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gem-Difluoroolefination of Diazo Compounds with $TMSCF_3$ or $TMSCF_2Br$: Transition-Metal-Free Cross-Coupling of Two Carbene Precursors

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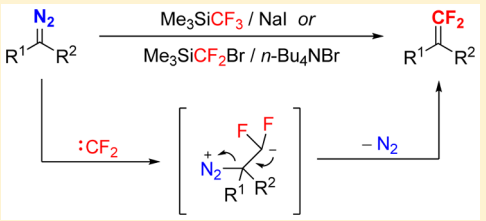
Supporting Information

ABSTRACT: A new olefination protocol for transition-metal-free cross-coupling of two carbene fragments arising from two different sources, namely, a nonfluorinated carbene fragment resulting from a diazo compound and a difluorocarbene fragment derived from Ruppert–Prakash reagent ($TMSCF_3$) or $TMSCF_2Br$, has been developed. This *gem*-difluoroolefination proceeds through the direct nucleophilic addition of diazo compounds to difluorocarbene followed by elimination of N_2. Compared to previously reported Cu-catalyzed *gem*-difluoroolefination of diazo compounds with $TMSCF_3$, which possesses a narrow substrate scope due to a demanding requirement on the reactivity of diazo compounds and in-situ-generated $CuCF_3$, this transition-metal-free protocol affords a general and efficient approach to various disubstituted 1,1-difluoroalkenes, including difluoroacrylates, diaryldifluoroolefins, as well as arylalkyldifluoroolefins. In view of the ready availability of diazo compounds and difluorocarbene reagents and versatile transformations of 1,1-difluoroalkenes, this new *gem*-difluoroolefination method is expected to find wide applications in organic synthesis.



1. INTRODUCTION

1,1-Difluoroalkenes are structurally unique organic compounds in medicinal chemistry that are usually explored in drug design as mechanism-based enzyme inhibitors yet with remarkable metabolic stability against P-450 family enzymes.[1,2] Moreover, 1,1-difluoroalkenes are versatile building blocks in organic synthesis, and the *gem*-difluorovinyl group can be transformed to many valuable functionalities.[3,4] To date, numerous approaches to synthesize 1,1-difluoroalkenes have been developed,[3] as represented by carbonyl olefination methods such as Wittig-type and Julia–Kocienski-type reactions.[5] However, most of these approaches need strong bases and suffer from disadvantages such as limited substrate scope and low efficiency.[3,5] Considering the wide applications of the difluorinated olefins, highly efficient and operationally simple approaches are still urgently desired.

Difluorocarbene is the most stable dihalocarbene and readily reacts with a series of both electron-rich and electron-poor substrates.[6] Traditional synthetic applications of difluorocarbene include (1) homocoupling at very high temperature to produce tetrafluoroethylene (TFE),[7] (2) reacting with heteroatom and carbon nucleophiles to afford difluoromethylation products,[6] and (3) undergoing [2 + 1] cycloaddition with alkynes or alkenes.[6] However, the direct reaction of difluorocarbene with a carbon nucleophile followed by β-elimination to give the 1,1-difluoroalkenes is rare.[8]

Diazo compounds have found wide applications in modern organic synthesis due to their capability in constructing structurally diverse molecules.[9] In their transformations, diazo compounds can serve as carbene precursors,[10] carbon nucleophiles,[11] and *N*-heterocycle precursors.[12] In recent years, the construction of C=C bonds with diazo compounds, which relies on coupling reactions involving transition metal–carbene species, has attracted much attention.[10b,13,14] These olefination processes are mainly achieved in two manners: (1) a diazo compound is converted to a transition metal–carbene species, which undergoes a migratory insertion followed by β-elimination (Scheme 1, eq a),[10b,13] and (2) a nucleophilic attack of a diazo compound on a transition metal–carbene species followed by β-elimination (Scheme 1, eq b).[14]

