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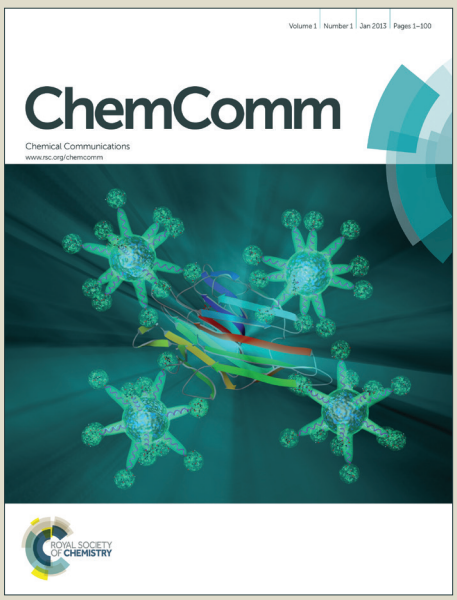

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ARTICLE TYPE

Direct condensation of functionalized sp^3 carbons with formanilides for enamine synthesis using *in situ* generated HMDS amide catalyst

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The efficient synthesis of functionalized enamines including β-enaminoesters was effectively accomplished by the direct condensation of functionalized sp^3 carbanion such as acetates with formamides using *in situ* generated HMDS base from catalytic cesium fluoride and stoichiometric tristrimethylsilylamine.

Functionalized enamines have been employed as versatile key intermediates for the organic synthesis and widely used for many transformations.[1] In particular β-enaminones are recognized to be as important precursors for the synthesis of benzene derivatives[2] and heteroaromatics[3] such as pyridines,[4] pyrroles,[5] pyridinones,[6] pyrimidines[7] and triazoles.[8] And these enamine structures are basic or partial structural moieties of important pharmaceutical drugs containing anticonvulsant,[9] anti-inflammatory,[10] antitumor agents[11] and quinolone antibacterials.[12] In addition, β-enaminones are used as very useful intermediates for the natural product syntheses.[13] Furthermore, these compounds show polyfunctionality: that have the nucleophilicity of enamines and electrophilicity of enones. Therefore these compounds enable variety of reactions, and a number of reviews about the chemistry of β-enaminones have been published.[14] Despite their synthetic potential for wide range application and importance, preparative methodologies of β-enaminones are rather limited (Fig. 1). The most well-known route to these compounds is direct condensation of amines with β-dicarbonyl compounds[15] or addition of amines to alkynes.[16] Another important methodology for the synthesis of functionalized enamines is the transition metal catalyzed amination of alkenyl halides, and this has been employed for recent natural product syntheses.[17] On the other hand, the novel C-C condensation method using Reformatsky reagents and formamides has reported for the preparation of these compounds without using β-dicarbonyl compounds or alkynes.[18] In addition to this condensation, our group also has developed a way to elaborate β-enaminones by the phosphazene base-catalyzed Peterson type reaction of formanilides with α-trimethylsilylalkyl compounds.[19]

Deprotonation of C(sp^3)–H bonds using metal amide bases followed by reaction with an electrophile has been recognized as a useful method to form C–C bonds. The utilization of strongly basic amide bases such as lithium amides and zinc amides for deprotonative functionalization has been investigated.[20] However, these procedures require stoichiometric amounts of organometallic reagents and need to be carried out at low temperature. Thus, a chemoselective organocatalytic process for deprotonative functionalization remains as an attractive challenge.

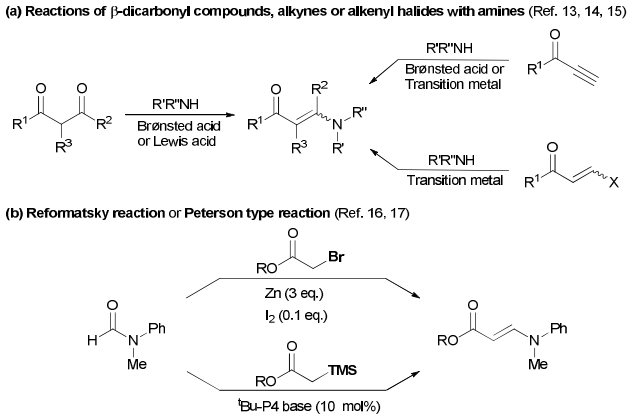


Fig. 1 Well-known synthetic methodologies of functionalized enamines.

Recently, we developed the catalytic deprotonation of aromatic C(sp^2)–H bonds using onium amide bases, generated *in situ* from the combination of aminosilanes and fluoride salts, and the subsequent reaction with carbonyl compounds proceeded smoothly at room temperature.[19] This method was suggested to be extendable for functionalization of activated C(sp^3)–H bonds α- to a carbonyl group. We expected that the system would be applicable to the synthesis of β-enaminones using formanilides as an electrophile. To the best of our knowledge, there has been no report for preparing of β-enaminones via deprotonative functionalization of acetic acid derivatives, therefore this simple methodology can be one of the challenging topics in enamine synthesis (Fig. 2).

