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Fe-Catalyzed insertion of fluoromethylcarbenes generated from sulfonium salts into X–H bonds (X = Si, C, P)†

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The Fe-catalyzed insertion of fluoromethylcarbenes including trifluoromethylcarbene and difluoromethylcarbene generated *in situ* from sulfonium salts ($Ph_2S^+CH_2CF_3$ ^-OTf and $Ph_2S^+CH_2CF_2H$ ^-OTf) into X–H (X = Si, C and P) bonds is described. The insertion of both carbenes into the Si–H bond occurred smoothly, and trifluoromethylcarbene could also insert into C–H and P–H bonds.

Fluoromethylcarbenes, including trifluoromethylcarbene (CF_3CH:)[1] and difluoromethylcarbene (HCF_2CH:),[2] have proven to be attractive synthetic tools for the incorporation of trifluoromethyl (CF_3) and difluoromethyl (HCF_2) fragments, both of which are valuable functionalities in medicinal chemistry,[3] materials chemistry,[4] and so on. Although X–H bond (X = C, Si, *etc.*) functionalization has received a great deal of attention due to its high efficiency and atom economy, and significant efforts have been directed toward the development of efficient methods for the insertion of carbenes into the X–H bond,[5] the insertion of fluoromethylcarbenes into the X–H bond remains challenging.

Trifluoromethyldiazomethane (CF_3CHN_2)[1d,g,6] and difluoromethyldiazomethane (HCF_2CHN_2)[2,7] have served as versatile intermediates in a variety of transformations. It was recently found that they can act as a trifluoromethylcarbene precursor[1] and a difluoromethylcarbene precursor,[2] respectively. But the insertion of fluoromethylcarbenes into the X–H bond has been limited to CF_3CHN_2.[1h–j] In 2012, the group of Ma reported that the Cu-catalyzed insertion of trifluoromethylcarbene produced from CF_3CHN_2 into the Csp–H bond occurred smoothly to afford the desired product in high yields.[1h] In 2015, Wang and co-workers described the insertion into N–H and O–H bonds catalyzed by a silver complex.[1i] Shortly afterwards, Gouverneur *et al.* found that the insertion strategy could be successfully applied to Si–H, B–H, P–H, S–H, and N–H bonds.[1j] Apparently, CF_3CHN_2 is efficient for the insertion into X–H bonds (X = C, Si, P, *etc.*). However, it is a potentially explosive and toxic gas, limiting its synthetic utility. Therefore, the development of mild protocols for the insertion of fluoromethylcarbenes into X–H bonds is highly desirable.

We have shown that fluorinated carbenes can be produced from fluorinated ylides including phosphonium ylides[8] and sulfonium ylides[9] under mild conditions. On the basis that trifluoromethyl sulfonium ylide ($Ph_2S^+CH^-CF_3$) and difluoromethyl sulfonium ylide ($Ph_2S^+CH^-CF_2H$) could be converted by FeCl(TPP) into trifluoromethylcarbene ($Fe{=}CHCF_3$)[9a] and difluoromethylcarbene ($Fe{=}CHCF_2H$),[9c] respectively, we have now investigated the use of both sulfonium ylides as fluoromethylcarbene precursors in the insertion into X–H bonds (X = Si, C, and P). Ylides $Ph_2S^+CH^-CF_3$ and $Ph_2S^+CH^-CF_2H$ were *in situ* generated from sulfonium salts $Ph_2S^+CH_2CF_3$ ^-OTf (**I**) and $Ph_2S^+CH_2CF_2H$ ^-OTf (**II**), respectively, *via* deprotonation by CsF.

We previously found that a reductant was not required in the Fe-catalyzed transformation of trifluoromethylcarbene,[9a] but it was necessary in the reaction of difluoromethylcarbene.[9c] Interestingly, in the Fe-catalyzed insertion of trifluoromethylcarbene into the Si–H bond in DMA, the presence of the reductant $Na_2S_2O_4$ could slightly increase the yield (Table 1, entry 3 *vs.* 1). A comparable yield was obtained in DMF (entry 4). Increasing the loading of salt **I** and CsF could lead to the increase in the yields (entries 6–8 *vs.* 3). The yield was further increased slightly by increasing the amount of the catalyst FeCl(TPP) (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine) from 1 mol% to 2 mol% (entry 9 *vs.* 8). However, 3 mol% of catalyst loading did not increase the yield (entry 10 *vs.* 9). The absence of the reductant $Na_2S_2O_4$ resulted in a lower yield (entry 11 *vs.* 9). Room temperature was found to be the appropriate reaction temperature. Irrespective of whether the temperature was elevated or lowered, the yields were decreased (entries 12–14 *vs.* 9).