On the basis of a Cu–carbene migratory insertion mechanism, we have developed a copper-catalyzed *gem*-difluoroolefination of diazo compounds with Ruppert–Prakash reagent ($TMSCF_3$) (Scheme 1, eq c).[15] However, the substrate scope of this difluoroolefination reaction is narrow, and it is only efficient for the synthesis of 1,1-diaryl-2,2-difluoroalkenes.[15] This limitation intrigued our interest in searching for new synthetic protocols to broaden the scope of this diazo *gem*-difluoroolefination method. We envisioned that diazo com-

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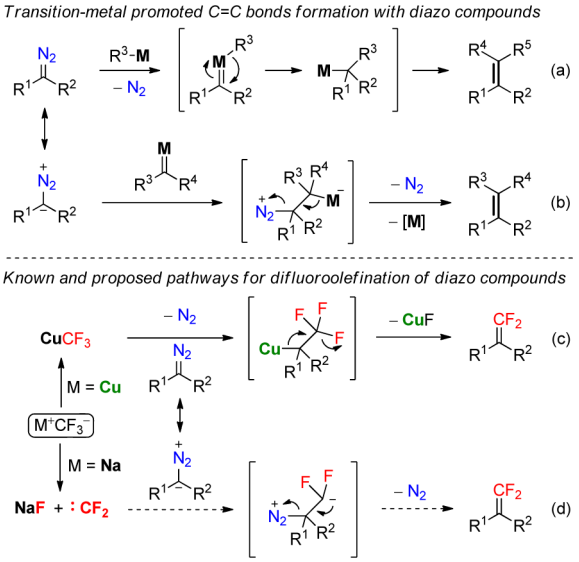
Scheme 1. Pathways of C=C Bond Formation with Diazo Compounds



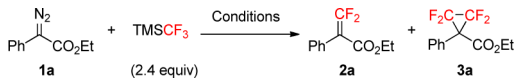
pounds, which contain a nucleophilic carbon center, may react directly with the electrophilic difluorocarbene to furnish the *gem*-difluoroolefins (Scheme 1, eq d). To our knowledge, cross-coupling reactions between diazo compounds and difluorocarbene species under transition-metal-free conditions have never been reported.[16] Herein, we report our success in the *gem*-difluoroolefination of diazo acetates, diaryldiazomethanes, and diazirines (the diazo compound surrogates) with two difluorocarbene reagents, $TMSCF_3$ and $TMSCF_2Br$, in the absence of transition metals.[17]

2. RESULTS AND DISCUSSION

We began our study using a stabilized diazo compound, phenyl diazoacetate **1a**, as a model substrate (Table 1) that had been found resistant to efficient *gem*-difluoroolefination by $TMSCF_3$ under copper catalysis, presumably due to the low reactivity of α-diazoacetates toward $CuCF_3$ in situ generated under such conditions.[15] Since $TMSCF_3$ is not only a trifluoromethylation reagent[18] but also is able to generate difluorocarbene species under transition-metal-free conditions at a wide range of temperatures (−50 to 110 °C),[19] we first chose this reagent as the difluorocarbene source. When employing a nonmetallic fluoride source, tetrabutylammonium triphenyldifluorosilicate (TBAT), which had been used for the difluorocyclopropanation of electron-rich alkenes at low temperatures, diazoacetate **1a**, however, did not react to give the desired difluoroolefin, probably due to the relatively low nucleophilicity of the stabilized diazo compound toward difluorocarbene at such temperatures. As a result, the fluoride-induced fast self-decomposition of $TMSCF_3$ overtook the desired olefination (Table 1, entry 1). When the less basic activator sodium iodide (NaI) was used instead of TBAT, a relatively slower release of difluorocarbene from $TMSCF_3$ was beneficial for the olefination reaction. By using a stoichiometric amount (2.2 equiv) of NaI as the initiator, the reaction proceeded smoothly at 60 °C to give difluoroolefin **2a** in 74% yield, with only 1% yield of tetrafluorocyclopropane as the side product, which arose from the further [2 + 1] cycloaddition between product **2a** and difluorocarbene (Table 1, entry 2).[20] Moreover, raising or lowering the temperature did not enhance the yield (Table 1, entries 3 and 4), and reducing the quantities of NaI initiator also resulted in a decrease of yield (Table 1, entry 5). Among several ethereal solvents tested, THF proved to be the best solvent [Table 1, entries 2, 5, and 6; see the Supporting Information (SI) for more details].