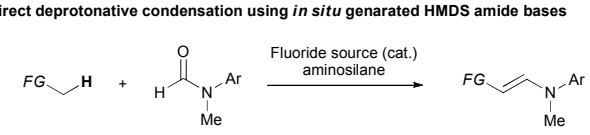
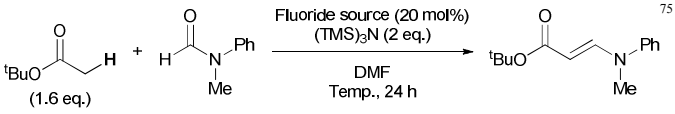


Fig. 2 New C-C condensation for enamine synthesis

In our initial investigation for our enamination, we chose ^{t}butyl

acetate (**1a**) and *N*-methylformanilide (**2a**) as substrates, using tris(trimethylsilyl)amine [$(TMS)_3N$] as an aminosilane. First, under the reaction conditions without silyl activators such as fluorides, the reaction did not proceed at all (Table 1, entry 1). When tetramethylammonium fluoride (TMAF) was used as a fluoride source, only the formation of *N*-methylaniline was observed as a byproduct, which was produced by deformylation of **2a** (entry 2). The use of CsF as another fluoride source showed excellent performance for the desired enamination and the enaminoester **3a** was successfully obtained in 74% (entry 3). By elevating the reaction temperature to 40 °C, the yield of **3a** increased to 76% (entry 4). Under the higher temperature conditions, the yield of the product decreased (entry 5).

Table 1 Deprotonative functionalization of ^{t}butyl acetate with *N*-methylformanilide



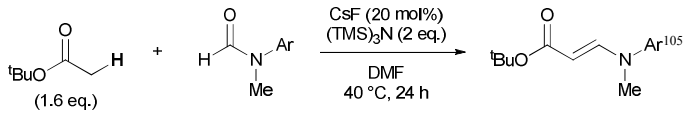
1a **2a** **3a**

Entry	Fluoride source	Temp.	Yield [b, d] (%)
1	none	rt	0 (0)
2	TMAF	rt	0 (25)
3	CsF	rt	74 [c] (6)
4	CsF	40 °C	76 [c] (10)
5	CsF	60 °C	56 (14)

[a] Reactions were carried out on a 0.20 mmol scale. [b] Determined by ^{1}H-NMR analysis. [c] Isolated yield. [d] Yield of byproduct (*N*-methylaniline) in parentheses.

To investigate further scope and limitation, we next focused our interest on the effect of the substituted group on the benzene ring of *N*-methylformanilide. Reactions with electrophiles which have electron-donating group such as methoxy and dimethylamino group at the *p*-position proceeded smoothly to generate **3b** and **3c** in 81% and 74% (Table2, entry 1, 2). To examine the influence by the position of substituted groups on the benzene ring, reactions of *N*-methylformanilide derivatives bearing a methyl group in the *p*-, *m*- and *o*-position were performed. In the case of substitution at the *p*- and *m*-position, corresponding enaminoesters **3d** and **3e** were obtained in good yields (entry 3, 4).

Table 2 Deprotonative functionalization of ^{t}butyl acetate with *N*-methylformanilide



1a **2b-i** **3b–i**

Entry	Ar	Yield [a] (%)	Entry	Ar	Yield [a] (%)
1	(*p*-OMe)C_6H_4 (**2b**)	**3b** : 81	5	(*o*-Me)C_6H_4 (**2f**)	**3f** : 0
2	(*p*-NMe_2)C_6H_4 (**2c**)	**3c** : 74	6	(*p*-I)C_6H_4 (**2g**)	**3g** : 44
3	(*p*-Me)C_6H_4 (**2d**)	**3d** : 82	7	(*p*-Br)C_6H_4 (**2h**)	**3h** : 47
4	(*m*-Me)C_6H_4 (**2e**)	**3e** : 84	8	(*p*-CN)C_6H_4 (**2i**)	**3i** : 7 [b]

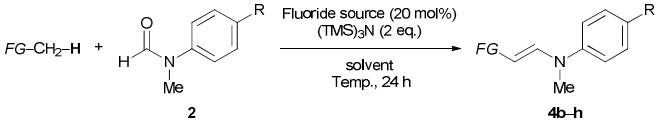
[a] Isolated yield. [b] Determined by ^{1}H-NMR analysis.

