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Indium Triiodide Catalyzed Reductive Functionalization of Amides via the Single-Stage Treatment of Hydrosilanes and Organosilicon Nucleophiles

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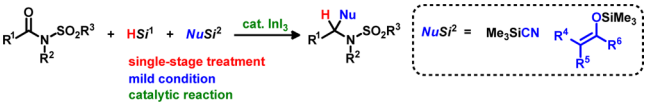
ABSTRACT



The indium triiodide catalyzed single-stage cascade reaction of *N*-sulfonyl amides with hydrosilanes and two types of organosilicon nucleophiles such as silyl cyanide and silyl enolates selectively promoted deoxygenative functionalization to give α-cyanoamines and *β*-aminocarbonyl compounds, respectively.

Much attention has been paid to the synthesis of functionalized amines. Among them, the reduction of prefunctionalized carboxamides is a promising tool because of the wide availability, stability, and the convenient installation of a variety of functional moieties. Unfortunately, reductions employing general metal hydrides such as $LiAlH_4$ and $NaBH_4$ have accomplished little achievement, perhaps because the functional groups can barely tolerate the harsh reduction conditions.[1] In recent advances, the catalytic reduction of prefunctionalized amides to the corresponding amines through the use of mild reducing reagents such as hydrosilanes has been extensively investigated (eq 1).[2] However, when using this method, the preparation of functionalized amides is troublesome. An alternative tool is the direct deoxygenative functionalization of simple amides. To achieve the transformation, in general, two kinds of species, metal hydrides such as $LiAlH_4$ and carbon nucleophiles such as Grignard reagents, were separately added under the respective controlled conditions.[3] Recently, two advanced strategies have been reported as shown in eqs 2 and 3.[4,5] One is a transformation via the iminium triflate intermediate (eq 2),[4] and the other employs a Weinreb amide, which forms a stable chelation intermediate via a reduction with DIBALH (eq 3).[5] However, even these examples require the stepwise addition of two different organometallic

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(2) For selected examples of the catalytic reduction of amides using hydrosilane, see: (a) Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017–1020. (b) Motoyama, Y.; Mitsui, K.; Ishida, T.; Nagashima, H. *J. Am. Chem. Soc.* **2005**, *127*, 13150–13151. (c) Hanada, S.; Tsutsumi, E.; Motoyama, Y.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 15032–15040. (d) Sunada, Y.; Kawakami, H.; Imaoka, T.; Motoyama, Y.; Nagashima, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9511–9514. (e) Sakai, N.; Fujii, K.; Konakahara, T. *Tetrahedron Lett.* **2008**, *49*, 6873–6875. (f) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9507–9510. (g) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 1770–1771. (h) Das, S.; Wendt, B.; Möller, K.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1662–1666. (i) Park, S.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 640–653. (j) Cheng, C.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 11304–11307. A part of the references are described here: (k) Addis, D.; Das, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6004–6011.

(3) For selected examples of the addition of Grignard reagents or organolithium reagents followed by the addition of a hydride, see: (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 1719–1722. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534–5535. (c) Vincent, G.; Guillot, R.; Kouklovsky, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1350–1353. One example was carried out by using acyclic amide; see: (d) Hwang, Y. C.; Chu, M.; Flower, F. W. *J. Org. Chem.* **1985**, *50*, 3885–3890. For selected examples of addition of metal hydride reagents followed by addition of carbon nucleophiles, see: (e) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373–5379. (f) Tschinkl, M.; Schier, A.; Riede, J.; Gabbaï, F. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545–3547.

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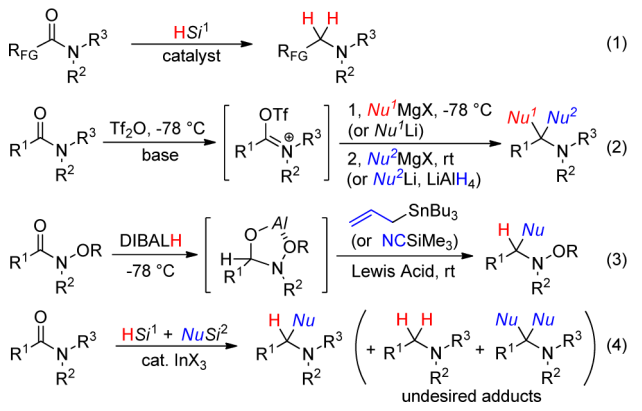
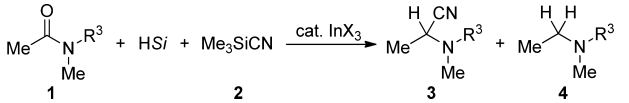
nucleophiles, more than an equimolar amount of additional reagents, and respective control of reaction temperature, which continues to prevent the introduction of feasible functional groups.[6]