To find more evidence to support the difluorocarbene pathway for this novel *gem*-difluoroolefination process, we examined the reaction of diazoacetate **1a** with $TMSCF_2Br$ (Table 2), a known difluorocarbene reagent that is less likely to directly introduce a bromodifluoromethyl group under non-equilibrium conditions.[21] By using tetrabutylammonium bromide (TBAB) as the initiator, reaction of **1a** at 110 °C in toluene gave 36% yield of *gem*-difluoroolefination product **2a** and a trace amount of tetrafluorocyclopropanation side product **3a** (2% yield) (Table 2, entry 1). An investigation of the solvent effect once again showed that the ethereal solvents were better than the other solvents, and tetrahydrofuran (THF) gave the highest yield (Table 2, entries 1, 2, 3, 5, and 6). Since diazo compounds are generally susceptible to high temperatures, decreasing the reaction temperature from 110 to 80 °C gave a better result (Table 2, entry 3); however, further lowering the temperature (such as 60 °C) led to a decrease of the yield of **2a**

Table 1. Survey of Reaction Conditions between Diazoacetate 1a and $TMSCF_3$[a]



entry	initiator (equiv)	solvent	temp (°C)	time (h)	yield (**2a**, %)[b]
1	TBAT (0.05)	THF	−50 to 25	12	0 (0)
2[c]	**NaI (2.2)**	**THF**	**60**	**5**	**74 (1)**
3	NaI (2.2)	THF	80	4	59 (<1)
4	NaI (2.2)	THF	45	4	66 (0)
5	NaI (1.5)	THF	60	5	67 (<1)
6	NaI (2.2)	1,4-dioxane	60	20	0 (0)
7	NaI (2.2)	DME	60	20	30 (0)

[a]All reactions were performed with 0.5 mmol of **1a**. [b]The yields of **2a** and **3a** were determined by ^{19}F NMR with $PhCF_3$ as an internal standard, and the yields of **3a** are given in parentheses. [c]Optimized conditions are highlighted in bold text.

Table 2. Survey of Reaction Conditions between Diazoacetate 1a and $TMSCF_2Br$[a]

entry	initiator (mol %)	solvent	temp (°C)	time (h)	yield (**2a**, %)[b]
1	*n*-Bu_4NBr (4)	toluene	110	2	36 (2)
2	*n*-Bu_4NBr (4)	THF	110	2	67 (5)
3[c]	***n*-Bu_4NBr (4)**	**THF**	**80**	**12**	**76 (3)**
4	*n*-Bu_4NBr (4)	THF	60	12	46 (0)
5	*n*-Bu_4NBr (4)	1,4-dioxane	80	12	76 (12)
6	*n*-Bu_4NBr (4)	DME	80	12	67 (5)
7	*n*-Bu_4NBr (4)	NMP	80	12	8 (0)
8	*n*-Bu_4NBr (16)	THF	80	8	63 (6)

[a]All reactions were performed with 0.5 mmol of **1a**. [b]The yields of **2a** and **3a** were determined by ^{19}F NMR with $PhCF_3$ as an internal standard, and the yields of **3a** are given in parentheses. [c]Optimized conditions are highlighted in bold text.