However, when a methyl group was substituted at the *o*-position, the reaction did not give the desired product (entry 5). Substrates which have halogen atom on the *p*-position of the benzene ring were also able to be utilized for this process, and the desired enaminoesters **3g** and **3h** were given in moderated yields (entry 6, 7). These results indicates that the reactivity of the formanilide is tunable with the substituents on the aromatic ring.

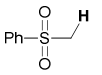
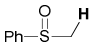
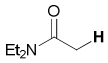
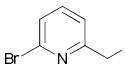
In addition, reactions with *N*-methylformanilide which have electron-withdrawing group such as cyano group at the *p*-position gave the enamine derivative in low yield (entry 8).

Subsequently, the reactions with other nucleophiles were examined other than ^{t}butyl acetate. The reaction of methyl phenyl sulfone which has relatively acidic α-proton (p*K*a = 29.0) than ^{t}butyl acetate (p*K*a = 30.3) and *N*-methylformanilide (**2a**) proceeded smoothly to give the desired product **4b** in 88% yield (Table 3, entry 1). Whereas, using acetonitrile (p*K*a = 31.3), methyl phenyl sulfoxide (p*K*a = 33.0) and *N*, *N*-diethylacetamide (p*K*a = 35.0), which contain less reactive α-proton, enamination reactions did not proceed well. After examining the various conditions, we found that the reaction using TMAF as a fluoride source and 4'-methoxy-*N*-methylformanilide as an electrophile (**2b**) under the solvent-free conditions improved the yields of product **4c**-**4e** up to 57-93% (entry 2-4). In this case, the use of *N*-methylformanilide as an electrophile did not gave a successful result, and the undesired deformylation reaction predominated. 2-Bromo-6-methylpyridine was used as a substrate to examine the scope of the reaction on the pyridine ring, and the smooth condensation was demonstrated with 4'-methoxy-*N*-methylformanilide by the use of CsF without affecting the bromo substituent (entry 5).

Table3 Deprotonative functionalization of $C(sp^3)$–H bonds



2 **4b–h**

Entry	*FG*–CH_2–**H**	**2** (R)	Fluoride source	Solvent	Temp. (°C)	Yield [a] (%)
1		**2a** (H)	CsF	DMF	50	**4b** : 88
2		**2b** (OMe)	TMAF	none	50	**4c** : 73
3		**2b** (OMe)	TMAF	none	50	**4d** : 93
4		**2b** (OMe)	TMAF	none	50	**4e** : 57 [b]
5		**2b** (OMe)	CsF	DMF	120	**4g** : 52

[a] Isolated yield. [b] Determined by ^{1}H-NMR analysis.

Plausible reaction mechanism for the formation of β-enaminoester and byproduct is shown in Fig. 3. Generation of HMDS amide bases first occurred from the combination of CsF and $(TMS)_3N$ and the base catalyst deprotonates $C(sp^3)$–H bond α- to a carbonyl group of ^{t}butyl acetate, forming cesium enolate **I**. Subsequently addition reaction of **I** to *N*-methylformanilides proceeds, which provides cesium alkoxide **II**. In the case of the use of *N*-methylformanilides possessing an electron-withdrawing

group at the *p*-position on the benzene ring, deformylation reaction becomes easier to take place and *N*-methylanilines might be produced as a main side product. The silylation of **II** with $(TMS)_3N$ generates the silyl ether **III** and an HMDS amide base that enables to achieve the catalytic cycle. The HMDS amide bases and/or other anionic species causes deprotonation of **III** to eliminate trimethylsilanoxide, consequently β-enaminoesters IV are produced. In our preliminary mechanistic experiments, the reaction was monitored by ^{1}H-NMR and the formation of the silanol and disiloxane were observed (see supporting information). Further studies to clarify this mechanism are under investigation with the further synthetic applications of this methodology.

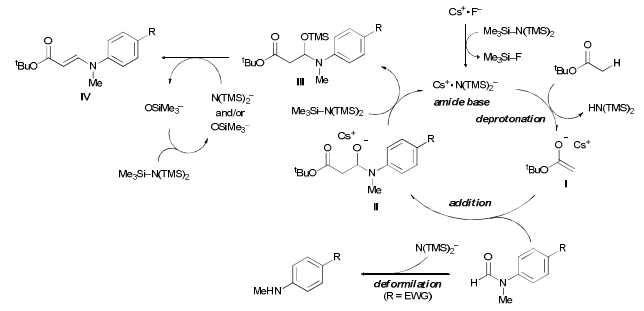


Fig. 3 Plausible reaction mechanism for formations of enamines

Conclusions

In conclusion, we have developed the novel, one-pot approach for the synthesis of functionalized enamines, including β-enaminoesters using HMDS amide bases, generated *in situ* from the combination of aminosilanes and fluoride salts. Further studies on the expanding of the scope and limitation toward substrates with diverse functionalities are in progress and further applications of this methodology are also underway.

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Notes and references

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