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Organocatalytic deprotonative functionalization of C(sp^2)–H and C(sp^3)–H bonds using *in situ* generated onium amide bases†

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Onium amides, generated *in situ* from the combination of aminosilanes and onium fluorides (R_4PF, R_4NF), are employed for the first time as bases for catalytic deprotonative functionalization of C(sp^2)–H and activated C(sp^3)–H bonds under mild conditions.

Deprotonation of aromatic C(sp^2)–H bonds has been widely used for the selective functionalization of (hetero)aryl compounds because aromatic molecules constitute important building blocks in the research fields of drug discovery and material sciences.[1] Stoichiometric amounts of a range of *metal* amide bases of lithium,[2] magnesium,[3] zinc,[4] copper,[5] aluminum,[6] and manganese[7] have been extensively employed in such processes; however, these bases are usually prepared from reactive organometallic reagents that are air- and moisture-sensitive and also require careful handling for safety.[8] On the other hand, organocatalytic processes[9] have recently emerged as an attractive tool in organic synthesis from the viewpoint of selectivity, safety, and sustainability. Deprotonative functionalization of (hetero)arenes using an organocatalyst is considered highly challenging and is still underdeveloped. With respect to our recent research projects, which aim to develop novel aromatic functionalization processes by use of organocatalysts,[10] we envisioned a deprotonation process involving onium amide species that might be formed from aminosilanes and onium fluorides. Although reports of *in situ* trapping of aryl *metal* intermediates with electrophiles have appeared in the literature,[11] our metal-free, organocatalytic approach is conceptually novel and would be the first sophisticated example of catalytic deprotonation of aromatic C(sp^2)–H bonds without generating organometallic aromatic species.

Our working hypothesis is shown in Fig. 1. A series of fluoride sources (QF), which were expected to catalytically generate the onium amide base **I** by reacting with aminosilanes, were selected for the process, including phosphazenium fluoride (P5F) and several quaternary ammonium fluorides, all of which are commercially available. Although Schwesinger reported that phosphazenium fluorides can be used as sources of highly reactive, naked fluoride ions in solution, little attention was paid to their synthetic use.[12] On the other hand, quaternary ammonium fluorides, particularly tetraalkylammonium fluorides, have been extensively employed as organic-soluble, practical fluoride sources in organic synthesis.[13] The reaction of such fluoride sources (QF) with $Me_3SiNR'_2$ would result in the formation of onium amides **I**, which could deprotonate the (hetero)aryl C(sp^2)–H compounds and provide (hetero)aryl anions **II**. The coupling of such anionic species with electrophiles (*e.g.*, ketones and aldehydes) would result in the formation of intermediate **III**, which could react with $Me_3SiNR'_2$ to give rise to the final product **IV** and onium amides **I**, rendering the process catalytic. At this juncture, it is worth noting that onium amide species **I** have never been employed for aromatic deprotonation reactions. Herein, we show a novel, simple, and efficient metal-free process for catalytic deprotonative functionalization using *in situ* generated onium amide bases. In addition to the C(sp^2)–H bonds of various heteroarenes, activated C(sp^3)–H bonds can also be effectively deprotonated using this method, and various electrophiles can be successfully coupled with such deprotonated species.

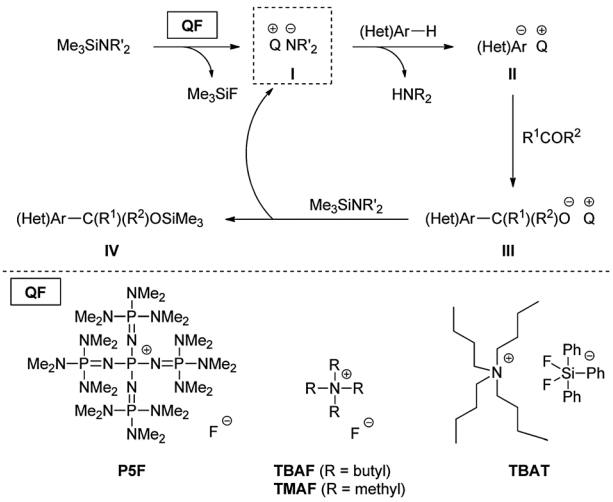

Fig. 1 Plausible mechanism for deprotonative functionalization processes using *in situ* generated onium amide bases.