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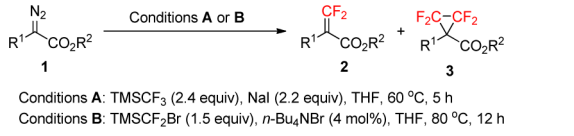
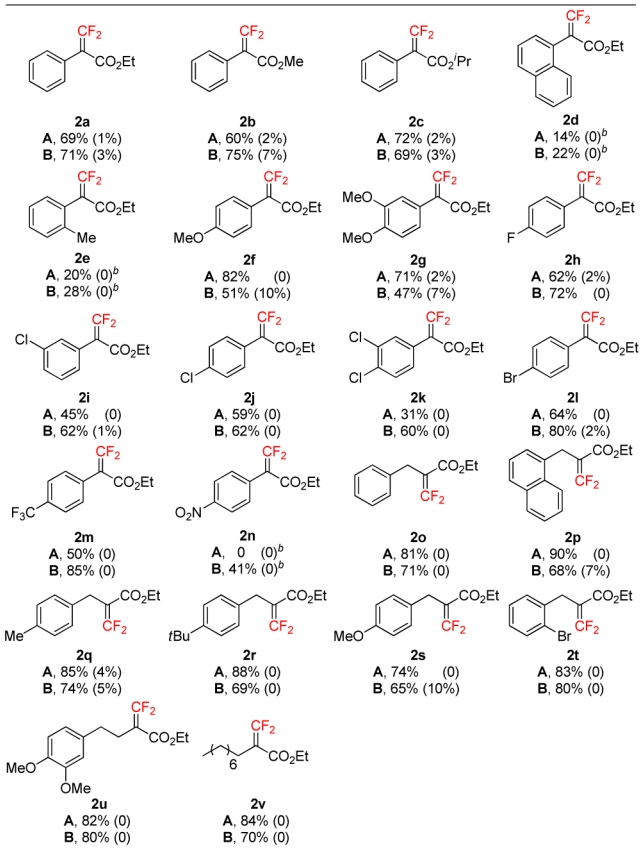
due to a slower generation of difluorocarbene species from $TMSCF_2Br$ (Table 1, entry 4). In addition, increasing the amount of initiator TBAB did not benefit the reaction (Table 1, entry 8; see SI for more details).

With the two optimized conditions in hand (entry 2 of Table 1 and entry 3 of Table 2), we investigated the scope of α-diazo acetates, and the results are shown in Table 3. Generally, aryl-, benzyl-, and simple alkyl-substituted diazoacetates reacted smoothly to give 1,1-difluoroalkenes **2** in moderate to good yields. Reactions with both electron-neutral and electron-deficient aryl-substituted diazoacetates prefer $TMSCF_2Br$ as the difluorocarbene source, while reactions with electron-rich aryl, benzyl, and alkyl diazoacetates prefer $TMSCF_3$ as the difluorocarbene source. The electron-donating and -withdrawing groups substituted on the phenyl ring, such as methoxy, fluorine, chlorine, bromine, and trifluoromethyl groups, had no significant effects on the yields (Table 3, **2f**–**2m**), whereas the strong electron-withdrawing nitro group led to only a moderate yield when using $TMSCF_2Br$ and no product at all when using $TMSCF_3$ (Table 3, **2n**). Furthermore, compared with reactions using $TMSCF_3$, reactions using $TMSCF_2Br$ usually afforded somewhat higher yields of tetrafluorocyclopropanation side products **3**, presumably due to the higher reaction temperature and prolonged reaction time required, especially in the cases of relatively electron-rich diazo acetates. The steric bulkiness of the ester group adjacent to the carbenic carbon had little influence on the reaction, and a change from methyl to ethyl to isopropyl esters gave similar yields of the corresponding 1,1-difluoroalkenes (Table 3, **2a**–**2c**); however, the substitution pattern of the aryl group adjacent to the carbenic carbon had a remarkable effect on the reaction. For example, 1-naphthyl- and 2-tolyl-substituted diazo acetates gave very low yields (Table 3, **2d** and **2e**). It is worthwhile noting that benzyl diazoacetates generally gave higher yields in this *gem*-difluoroolefination than those in previously reported copper-promoted trifluoromethylation,[22] probably because the formation of carbene intermediates (undergoing 1,2-H shift) from diazo compounds is disfavored in these reactions (Table 3, **2p**–**2t**).

