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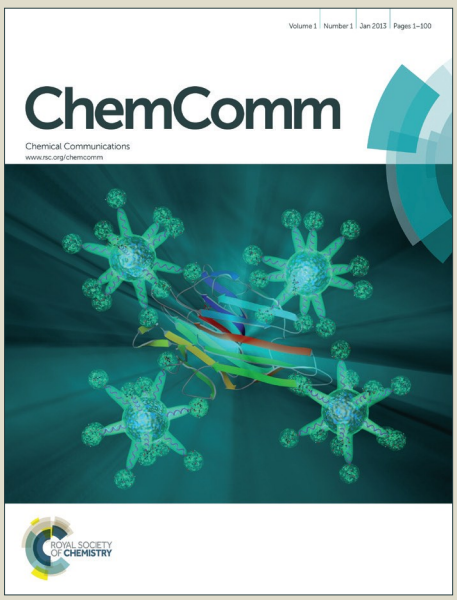

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ARTICLE

Catalytic Reduction of Amides to Amines by Electrophilic Phosphonium Cations via FLP Hydrosilylation

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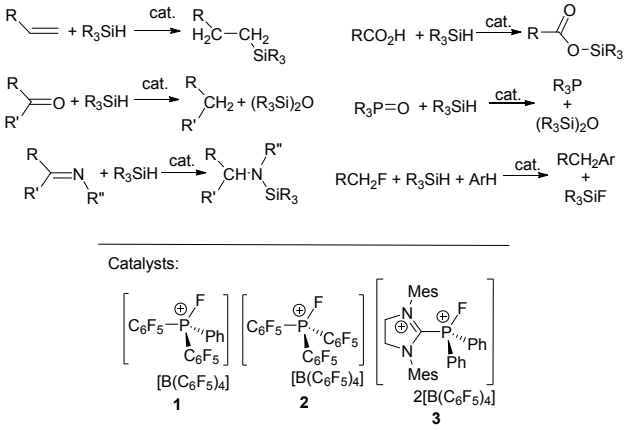
A catalytic methodology for the conversion of amides to amines is reported. Of the 25 examples described, 14 examples involve the reduction of N-trifluoroacetamides to the corresponding trifluoroethylamines. These reductions are achieved by catalytic hydrosilylation of the amide mediated by an electrophilic phosphonium cation (EPC) catalyst.

Amines are an important class of compounds in both chemistry and biology.[1-2] They are a vital functional group used by the pharmaceutical industry for pesticides and drug development.[3] As well, there is increasing use for the preparation of advanced materials.[4-6] The reduction of amides to amines is an attractive strategy for amine synthesis given the large variety of commercially available amides.[7-8] The most common method for amide reduction is the use of stoichiometric aluminium and boron hydrides.[9-14] In spite of their wide spread use, such methods suffer from the production of stoichiometric by-products, over reduction, and the challenge of purification. As a result there has been increasing interest in catalytic transformations of amides to amines. The direct hydrogenation of amides has been described by Cole-Hamilton and coworkers[15-16] using ruthenium catalysts at temperatures above 160 °C and 40 bar of H_2. Subsequent studies by the groups of Breit and Thompson explored mixed metal heterogeneous catalysts for such hydrogenations. [17-18] Using an alternative approach a series of studies have explored the transition metal catalysts incorporating Mo, Rh, Ru, Pt, Pd, and Ir for hydrosilylative reduction of amides to amines.[19-30]

Metal-free approaches to amide reduction have begun to garner some recent attention. To this end, the Adronov group[31] have used $B(C_6F_5)_3$ to effect catalytic hydrosilylation of tertiary amides. The Huang group was able to expand this scope to secondary amides with a protocol using a triflate anhydride pre-treatment of the amides.[32]

