Difluorocarbene Hot Paper

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Reaction of Diazo Compounds with Difluorocarbene: An Efficient Approach towards 1,1-Difluoroolefins

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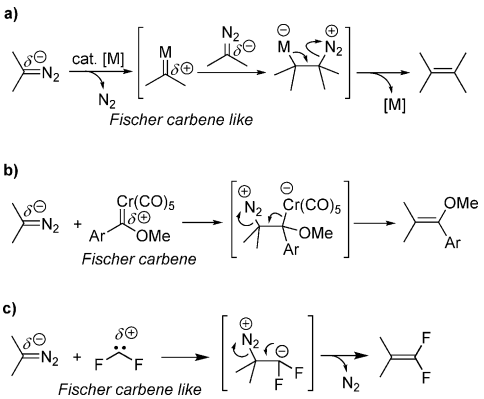
Abstract: *A transition-metal-free difluoromethylenation of diazo compounds that proceeds under mild conditions has been developed and is based on the use of $TMSCF_2Br$ as the difluoromethylene source and tetrabutylammonium bromide (TBAB) as the promoter. The chemoselective formal carbene dimerization reaction is achieved owing to the electronic properties and the relative stability of the difluorocarbene intermediate.*

Diazo compounds are versatile intermediates in organic synthesis that have most commonly been employed as carbene precursors in transition-metal-catalyzed reactions.[1] They are ambiphilic reagents as the carbon atom bearing the diazo group has a partial negative charge and is thus nucleophilic. In the presence of a catalyst (typically late transition metals, such as Rh^{II} and Cu^{I}), metal carbene species can be generated from diazo compounds through coordination of the negatively polarized carbon atom to the empty d orbital of the metal followed by dinitrogen extrusion. Interestingly, the metal carbene species generated in most catalytic reactions have an electron-deficient carbene center and thus are Fischer carbene complexes. The highly reactive metal carbene species further undergo typical carbene transformations, such as C–H insertion, cyclopropanation, and ylide formation. Aside from these common transformations, formal carbene dimerizations are also frequently encountered. Mechanistically, carbene dimerization is attributed to the reversal of the polarity of the carbon atom bearing the diazo group in the process of metal carbene formation. The negatively polarized carbon atom of a diazo substrate could attack the electron-deficient carbene carbon atom of the metal carbene, which is then followed by the release of dinitrogen and the metal catalyst to generate a double bond (Scheme 1 a).

Formal carbene dimerizations are normally considered as unwanted side reactions. However, they also show potential in an efficient approach towards the synthesis of functionalized alkenes, although the inevitable problems associated with chemo- and stereoselectivity have to be addressed. Early explorations of carbene dimerization focused on intramolecular carbene dimerizations for the construction of ring systems.[2,3] For example, Doyle and co-workers explored Rh^{II}-catalyzed reactions of bis(diazocarbonyl) compounds to construct macrocycles.[3c] Che and co-workers achieved similar cyclizations with their Ru^{II} porphyrin catalyst.[3d] A related strategy has also been explored by our group for the synthesis of polycyclic aromatic compounds with bis(*N*-tosylhydrazones).[4] Chemo- and stereoselective carbene dimerization reactions of two different diazo substrates are obviously more challenging.[5,6] In this context, the groups of Davies[5a] and Sun[5b–e] have recently reported successful examples of intermolecular carbene dimerizations. Their approaches were based on fine-tuning the reactivity of two different diazo substrates. Furthermore, we have reported the reaction of diazo compounds (in situ generated from *N*-tosylhydrazones) with Cr^0 Fischer carbene complexes under catalyst-free conditions (Scheme 1 b).[7]



Scheme 1. Chemoselective carbene dimerization for C=C bond construction.

Among free carbene species, difluorocarbene possesses several special properties that are attributed to the fluorine substituents.[8] On the one hand, difluorocarbene is electrophilic in nature owing to the strongly electron-withdrawing nature of the fluorine substituents. On the other hand, fluorine is an excellent π-electron donor and could stabilize the singlet difluorocarbene. In terms of its electronic properties and stability, difluorocarbene is considered to be somewhat similar to a Fischer carbene.[9] Therefore, it is conceivable that nucleophilic diazo compounds may react with electron-deficient difluorocarbene in a chemoselective

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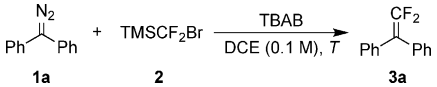
manner to generate double bonds. Herein, we report our investigations along this line. The developed reaction provides a unique approach towards the synthesis of 1,1-difluoroolefins (Scheme 1c).[10]