Herein, we report a simple, useful, and energy-efficient single-stage synthesis of functionalized amines from amides using hydrosilanes and organosilicon nucleophiles in the presence of an indium(III) catalyst, wherein hydrosilylation and functionalization take place automatically in the desired order (eq 4). This procedure can avoid the prefunctionalization of amides and the stepwise controlled treatments. In contrast to a stepwise addition, single-stage synthesis, however, usually generates two undesired adducts because the conditions cannot be controlled in accordance with each of the nucleophiles, as shown in eq 4.



We have previously reported the indium(III)-catalyzed reductive functionalization of esters using $HSiMe_2Ph$ and organosilicon nucleophiles such as allylsilane and silyl enolates, in which the alkoxy moiety is selectively substituted.[7] Unfortunately, the previous system did not work in the reductive cyanation of *N*-benzyl amide **1a** and

Table 1. Optimization of Reductive Cyanation of Amides **1**[a]



entry	amide **1**; R^3	H*Si* (mmol)	InX_3	yield (%)[b] **3**	yield (%)[b] **4**
1[c]	**1a**; Bn	$HSiMe_2Ph$ (1.5)	InI_3	trace	trace
2[c]	**1b**; Boc	$HSiMe_2Ph$ (1.5)	InI_3	0	0
3	**1c**; Ts	$HSiMe_2Ph$ (1.5)	InI_3	81	14
4	**1c**; Ts	$HSiMePh_2$ (1.5)	InI_3	91	4
5	**1c**; Ts	$HSiEt_3$ (1.5)	InI_3	58	13
6	**1c**; Ts	H_3SiPh (1.5)	InI_3	94	6
7	**1c**; Ts	PMHS (1.5)	InI_3	28	0
8	**1c**; Ts	TMDS (1.5)	InI_3	77	9
9	**1c**; Ts	H_3SiPh (1.0)	InI_3	96 (88)	4
10[c]	**1c**; Ts	H_3SiPh (1.0)	$InCl_3$	0	0
11	**1c**; Ts	H_3SiPh (1.0)	$InBr_3$	92	4
12[c]	**1c**; Ts	H_3SiPh (1.0)	$In(OTf)_3$	0	0
13[d]	**1c**; Ts	H_3SiPh (1.0)	InI_3	88	2
14	**1c**; Ts	$HSiEt_3$ (1.5)	$InBr_3$	49	3
15[e]	**1c**; Ts	–	InI_3	0	0
16[e]	**1c**; Ts	H_3SiPh (1.0)	InI_3	–	99

[a] Reaction conditions: To a solution of **1** (1 mmol), **2** (2 mmol), and InX_3 (0.05 mmol) in dichloromethane (1 mL) was added H*Si*. The reaction mixture was stirred for 1 h at rt. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Value in parentheses indicates isolated yield. [c] >90% of **1** was recovered. [d] Solvent-free conditions. [e] No addition of **2**. PMHS = polymethylhydrosiloxane, TMDS = 1,1,3,3-tetramethylhydrodisiloxane

N-Boc amide **1b** (Table 1, entries 1 and 2). Gratifyingly, an employment of *N*-tosyl amide **1c** afforded α-cyanoamine **3c** in an 80% yield along with 10% of undesired amine **4c** via the single-stage treatment, where to a mixture of InI_3, amide **1c**, and silyl cyanide **2** in dichloromethane was added $HSiMe_2Ph$ (Table 1, entry 3).[8] It was noted that the final addition of hydrosilane to the reaction mixture was a crucial procedure. To optimize the reaction conditions, investigations of hydrosilanes and indium(III) catalysts were carried out (Table 1, entries 4–12). H_3SiPh gave a higher yield of **3c** than other hydrosilanes (Table 1, entries 4–8). In addition, the use of a strictly equimolar amount of H_3SiPh gave the best outcome (Table 1, entry 9). The most appropriate catalyst proved to be InI_3, because it had a high turnover frequency (Table 1, entries 9–12). In contrast, no reaction was promoted by either $InCl_3$ or $In(OTf)_3$.[9] Solvent-free conditions also provided good results (Table 1, entry 13). The $InBr_3/HSiEt_3$ system for the reduction of amides reported by Sakai[2e] gave a low yield of **3c** (Table 1, entry 14). It was notable that no reaction of *N*-tosyl amide **1c** with silyl cyanide **2** was observed in the absence of hydrosilane,[10] while H_3SiPh readily gave dihydrogenated product **4c** in the absence of silyl cyanide **2**