To extend the synthetic application of this transition-metal-free olefination protocol, we further investigated the reaction of diaryldiazomethanes (Table 4). Because these substrates are more thermally labile than the diazoacetates and their *gem*-difluoroolefination products are more reactive toward difluorocarbene, their reaction with $TMSCF_2Br$ at high temperatures (80–110 °C) gave only moderate yields of diaryldifluoroolefins **5**, accompanying a substantial amount of tetrafluorocyclopro-

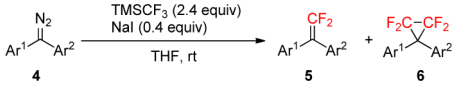
Table 3. *gem*-Difluoroolefination of α-Diazoacetates[a]

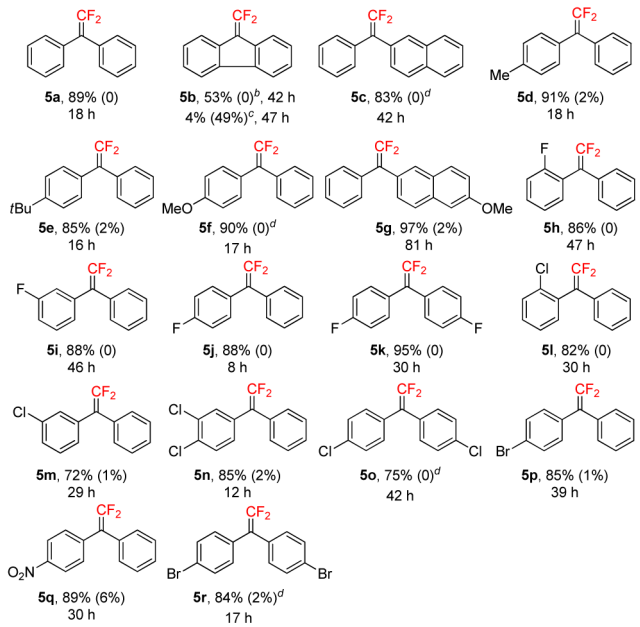




[a]All reactions were performed on 0.5 mmol scale. Unless otherwise noted, the yields given refer to the isolated yields of **2**. The data in the parentheses refer to the yields of side product **3** as determined by ^{19}F NMR analysis of the reaction mixture using $PhCF_3$ as an internal standard. [b]The yields of the products were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

Table 4. *gem*-Difluoroolefination of Diaryldiazomethanes[a]





[a]All reactions were performed on 0.5 mmol scale. Unless otherwise noted, the yields given refer to the isolated yields of **5**. The data in the parentheses refer to the yields of side product **6** as determined by ^{19}F NMR analysis of the reaction mixture using $PhCF_3$ as an internal standard. [b]A 1.3 equiv portion of $TMSCF_3$ was used. [c]A 3.0 equiv portion of $TMSCF_3$ was used, and the yields of the products were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [d]Both 0.8 equiv of NaI and 2.0 equiv of $TMSCF_3$ were used.