First, we examined the reaction of diphenyldiazomethane (**1a**) as the diazo substrate, $TMSCF_2Br$ (**2**), a difluorocarbene precursor introduced by Hu and co-workers,[11] as the source of difluorocarbene, and tetrabutylammonium bromide (TBAB) as the initiator to generate difluorocarbene in 1,2-dichloroethane (DCE). Gratifyingly, in the initial experiment, product **3a** was isolated in 38% yield, whereas $TMSCF_2Br$ (**2**) remained largely unchanged as observed by ^{19}F NMR spectroscopy (Table 1, entry 1). Encouraged by this result, we

Table 1: Optimization of the reaction conditions.[a]



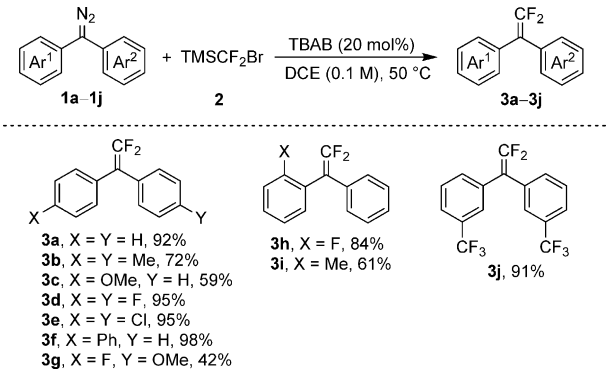
1a **2** **3a**

Entry	**1a**/**2**	TBAB [mol%]	*T* [°C]	Yield[b] [%]
1	1:2	20	25	38
2	1.2:1	20	50	70
3	1.5:1	20	50	81
4	1.5:1	10	50	40
5	1.5:1	30	50	28
6	1.5:1	20	50	92[c]

[a] The reactions shown in entries 1–5 were run on 0.1 mmol scale, and the reaction in entry 6 was run on 0.2 mmol scale. [b] Unless otherwise noted, yields were determined by ^{19}F NMR spectroscopy (300 MHz) with trifluorotoluene as the internal standard. [c] Yields of isolated products after column chromatography. TBAB = tetrabutylammonium bromide, DCE = 1,2-dichloroethane.

proceeded to further optimize the reaction conditions. The reaction was significantly affected by the reaction temperature. At 50°C, the desired product was formed in 70% yield while 18% of the $TMSCF_2Br$ remained unchanged (as determined by ^{19}F NMR spectroscopy; entry 2). Increasing the loading of the diazo substrate further improved the yield to 81% yield (^{19}F NMR; entry 3). The TBAB loading also significantly affected the reaction, and 20 mol% of TBAB afforded the best results (entries 3–5). Finally, the reaction was run on 0.2 mmol scale, and the desired product was isolated in 92% yield (entry 6).

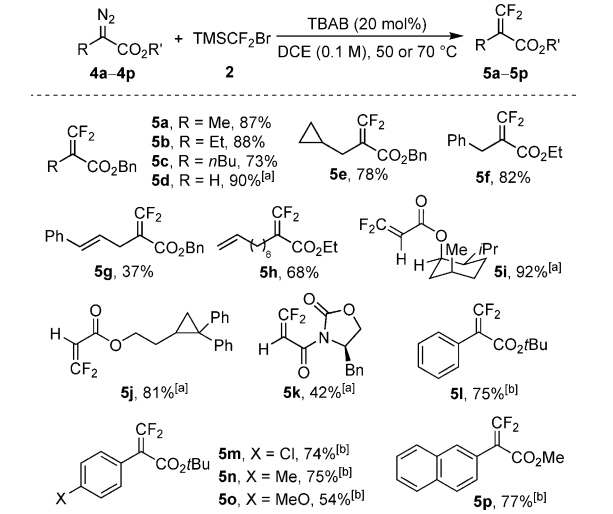
With the optimized reaction conditions in hand, the substrate scope of this reaction was investigated with a series of diaryl diazomethanes. As illustrated in Scheme 2, various diaryl diazomethanes reacted smoothly with $TMSCF_2Br$ to afford the corresponding 1,1-difluoroolefins in good to excellent yields. The electronic nature of the substituents on the aromatic ring moderately affected the yields. The reactions of substrates bearing electron-withdrawing substituents afforded the products in excellent yields (**3d**, **3e**, **3h**, **3j**). However, substrates bearing electron-donating substituents gave the corresponding products in only moderate yields (**3b**, **3c**, **3g**). The variation in yields was attributed to the stability of the diazo substrates. Diaryl diazomethanes with electron-donating substituents are less stable than their counterparts bearing electron-withdrawing substituents. On



Scheme 2. Difluoromethylenation with diaryl diazomethanes. The reactions were run on 0.2 mmol scale (**1**/**2** = 1.5:1). Yields of isolated products after column chromatography on silica gel are given.

the other hand, the reaction efficiency was also affected by steric effects, as a more sterically hindered diazo substrate resulted in diminished yield (**3i**).