(4) (a) Larouche-Gauthier, R.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4501–4504. (b) Bélanger, G.; O'Brien, G.; Larouche-Gauthier, R. *Org. Lett.* **2011**, *13*, 4268–4271. (c) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew, Chem., Int. Ed.* **2010**, *49*, 3037–3040. (d) Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Chem.—Eur. J.* **2010**, *16*, 12792–12796. (e) Xiao, K.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 8314–8317. (f) Huo, H.-H.; Zhang, H.-K.; Xia, X.-E.; Huang, P.-Q. *Org. Lett.* **2012**, *14*, 4834–4937. Metal-free reduction of amides using Hantzsch ester; see: (g) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18–19. (h) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817–12819.

(5) (a) Shirokake, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6369–6372. (b) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950–953. The introduction of two kinds of carbon nucleophiles was achieved; see: (c) Yanagita, Y.; Nakamura, H.; Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Chem.—Eur. J.* **2013**, *19*, 678–684.

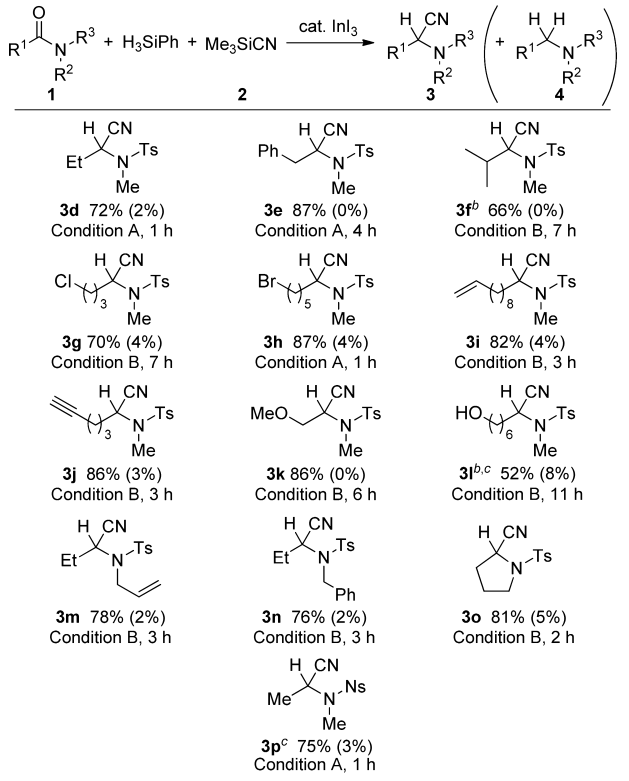
(6) For a review of the deoxygenative functionalization of carbonyl compounds, see: (a) Seebach, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 96–101. For selected examples of an amide to a *N,O*-aminal followed by nucleophilic addition, see: (b) Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706–9707. (c) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469–1471. For selected examples of the functionalization of thioamides to produce functionalized amines, see: (d) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968–5969. (e) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780–781. (f) Agosti, A.; Britto, S.; Renaud, P. *Org. Lett.* **2008**, *10*, 1417–1420. (g) Murai, T.; Mutoh, Y. *Chem. Lett.* **2012**, *41*, 2–8.

(7) (a) Nishimoto, Y.; Inamoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2010**, 3382–3386. (b) Inamoto, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2012**, *14*, 1168–1171.

(8) The addition order was important. To a mixture of InI_3, amide **1c**, and $HSiMe_2Ph$ was added silyl cyanide **2** to give only amine **4c**. See Supporting Information (SI) for the detailed experiment.

(9) Further optimizations of reaction conditions are shown in the SI.