In developing metal-free catalysts, we recently uncovered the highly electrophilic fluorophosphonium cations (EPCs) which derived their Lewis acidity from a σ*-orbital on the P atom.[33] These species have been shown to be active Lewis acid catalysts for a variety of reactions. In particular the species $[(C_6F_5)_2PhPF][B(C_6F_5)_4]$ **1**, $[(C_6F_5)_3PF][B(C_6F_5)_4]$ **2**[33] and $[(SIMes)PFPh_2][B(C_6F_5)_4]_2$ **3**[34] are potent catalysts for the hydrosilylation[35-36] or the transfer hydrogenation of olefins,[37] the hydrodefluorination of fluoroalkanes,[33-34] dehydrocoupling of silanes with amines, phenols, thiols or carboxylic acids,[37] the hydrodeoxygenation of ketones[38] and the reduction of phosphine oxides.[39] Most recently, we have exploited EPCs to effect alkyl C-F and CF_3 bond arylations as well as sp^3-sp^3 C-C coupling.[40-41] In this paper we demonstrate the ability of EPCs to catalyse the reductive hydrosilylation of amides. Moreover, this protocol is applied to reduce N-trifluoroacetamide derivatives to give trifluoroethylamines.



Scheme 1 Examples of catalysis by Electrophilic Phosphonium Cations (EPCs)

Attempts to employ 3 mol% of the EPCs **1-3** as catalysts for the hydrosilylative reduction of N,N-dimethylbenzamide were screened in the presence of 2.1 equivalents of a series of silanes at 100 °C (Table 1). In general the observed reactivity trends for each silane parallels the increasing Lewis acidity of the EPCs, **1** < **2** < **3**. Similarly, conversion to the amine was

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enhanced with increasing hydricity of the silane employed. Thus, low conversions were generally observed with Et_3SiH and Ph_3SiH, while essentially quantitative conversion was seen for each catalyst with the use of $PhSiH_3$.

Table 1. N,N-dimethylbenzamide reductions using **1**, **2** and **3** as catalyst.[a]

	Catalyst	Silane	Conv. (%)
1	**1**	Et_3SiH	0
2	**1**	Ph_3SiH	0
3	**1**	Ph_2SiH_2	9
4	**1**	$HSiMe(OEt)_2$	5
5	**1**	$(HSiMe_2)_2O$	65
6	**1**	$PhSiH_3$	98
7	**2**	Et_3SiH	9
8	**2**	Ph_3SiH	0
9	**2**	Ph_2SiH_2	26
10	**2**	$HSiMe(OEt)_2$	55
11	**2**	$(HSiMe_2)_2O$	89
12	**2**	$PhSiH_3$	99
13	**3**	Et_3SiH	11
14	**3**	Ph_3SiH	6
15	**3**	Ph_2SiH_2	45
16	**3**	$HSiMe(OEt)_2$	12
17	**3**	$(HSiMe_2)_2O$	92
18	**3**	$PhSiH_3$	98

[a] The mixture was heated to 100 °C for 24 h in C_6D_5Br. Conversions determined by ^1H NMR spectroscopy.

With the optimal silane established, the substrate scope of the reduction of tertiary amides to amines was probed using the catalyst **2** and **3** (Table 2). High conversions of the amide to the amine were observed for the N,N-dimethyl *p*-Cl, *p*-Br, and *o*-methoxy-benzamides and pyrrole-*p*-methyl-benzamide with no significant difference in activity between catalyst **2** and **3**, while the N,N-dimethyl-*p*-nitro- benzamide was reduced to the corresponding amine in 78 and 74% conversions using **2** and **3** as the catalyst, respectively. Similarly, N-benzyl-N-ethyl-4-methoxybenzamide was reduced in 88 and 87% to the corresponding amine using **2** and **3** as the catalyst, respectively. In a similar fashion, the aliphatic amide N,N-diethylpropionamide as well as N-phenyl-benzamide, N-*p*-bromophenylbenzamide and N-*p*-nitrophenyl-benzamide, were reduced by both catalyst **2** and **3** in high conversions. No conversion was observed for N,N dimethyl-*p*-aminobenzamide, benzamide, N-methylbenzamide or N-benzylbenzamide. These latter cases suggest that more basic amides may inhibit the reduction. This view is consistent with stoichiometric reactions of **3** with N-phenylbenzamide which show a shift in the ^{31}P NMR to 68.7 ppm, from 78.1 ppm. Similarly, addition of N-benzylbenzamide to **3** showed a ^{31}P resonance at 36.0 ppm. In both cases the P-F coupling constant is decreased, consistent coordination of the amide to the Lewis acid P centre in **3**. Presumably binding to **3** precludes the catalytic cycle.