To further expand the substrate scope, we next examined diazo compounds bearing electron-withdrawing ester groups. As shown in Scheme 3, when alkyl diazoester **4a** was used as



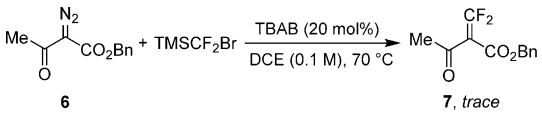
Scheme 3. Difluoromethylenation with diazoesters. Unless otherwise noted, the reactions were run on 0.2 mmol scale (**4**/**2** = 1.5:1). Yields of isolated products after column chromatography on silica gel are given. For **4a**–**4c** and **4e**–**4h**, the reaction temperature was 50°C; all other reactions were run at 70°C. [a] **4**/**2** = 1:1.5. [b] **4**/**2** = 1:2.0; yields determined by ^{19}F NMR spectroscopy (300 MHz) with trifluorotoluene as the internal standard.

the substrate, the corresponding 1,1-difluoroolefination product **5a** could be isolated in 87% yield. Encouraged by this result, we further studied other alkyl diazoesters. Diazoesters with various alkyl substituents afforded the corresponding 1,1-difluoroolefins in good yields (**5b**, **5c**, **5e**). Double bonds, which easily undergo cyclopropanation with difluorocarbene,[8] are compatible with the current reaction conditions (**5g**, **5h**).

Diazoacetates **4d** and **4i–4k** were also examined in this transformation. With benzyl diazoacetate **4d** as the substrate, the corresponding product **5d** was obtained in about 30% yield (^{19}F NMR) under identical reaction conditions. The diminished yield may be attributed to the fact that these diazoesters (**4d**, **4i–4k**) are less nucleophilic than the diazo substrates **1a–1j**, **4a–4c**, and **4e–4h**. As these diazo substrates are more stable, the reaction temperature was then raised from 50 °C to 70 °C. Under the modified reaction conditions, product **5d** could be obtained in 90% yield. The reaction also proceeded efficiently with other diazoacetates (Scheme 3, **4i–4k**).

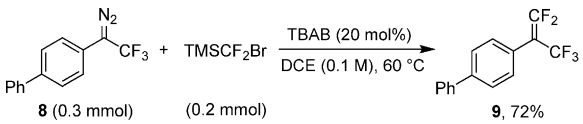
Next, we examined aryl diazoesters (Scheme 3, **4l–4p**), which are relatively stable donor–acceptor diazoesters that are widely explored in transition-metal-catalyzed carbene transfer reactions.[12] The initial reaction with phenyldiazoacetate **4l** at 70 °C afforded the desired product **5l**, but the product contained an inseparable chlorination side product. As the chlorine should originate from the solvent (DCE), we screened other solvents. However, our experiments indicated that DCE still afforded the best results in terms of the yield of the desired product. Therefore, we examined the reactions of aryl diazoesters **4m–4p** under the original reaction conditions. The corresponding products **5m–5p** were obtained in moderately high yields as determined by ^{19}F NMR spectroscopy (300 MHz). However, in all cases, the products contained minor amounts of inseparable chlorinated side products.

The stable β-keto α-diazoester **6** was also subjected to the above reaction conditions. However, only trace amounts of the desired product **7** could be detected by ^{19}F NMR spectroscopy [Eq. (1)]. The low yield was attributed to the



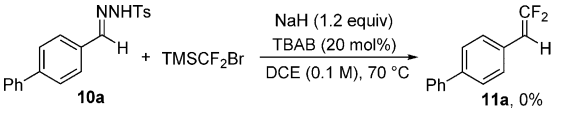
(1)

low nucleophilicity of the carbon atom that bears the diazo group in the substrate. On the other hand, the reaction with diazo substrate **8**, which bears an electron-withdrawing CF_3 substituent, afforded the corresponding polyfluorinated 1,1-difluoroolefin **9** in good yield [Eq. (2)].