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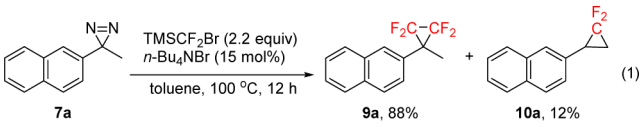
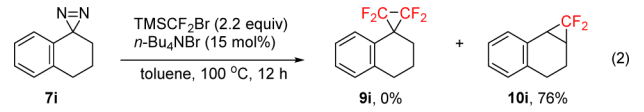
panation side products **6** (see the SI for more details). When $TMSCF_3$ was used instead of $TMSCF_2Br$, a control of the release of difluorocarbene by using a substoichiometric amount of NaI and conducting the reaction at room temperature converted a variety of diaryldiazomethanes **4** into diaryldifluoroolefins **5** in good to excellent yields, with minimized amounts of side products **6**. Not only the halogen substituents, such as fluorine, chlorine, and bromine, were amenable to the reaction (Table 4, **5h**–**5p** and **5r**) but also the electron-donating methoxy group and electron-withdrawing nitro group were compatible (Table 4, **5f**, **5g**, and **5q**). Note that the ortho-substituted diaryldiazomethanes also reacted smoothly to give good yields of difluoroolefins (Table 4, **5h** and **5l**). In contrast to the previously developed copper-catalyzed *gem*-difluoroolefination with $TMSCF_3$,[15] this NaI-catalyzed olefination process precluded the involvement of side reactions of transition metal–carbene complexes, thus largely improving the yield of diaryldifluoroolefins.

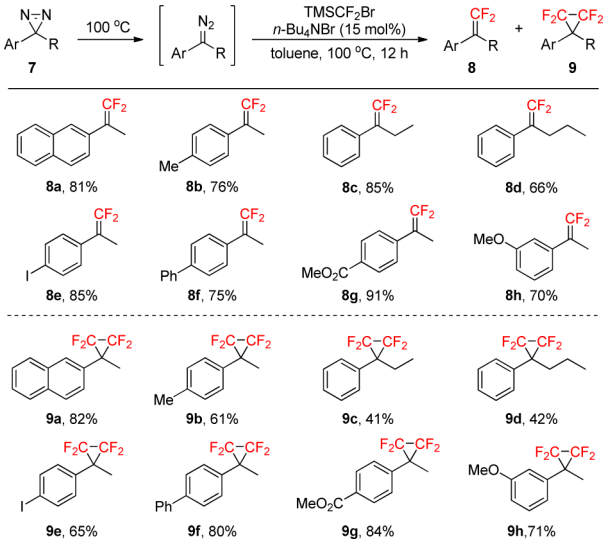
Encouraged by the high efficiency of this olefination protocol, we next investigated the *gem*-difluoroolefination of less stabilized diazo compounds, namely, arylalkyldiazomethanes (Table 5). Since such compounds are inherently unstable and challenging to prepare,[10] we used the stable diazirines as their surrogates, which can isomerize to the less stable diazo compounds upon heating.[23] In this case, the combination of $TMSCF_2Br$/TBAB(cat.) was chosen as the optimal olefination system, which was expected to produce the difluorocarbene species with a reaction rate comparable to that of the in situ formation of arylalkyldiazomethanes under thermal conditions. To avoid the further [2 + 1] addition between the relatively electron rich 1,1-difluoroalkene products and difluorocarbene (see the SI for more details), $TMSCF_2Br$ was used as the limiting reactant, and the reaction between acyclic diazirines **7** and $TMSCF_2Br$ (in 2:1 molar ratio) under the catalysis of 15 mol % of TBAB in toluene as solvent at 100 °C afforded *gem*-difluoroolefins **8** as the sole fluorinated products in 66–91% yields (Table 5, **8a**–**8h**). The competitive denitrogenative 1,2-hygrogen shift of diazo compounds to alkenes did not interfere with this *gem*-difluoroolefination reaction, and both electron-deficient and electron-rich aryl substituents are amenable. On the other hand, simply changing the ratio of diazirines to $TMSCF_2Br$ from 2:1 to 1:2.2 resulted in the predominant formation of cyclopropanation products, with the tetrafluorocyclopropanes **9** derived from 1,1-difluoroalkenes **8** as the major products, along with *gem*-difluorocyclopropanes derived from nonfluorinated alkenes as the minor products (Table 5, **9a**–**9h**). Taking the reaction of **7a** as an example, a ^{19}F NMR analysis of the reaction mixture showed that the tetrafluorocyclopropane **9a** and difluorocyclopropane **10a** were formed in 88% and 12% yields, respectively (eq 1), which indicates that the reaction of acyclic arylalkyl diazomethanes with difluorocarbene is much faster than its denitrogenative rearrangement to alkenes. Interestingly, cyclic diazirine compound **7i** readily underwent the denitrogenative 1,2-hygrogen shift reaction to give 1,2-dihydronaphthalene rather than the *gem*-difluoroolefination product, as was evidenced by the isolation of its difluorocyclopropanation product **10i** in 76% yield when excess $TMSCF_2Br$ was used (eq 2).