In extending the scope of these amide reductions, a series of 2,2,2-trifluoro substituted acetamides were prepared from reactions of an amine and trifluoroacetic anhydride at room temperature. For these amides, catalyst and silane screening were again performed in order to ascertain the optimal selections (see SI). In these cases, catalyst **3** was used in combination with tetramethyldisiloxane to effect the amide reductions at temperatures of either 50 or 100 °C. In this fashion 2,2,2-trifluoroethyl substituted amines were derived from N-phenyl 2,2,2-trifluoroacetamide, and its *p*-bromo, *p*-chloro, *p*-methyl and *p*-isopropyl substituted analogues as well as from 2,2,2-trifluoro-N-3,5-dimethylphenylacetamide. In all cases, the conversions exceeded 92% and in isolated yields ranged from 80-92% (Table 3 Entries 1-5). The reductions of N-benzyl-2,2,2-trifluoroacetamide (Entry 6), and the N-isopropyl-, N,N-diphenyl, N,N-dibenzyl derivatives of 2,2,2-trifluoroacetamide (Entries 11, 13, 14) to the corresponding amines were achieved in moderate conversion of 59-74% under similar conditions. 2,2,2-trifluoroacetamide as well as the corresponding derivatives derived from N-*p*-methyl and p-methoxybenzyl and N-benzhydryl amines and p-cyanoaniline gave generally low yields of the targeting amide reduction products (6-24%). These latter results are consistent with previous observations suggesting that basic amide N-atoms or donor substituents inhibit catalysis by binding to the fluorophosphonium cation. In the case of N-benzhydyl derivative (Entry 9) steric issues may also impede catalytic reduction.

Table 2. Amide reductions using **2** and **3** as catalyst.[a]

	Substrate	Cat	Conv (Yld %)	Product
1	*p*-$ClC_6H_4C(O)NMe_2$	**2**	99	*p*-$ClC_6H_4CH_2NMe_2$
2	*p*-$ClC_6H_4C(O)NMe_2$	**3**	99(72)	*p*-$ClC_6H_4CH_2NMe_2$
3	*p*-$BrC_6H_4C(O)NMe_2$	**2**	99	*p*-$BrC_6H_4CH_2NMe_2$
4	*p*-$BrC_6H_4C(O)NMe_2$	**3**	98(96)	*p*-$BrC_6H_4CH_2NMe_2$
5	*m*-$MeOC_6H_4C(O)NMe_2$	**2**	99	*m*-$MeOC_6H_4CH_2NMe_2$
6	*m*-$MeOC_6H_4C(O)NMe_2$	**3**	99(74)	*m*-$MeOC_6H_4CH_2NMe_2$
7	*p*-$MeC_6H_4C(O)N(CH_2)_4$	**2**	99	*p*-$MeC_6H_4CH_2N(CH_2)_4$
8	*p*-$MeC_6H_4C(O)N(CH_2)_4$	**3**	99	*p*-$MeC_6H_4CH_2N(CH_2)_4$
9	*p*-$NO_2C_6H_4C(O)NMe_2$	**2**	78	*p*-$NO_2C_6H_4CH_2NMe_2$
10	*p*-$NO_2C_6H_4C(O)NMe_2$	**3**	74	*p*-$NO_2C_6H_4CH_2NMe_2$
11	*p*-$MeOC_6H_4C(O)NEt(Bn)$	**2**	88	*p*-$MeOC_6H_4CH_2NEt(Bn)$
12	*p*-$MeOC_6H_4C(O)NEt(Bn)$	**3**	87	*p*-$MeOC_6H_4CH_2NEt(Bn)$
13	$EtC(O)NEt_2$	**2**	99	$PrNEt_2$
14	$EtC(O)NEt_2$	**3**	87	$PrNEt_2$
15	PhC(O)NH(Ph)	**2**	99	$PhCH_2NHPh$
16	PhC(O)NH(Ph)	**3**	94	$PhCH_2NHPh$
17	PhC(O)NH(*p*-BrC_6H)	**2**	99	$PhCH_2NH$(*p*-BrC_6H_4)
18	PhC(O)NH(*p*-BrC_6H)	**3**	99	$PhCH_2NH$(*p*-BrC_6H_4)
19	PhC(O)NH(C_6H_4-*p*-NO_2)	**2**	99	$PhCH_2NH$(C_6H_4-*p*-NO_2)
20	PhC(O)NH(C_6H_4-*p*-NO_2)	**3**	99	$PhCH_2NH$(C_6H_4-*p*-NO_2)
21	*p*-$H_2NC_6H_4C(O)NMe_2$	**2**	0	
22	*p*-$H_2NC_6H_4C(O)NMe_2$	**3**	0	
23	PhC(O)NH_2	**2**	0	
24	PhC(O)NH_2	**3**	0	
25	PhC(O)NH(Me)	**2**	0	
26	PhC(O)NH(Me)	**3**	0	
27	PhC(O)NH(Bn)	**2**	0	
28	PhC(O)NH(Bn)	**3**	0	