To probe the viability of the anticipated deprotonation process, the reaction of benzothiazole (**1a**, pK_a = 27.3 at 2-position)[14] with benzophenone (**2a**) in toluene using 5 mol%

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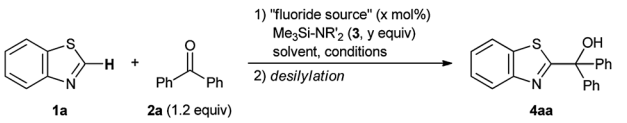
of P5F as a fluoride source in the presence of various aminosilanes (**3**) was evaluated. Although the use of diisopropylaminotrimethylsilane (DIATMS, **3a**) afforded no desired product **4aa** (Table 1, entry 1), we were pleased to find that the reaction with diethylaminotrimethylsilane (DEATMS, **3b**) did proceed, which resulted in the formation of **4aa** in high yield at 100 °C (entry 2).[15] Interestingly, the reaction proceeded smoothly at a decreased temperature (80 °C) when dimethylaminotrimethylsilane (DMATMS, **3c**) was employed (entry 4 *vs.* entry 3). In addition, further examination revealed that the reaction occurred efficiently even at room temperature with *in situ* generated bis(trimethylsilyl)amide, which resulted from a combination of tris(trimethylsilyl)amine (TTMS, **3d**) and a catalytic amount of P5F (entry 7).[16] On the other hand, essentially no product was obtained from the reaction in the absence of P5F (entry 8). Having achieved this novel, high-yielding deprotonative functionalization process, the effect of other fluoride sources was later evaluated. Tetraalkylammonium fluorides such as TBAF[17] and TMAF in the presence of aminosilane **3c** were found to be nearly as suitable as fluoride sources for the process, and the product **4aa** was obtained in good yields, although a semi-catalytic amount of fluoride was necessary (entries 9 and 10). On the other hand, TBAT turned out not suitable for the process (entry 11).[18]

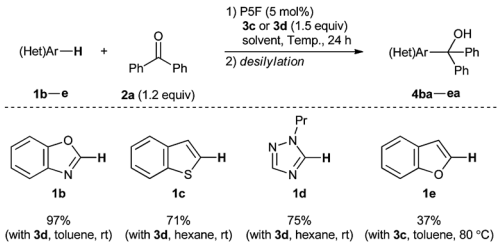
The newly developed method was further investigated in the reaction of other classes of heterocycles (Scheme 1). Benzoxazole (**1b**, pK_a = 24.8 at the 2-position) exhibited high reactivity similar to that of benzothiazole (**1a**) in the presence of P5F and aminosilane **3d** and produced **4ba** in nearly quantitative yield. The reactions of benzothiophene (**1c**, pK_a = 32.0 at the 2-position) and 1-propyltriazole (**1d**, pK_a = 30.3 at the 5-position) also

Table 1 Effect of reaction parameters[a]



Entry	"F⁻" (x mol%)	R′	3 (y equiv)	Solvent	Conditions	Yield[b] (%)
1	P5F (5)	^{i}Pr (DIATMS)	**3a** (1.5)	Toluene	100 °C, 48 h	0
2	P5F (5)	Et (DEATMS)	**3b** (1.5)	Toluene	100 °C, 48 h	87
3	P5F (5)	Et (DEATMS)	**3b** (1.5)	Toluene	80 °C, 24 h	36
4	P5F (5)	Me (DMATMS)	**3c** (1.5)	Toluene	80 °C, 24 h	88
5	P5F (5)	Me (DMATMS)	**3c** (1.5)	Toluene	rt, 24 h	38
6	P5F (5)	TMS (TTMS)	**3d** (1.5)	Toluene	80 °C, 24 h	83
7	P5F (5)	TMS (TTMS)	**3d** (1.5)	Toluene	rt, 24 h	94
8[c]	P5F (5)	TMS (TTMS)	**3d** (1.5)	Toluene	rt, 24 h	0
9	TBAF (50)	Me (DMATMS)	**3c** (5)	DMSO	rt, 24 h	79
10	TMAF (50)	Me (DMATMS)	**3c** (5)	THF	rt, 24 h	71
11	TBAT (50)	Me (DMATMS)	**3c** (5)	THF	rt, 24 h	27

[a] Performed on a 0.15 mmol scale. [b] Isolated yield after desilylation. [c] In the absence of P5F.



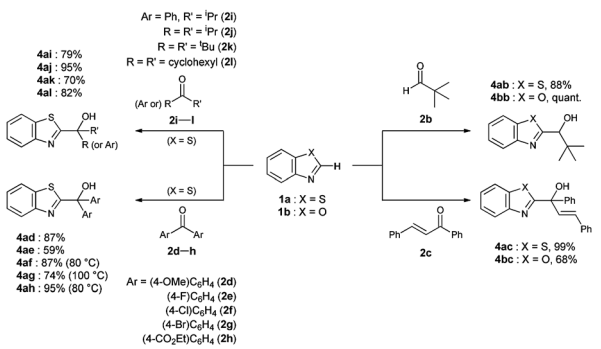
Scheme 1 Deprotonative functionalization of various heteroarenes.