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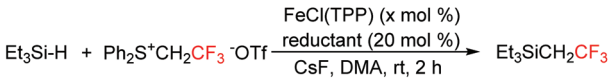
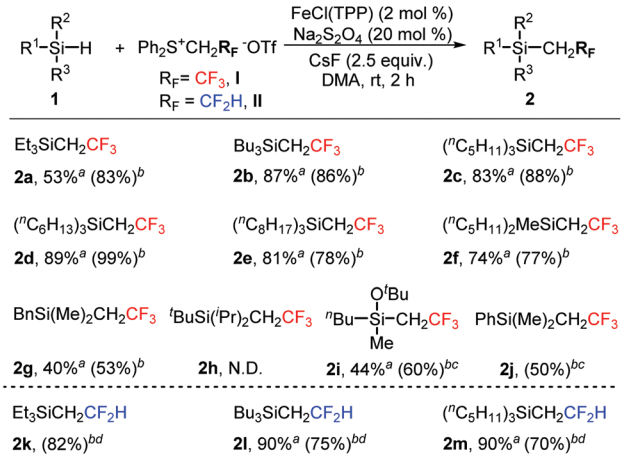
Table 1 Optimization of reaction conditions for the insertion into the Si–H bond[a]



Entry	Reductant	*x*	Ratio[b]	Yield[c] (%)
1	—	1	1 : 1 : 1.1	41
2	Zn	1	1 : 1.1 : 1.2	43
3	$Na_2S_2O_4$	1	1 : 1.1 : 1.2	50
4[d]	$Na_2S_2O_4$	1	1 : 1.1 : 1.2	45
5	$Na_2S_2O_4$	1	1.3 : 1 : 1.2	56
6	$Na_2S_2O_4$	1	1 : 1.3 : 1.5	66
7	$Na_2S_2O_4$	1	1 : 1.5 : 1.8	70
8	$Na_2S_2O_4$	1	1 : 2 : 2.5	79
9	$Na_2S_2O_4$	2	1 : 2 : 2.5	83
10	$Na_2S_2O_4$	3	1 : 2 : 2.5	81
11	—	2	1 : 2 : 2.5	70
12[e]	$Na_2S_2O_4$	2	1 : 2 : 2.5	53
13[f]	$Na_2S_2O_4$	2	1 : 2 : 2.5	45
14[g]	$Na_2S_2O_4$	2	1 : 2 : 2.5	64

[a] Reaction conditions: **1a** (0.2 mmol), sulfonium salt **I**, FeCl(TPP), reductant, and CsF in DMA (1.5 mL) at rt for 2 h. [b] Molar ratio of **1a** : salt **I** : CsF. [c] The yields were determined by ^{19}FNMR. [d] DMF was used as the reaction solvent instead of DMA. [e] The reaction temperature was 40 °C. [f] The reaction temperature was 50 °C. [g] The reaction temperature was 0 °C.

With the optimal reaction conditions in hand (Table 1, entry 9), we then investigated the substrate scope for the insertion of fluoromethylcarbenes into the Si–H bond. As shown in Scheme 1, trialkylsilanes could be smoothly converted into the desired products in moderate to good yields (**2a–2g**). Severe steric effects would result in the complete suppression of Si–H bond insertion (**2h**). For a slightly hindered substrate, a moderate yield was obtained under slightly modified reaction conditions (**2i**). Phenylsilane showed a much lower reactivity and the modified conditions gave the expected product in only 50% yield (**2j**). The product was so volatile that we failed to isolate it from the reaction solvent toluene. Besides trifluoromethylcarbene, difluoromethylcarbene could also be inserted well into the Si–H bond (**2k–2m**).