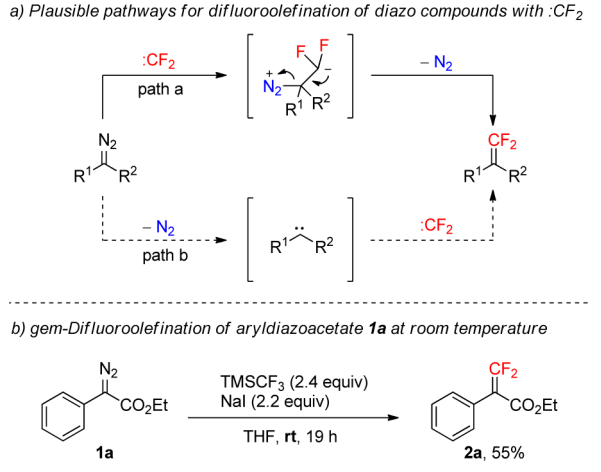
As for the mechanism of this *gem*-difluoroolefination, in addition to the initially mentioned nucleophilic reaction pathway (Scheme 2a, path a), the other pathway involving the cross-coupling of two carbenes could not be ruled out at this stage because diazo compounds can release carbene under thermolysis[24] (Scheme 2a, path b). To better understand the mechanism, we carried out the reaction of aryldiazoacetate **1a**, a substrate that is stable toward diazo decomposition under common laboratory conditions,[10a] with $TMSCF_3$/NaI at room

Table 5. *gem*-Difluoroolefination and Tetrafluorocyclopropanation of Diazirines[a]



[a]Conditions: for compounds **8a**–**8h**, 7/$TMSCF_2Br$ = 2:1; for compounds **9a**–**9h**, 7/$TMSCF_2Br$ = 1:2.2. All reactions were performed on 0.5 mmol scale.

Scheme 2. Proposed Mechanism for *gem*-Difluoroolefination of Diazo Compounds with Difluorocarbene



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temperature. As shown in Scheme 2b, the olefination proceeded smoothly to afford 1,1-difluoroalkene **2a** in moderate yield, albeit in somewhat lower yield than the reaction performed at 60 °C. This result suggests that a direct carbene−carbene cross-coupling (Scheme 2a, path b) is less likely to occur as the major pathway.

3. CONCLUSION

In conclusion, we have developed a new *gem*-difluoroolefination protocol by transition-metal-free cross-coupling of two carbene fragments arising from two different sources, a nonfluorinated carbene fragment resulting from a diazo compound and a difluorocarbene fragment derived from $TMSCF_3$ or $TMSCF_2Br$. This olefination proceeds through the direct C-difluoromethylenation of diazo compounds by electrophilic difluorocarbene followed by β-elimination of N_2. Compared to previously reported Cu-catalyzed *gem*-difluoroolefination of diazo compounds with $TMSCF_3$,[15] which possesses a narrow substrate scope due to a demanding requirement on the reactivity of diazo compounds and in-situ-generated $CuCF_3$, this protocol affords a general and efficient approach to various disubstituted 1,1-difluoroalkenes, including difluoroacrylates, diaryldifluoroolefins, as well as arylalkyldifluoroolefins. Considering the ready availability of diazo compounds and difluorocarbene reagents and versatile transformations of 1,1-difluoroalkenes, this method is expected to find wide applications in organic synthesis. This type of intriguing C=C bond formation reaction is currently under further investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09888.

Tables of reaction condition development, full experimental protocols, and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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