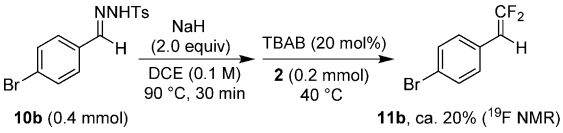
(2)

N-Tosylhydrazones are bench-stable and easily prepared. They have been widely explored as precursors of diazo compounds, especially for the in situ generation of non-stabilized diazo compounds.[13] Thus we proceeded to examine whether *N*-tosylhydrazones are suitable substrates for the current transformation. 4-Biphenylcarboxaldehyde *N*-tosylhydrazone (**10a**) was subjected to the above reaction conditions, but the desired product **11a** could not be detected [Eq. (3)]. We reasoned that the high temperature needed for the conversion of the *N*-tosylhydrazone into the diazo



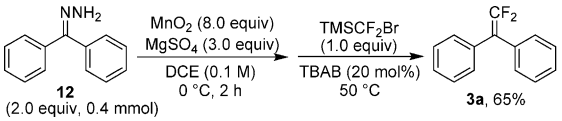
(3)

compound might not be compatible with the current reaction. Indeed, when the conversion of *N*-tosylhydrazone **10b** into the diazo intermediate was carried out before the addition of $TMSCF_2Br$ and TBAB, the desired product **11b** could be obtained in approximately 20% yield [^{19}F NMR; Eq. (4)].



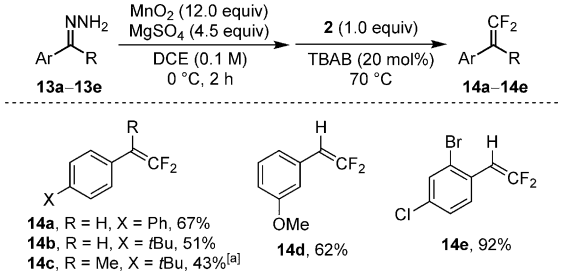
(4)

Furthermore, we explored the use of benzophenone hydrazone (**12**) as a precursor that could generate diphenyl diazomethane by treatment with an oxidant at low temperature. The solution containing the diazo substrate was clean upon filtration. Treatment of this solution with $TMSCF_2Br$ and TBAB afforded product **3a** in 65% yield [Eq. (5)].



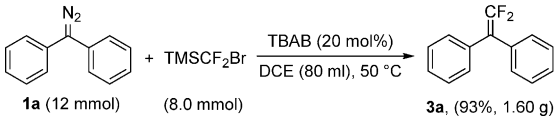
(5)

Furthermore, a series of hydrazones, **13a–13e**, were subjected to the reaction with $TMSCF_2Br$ under identical conditions to those shown in Eq. (5). The reactions afforded the corresponding 1,1-difluoroolefination products **14a–14e** in moderate to good yields (Scheme 4).

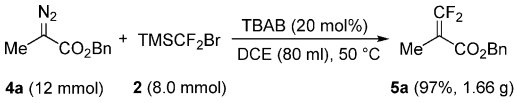


Scheme 4. Difluoromethylenation with hydrazones. The reactions were run on 0.2 mmol scale (**13**/**2** = 3.0:1.0). Yields of isolated products after column chromatography on silica gel are given. [a] The second step was carried out at 60 °C.

Finally, to demonstrate the practical usefulness of this reaction, gram-scale experiments were carried out with diazo substrates **1a** and **4a** [Eq. (6) and (7)]. Under the optimized reaction conditions, the desired 1,1-difluoroolefination products **3a** and **5a** were obtained in excellent yields.



(6)



(7)

To gain insights into the reaction mechanism, the progress of the reaction of **1a** was monitored by ^{19}F NMR spectroscopy. However, only $TMSCF_2Br$ and product **3a** could be detected, and no intermediates were observed. We thus suggest that the reaction proceeds by nucleophilic addition of the diazo substrate to difluorocarbene as shown in Scheme 1c. However, alternative mechanisms may also be operative. Further rigorous experiments are required to elucidate the detailed reaction mechanism.

In summary, we have developed an efficient method for the synthesis of 1,1-difluoroolefins. The transition-metal-free reaction proceeds under mild conditions and tolerates various functional groups. Moreover, the "Fischer carbene like" properties of difluorocarbene were explored, which may open up new possibilities for the application of difluorocarbene in organic synthesis.[14]

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