[a] The mixture was heated to 100 °C for 24 h in C_6D_5Br. Conversions determined by ^1H NMR spectroscopy.

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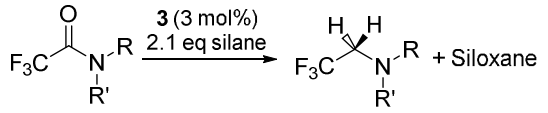
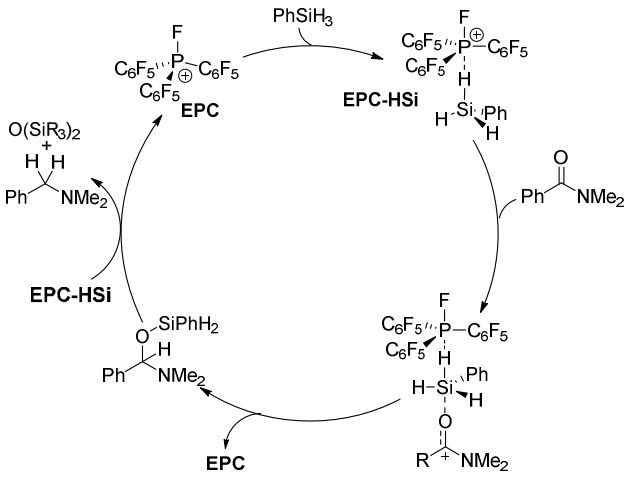
Table 3. 2,2,2-trifluoroacetamide reductions using **3** as catalyst.



