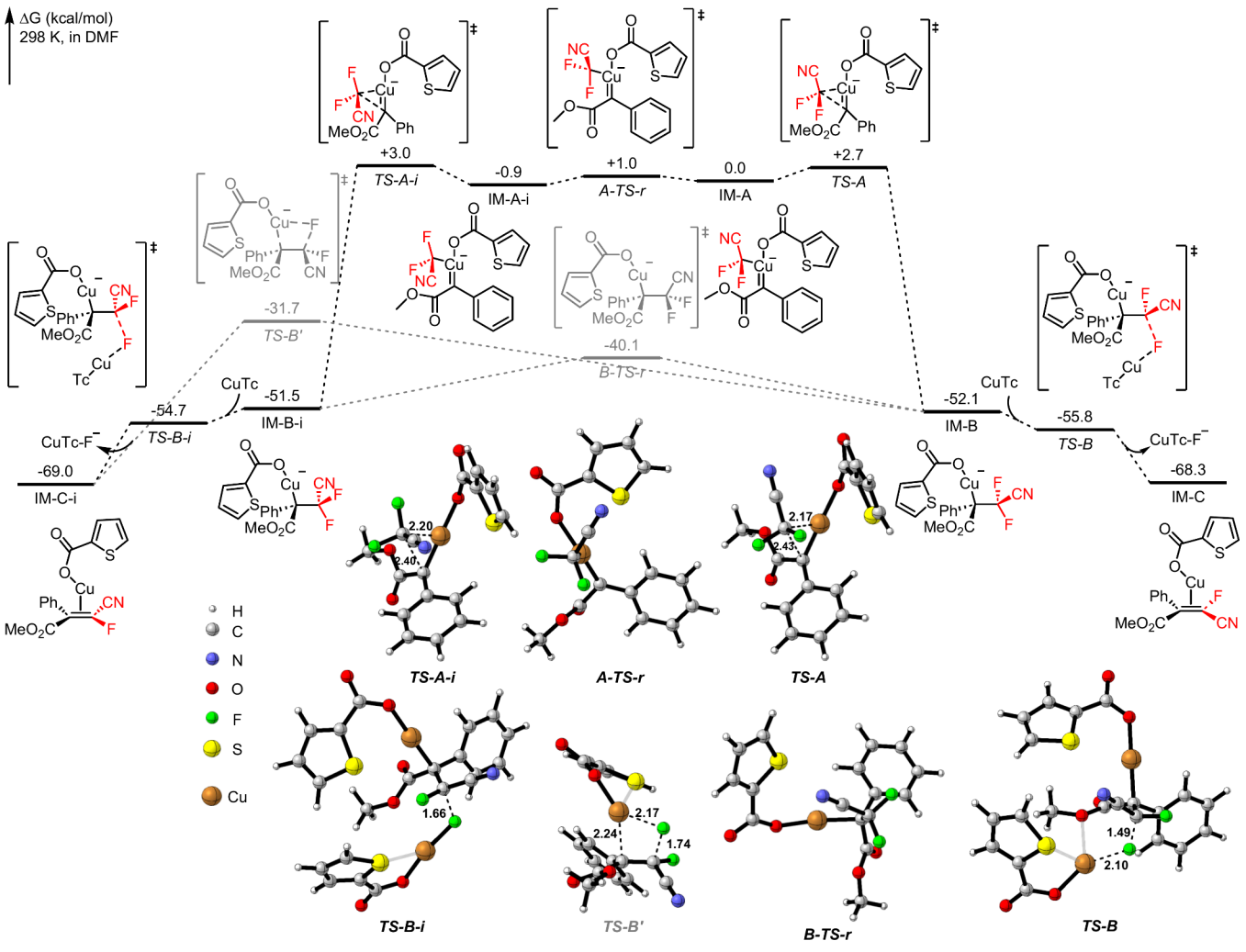
metalation of $TMSCF_2CN$ to the copper center, generating the **CuTc-CF_2CN** intermediate.[15] Subsequently, the **CuTc-CF_2CN** reacts with diazo compound **1** to form copper-carbene intermediate **IM-A**. This intermediate then undergoes migratory insertion to give **IM-B**, which subsequently participates in a CuTc-promoted *anti-β*-fluoride elimination to afford the copper-olefin complex **IM-C**. The formation of this complex indicates that extending the reaction time leads to diminished yields. Finally, after workup, the monofluoroolefin product **3** is obtained.

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have developed a copper-mediated approach for the synthesis of 2-fluoroacrylonitrile scaffolds from diazo compounds and $TMSCF_2CN$. This method provides the products in good yields with high stereo-

Scheme 4. Potential Energy Surface for Cu−F *β*-Elimination



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selectivity. The protocol exhibits broad functional group tolerance, allowing efficient access to a diverse array of 2-fluoroacrylonitriles that hold promise for applications in drug discovery and the synthesis of complex molecules.

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.6c02581.

Experimental procedures; ^{1}H, ^{19}F, and ^{13}C NMR characterization data; DFT calculation data; and copies of NMR spectra (PDF)

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Author Contributions

$^{\nabla}$L.Y. and K.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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