proceeded efficiently using the P5F–**3d** combination, particularly when hexane was used as the solvent instead of toluene. On the other hand, only moderate yield was obtained from the reaction of benzofuran (**1e**, pK_a = 33.2 at the 2-position) even at the elevated temperature.[19]

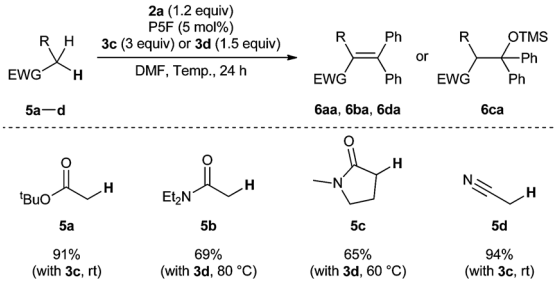
It was found that other electrophiles such as pivalaldehyde (**2b**), (*E*)-chalcone (**2c**), as well as substituted benzophenones **2d–h** also successfully participated in the reactions of **1a** and **1b** in the presence of 5 mol% P5F and 1.5 equiv. of TTMS **3d** (Scheme 2). Moreover, alkyl aryl ketone **2i** and dialkyl ketones **2j–l** have proved to be reactive in the reaction of **1a**. Each transformation efficiently proceeded and coupling products were obtained generally in good to high yields. Good functional group tolerance (*e.g.*, alkoxycarbonyl group, halogen atoms) was also observed.[20]

Extensive studies revealed that the above-mentioned deprotonative functionalization method is applicable not only to the C(sp^2)–H bonds of heteroarenes but also aliphatic C(sp^3)–H bonds α- to a carbonyl group. We note that only an approach that utilizes a stoichiometric amount of *metal-based* amide bases has been employed for such transformations involving C(sp^3)–H deprotonative functionalization.[21] Thus, the reactions of ^{t}butyl acetate (**5a**) and *N*,*N*-diethylacetamide (**5b**) with **2a** in the presence of aminosilane **3c** or **3d** proceeded smoothly in DMF using 5 mol% P5F and afforded the α,β-unsaturated carbonyl compounds **6aa** and **6ba** in good to high yields (Scheme 3). This approach might serve as a convenient and applicable synthetic method for substituted alkenes, which is complementary to the well-established Wittig and Peterson olefination reactions. An *N*-alkyl lactam such as *N*-methylpyrrolidone (**5c**) was also successfully employed for this transformation to give the silyl ether product **6ca**. Moreover, acetonitrile (**5d**) was found to be a suitable substrate for the process, giving rise to **6da** in high yield.

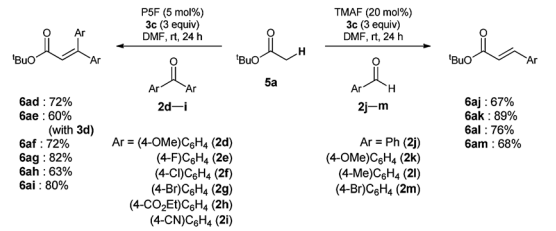
A series of substituted benzophenones **2d–i** and benzaldehydes **2j–m** successfully participated in the reaction with



Scheme 2 Use of other electrophiles [reaction conditions: (1) **1a** or **1b**, 1.2 equiv. of electrophile **2**, 5 mol% of P5F, 1.5 equiv. of **3d**, toluene, rt, 24 h; (2) desilylation].



Scheme 3 Deprotonative functionalization of C(sp^3)–H bonds.



Scheme 4 Reactions of **5a** with benzophenones and benzaldehydes.

acetate **5a** using a combination of **3c** and a fluoride source such as P5F or TMAF and produced the corresponding tri- and disubstituted alkenes **6ad–am** in high yields (Scheme 4). The process tolerates various functional groups such as alkoxycarbonyl and cyano groups and halogen atoms.

In summary, the work presented in this communication contains the first examples of organocatalytic deprotonative transformations using *in situ* generated onium amide bases. This conceptually new, metal-free, C–H functionalization employs catalytic systems based on the combination of aminosilanes and several types of fluoride sources that successfully effect the functionalization of C(sp^2)–H bonds of various heteroarenes under mild reaction conditions. This method provides a novel approach for manipulating an aromatic carbanion, and thus offers an operationally simple, applicable, and sustainable methodology for use in synthetic organic chemistry. In addition, functionalization of C(sp^3)–H bonds α- to a carbonyl group was also achieved *via* a similar deprotonative functionalization process in the presence of an onium amide base, which represents the versatility of this method. Future work will focus on investigation of the precise reaction mechanism of the process and exploration of the further synthetic scope of this type of deprotonative functionalization.

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19 In general, unreacted starting materials are recovered when the reaction gives a decreased yield.

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