Scheme 1 Substrate scope for the insertion of methylcarbenes into the Si–H bond. [a] Isolated yields; [b] the yields in parentheses were determined by ^{19}F NMR spectroscopy; [c] Cs_2CO_3 was used instead of CsF, toluene was used instead of DMA, and the reaction temperature was 80 °C; [d] Zn was used instead of $Na_2S_2O_4$ and DMF was used instead of DMA.

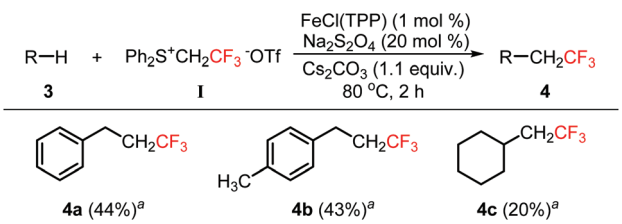
Organosilicon compounds are highly attractive scaffolds and have found widespread applications in organic synthesis,[10] materials chemistry,[11] and pharmaceuticals.[12] Si–H bond functionalization is one of the most straightforward protocols to synthesize organosilicon derivatives. This carbene insertion strategy is worth paying attention since it allows for the convenient formation of the Si–C bond and the incorporation of fluoromethyl groups.

Inert C–H bond functionalization is a challenging research area and a powerful tool for organic synthesis.[13] The insertion of fluoromethylcarbenes into the inert Csp^3–H bond was also investigated. Although a large number of reaction conditions were screened, we could not identify optimal conditions to obtain a high yield (see the ESI†). Fortunately, we found that moderate yields could be obtained for the insertion of trifluoromethylcarbene into the benzyl C–H bond (Scheme 2, **4a–4b**). For the alkyl C–H bond, the yield was quite low (**4c**). In these reactions, substrates **3** have to be used as the reaction solvent. Therefore, it was quite difficult to isolate the products from substrates **3** due to their similar polarity and the high volatility of products **4**.

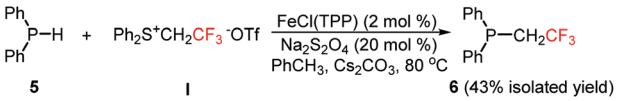
Phosphines are widely used in synthetic chemistry. For example, they can act as ligands in organometallic chemistry,[14] and as catalysts in the Morita–Baylis–Hillman reaction.[15] P–H functionalization is apparently an efficient strategy to prepare organophosphines. Trifluoromethylcarbene was found to be able to insert into the P–H bond to furnish the desired product in a moderate yield (Scheme 3).

Other X–H (X = N or S) bond insertions were also investigated. For the insertion into the N–H bond in arylamines such as 4-chlorophenylamine (4-$ClC_6H_4NH_2$), no desired product was produced. The S–H bond in thiophenol (PhSH) could react with sulfonium salt **I** to give sulfur ether ($PhSCH_2CF_3$). But the reaction may not proceed *via* trifluoromethylcarbene insertion into the S–H bond since thiophenol could act as a nucleophile to directly attack salt **I** under basic conditions.

Based on the above results and our previous observations,[9a,c] we propose that the reaction may proceed through a concerted X–H insertion. The Fe-carbene (Fe=CHR_F, R_F = CF_3



Scheme 2 Insertion of trifluoromethylcarbene into the inert C–H bond. [a] The yields were determined by ^{19}F NMR spectroscopy.



Scheme 3 Insertion of trifluoromethylcarbene into the P–H bond.

Scheme 4 The proposed transition state.

or CF_2H) generated *in situ* is highly reactive, and thus would be readily trapped by the X–H bond (Scheme 4). The cleavage of the X–H bond and the formation of C–H and C–X bonds would occur simultaneously to give the final products.

Conclusions

In conclusion, we have described the Fe-catalyzed insertion of fluoromethylcarbenes including trifluoromethylcarbene and difluoromethylcarbene into Si–H, C–H and P–H bonds. This work represents the first protocol for the insertion of difluoromethylcarbene into the Si–H bond, and the mild strategy for the insertion of fluoromethylcarbenes into X–H (X = Si, C and P) bonds. The fluoromethylcarbene insertion strategy may find synthetic utility in other research areas.

Conflict of interest

The authors declare no competing financial interest.

Acknowledgements

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