	Substrate	T (°C)	Conv (Yld %)	Product
1	$CF_3C(O)NH(Ph)$	50	92(80)	$CF_3CH_2NH(Ph)$
2	$CF_3C(O)NH(p\text{-}C_6H_4Br)$	50	97(92)	$CF_3CH_2NH(p\text{-}C_6H_4Br)$
3	$CF_3C(O)NH(p\text{-}C_6H_4Cl)$	50	99(89)	$CF_3CH_2NH(p\text{-}C_6H_4Cl)$
4	$CF_3C(O)NH(p\text{-}C_6H_4i\text{-}Pr)$	50	99(82)	$CF_3CH_2NH(p\text{-}C_6H_4i\text{-}Pr)$
5	$CF_3C(O)NH(3.5\text{-}C_6H_3Me_2)$	50	99(88)	$CF_3CH_2NH(3.5\text{-}C_6H_3Me_2)$
6	$CF_3C(O)NH(CH_2Ph)$	100	59	$CF_3CH_2NH(CH_2Ph)$
7	$CF_3C(O)NH(CH_2\ p\text{-}C_6H_4Me)$	100	24	$CF_3CH_2NH(CH_2\ p\text{-}C_6H_4Me)$
8	$CF_3C(O)NH(CH_2\ p\text{-}C_6H_4OMe)$	100	11	$CF_3CH_2NH(CH_2\ p\text{-}C_6H_4OMe)$
9	$CF_3C(O)NH(CH(Ph)_2)$	100	19	$CF_3CH_2NH(CH(Ph)_2)$
10	$CF_3C(O)NH(p\text{-}C_6H_4CN)$	100	11	$CF_3CH_2NH(p\text{-}C_6H_4CN)$
11	$CF_3C(O)NH(i\text{-}Pr)$	100	64	$CF_3CH_2NH(i\text{-}Pr)$
12	$CF_3C(O)NH_2$	100	6	$CF_3CH_2NH_2$
13	$CF_3C(O)NPh_2$	100	66(64)	$CF_3CH_2NPh_2$
14	$CF_3C(O)N(CH_2Ph)_2$	50	74(69)	$CF_3CH_2N(CH_2Ph)_2$

Conditions: $(HSiMe_2)_2O$ (2.1 eq.), **3** (3 mol%), substrate (0.15 mmol, 1.0 eq) in CD_2Cl_2, heated. Conversions determined by ^1H NMR spectroscopy.



Scheme 2 Proposed Mechanism of Amide reduction by EPCs.

This reduction is thought to proceed via an FLP-type mechanism involving the action of the Lewis acid and the amide on the SiH fragment. This Initial interaction of silane by the Lewis acidic P centre is thought to weakening the Si-H bond and facilitate nucleophilic attack of the Si centre by the amide. The transient $R_2NCH(OSiR'_3)R''$ is thought react further with silane to liberate silylether and the amine, freeing the phosphonium cation for further catalysis (Scheme 2). This proposed mechanism of the amide reduction is directly analogous to that proposed for hydrosilylations mediated by Lewis acids. In the case of $B(C_6F_5)_3$[42-43] Piers and coworkers[42] established 20 years ago that the hydrosilylation of ketones proceeds via Lewis acid activation of silane followed by carbonyl attack at silicon. This mechanism was subsequently confirmed by the elegant experiments of Oestereich et al.[43] An analogous FLP mechanism has been suggested for hydrosilylations mediated by EPCs.[35-36] Moreover, this proposed mechanism is directly analogous to that proposed and supported by computational studies for the phosphonium mediated reduction of phosphine oxides. Moreover the present proposal is consistent with the ^{31}P and ^{19}F NMR data showing that the EPC catalyst is intact after catalysis.

The above amide reductions of trifluoroacetamide derivatives provide a new avenue to 2,2,2-trifluoroethyl substituted amines, an important moiety in drug candidates.[44-48] Previous efforts have focused on nucleophilic substitution by amines,[49] use of hypervalent-iodine-CH_2CF_3 reagents,[50] Pd catalysed Buchwald-Hartwig couplings[51] and a protocol based on diazomethane in combination with silver salts.[52] The present work provides a metal-free and catalytic approach to such trifluoroethylamine derivatives.

Conclusion

In summary, EPCs act as catalysts for the hydrosilylation/reduction of amides affording the corresponding amines. Notably, high chemoselectivity for reductions of 2,2,2-subsituted acetamides was observed, providing a facile route to N-trifluoroethyl substituted amines. This reactivity further affirms that EPCs are effective metal-free, Lewis acid catalysts. We are continuing to explore the utility of this amide reductions in synthetic chemistry as well as exploring the versatility of EPCs in catalytic reactions of interest. The results of these studies will be reported in due course.

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Notes and references

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