Scheme 1. Reaction of *N*-Sulfonyl Amides **1** with H_3SiPh and Silyl Cyanide **2**[a]

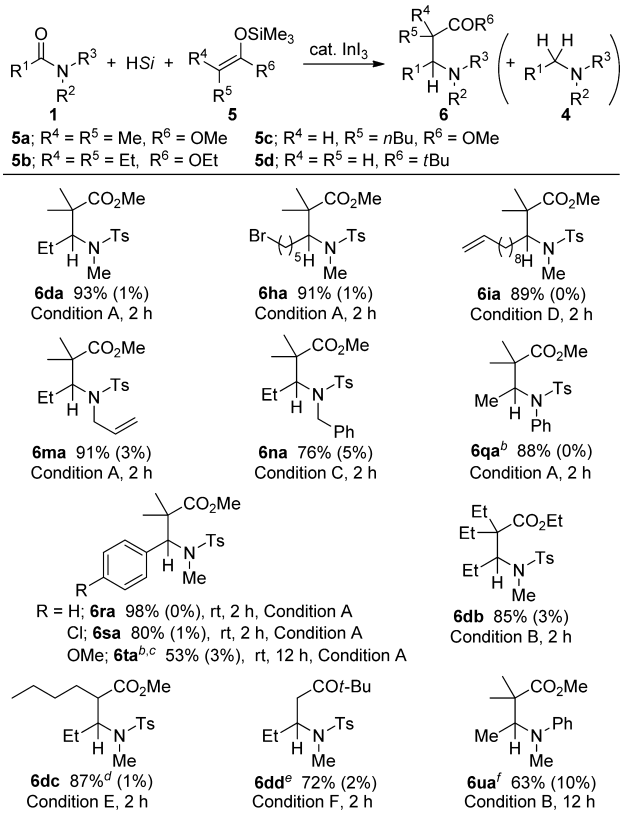


[a] To a solution of **1** (1 mmol), **2** (2 mmol), and InI_3 (0.05 mmol) in solvent (1 mL) was added H_3SiPh. Condition A: dichloromethane, rt. Condition B: 1,2-dichloroethane, 80 °C. Isolated yield of **3**. Values in parentheses indicate NMR yields of **4**. [b] H_3SiPh (1.5 mmol). [c] InI_3 (10 mol %).

(Table 1, entries 15 and 16).[11] These results indicate that the reactivity of hydrosilanes toward amides **1c** was apparently higher than that of silyl cyanide **2**. Additionally, it was very strange and interesting that the second hydride attack was effectively suppressed to produce the desired cyanation product **3c**.

Scheme 1 summarizes the scope of applicable *N*-sulfonyl amides **1**. Simple amides were suitable to give the desired products **3d** and **3e** in 72 and 87% yields, respectively, along with a negligible amount of side products **4**, which were easily removed by column chromatography. A hindered amide effectively afforded product **3f** under heating conditions. Functional groups such as chloro-, bromo-, alkene-, alkyne-, methoxy-, and hydroxy-groups were compatible with this system to give the corresponding functionalized amines **3g**–**l** in high yields. The use of *N*-allylamide and *N*-benzylamide gave high yields of α-cyanoamines **3m** and **3n**, respectively, without deprotection of the allyl- and benzyl-moieties. Five-membered lactam was also applicable to provide cyclic α-cyanoamine **3o** in an

Scheme 2. Reaction of Amides **1** with Hydrosilanes and Silyl Enolates **5**[a]



[a] To a solution of **1** (1 mmol), **5** (1.5 mmol), and InI_3 (0.05 mmol) in solvent (1 mL) was added H*Si*. Isolated yield of **6**. Values in parentheses indicate NMR yields of **4**. Condition A: H_3SiPh (1 mmol), dichloromethane, rt. Condition B: H_3SiPh (1 mmol), 1,2-dichloroethane, 80 °C. Condition C: $HSiMe_2Ph$ (1.5 mmol), dichloromethane, rt. Condition D: $HSiMe_2Ph$ (1.5 mmol), 1,2-dichloroethane, 80 °C. Condition E: $HSiMe_2Ph$ (1.5 mmol), 1,2-dichloroethane, 50 °C. Condition F: $HSiMePh_2$ (1.5 mmol), dichloromethane, rt. [b] H_3SiPh (1.5 mmol). [c] Solvent-free conditions. [d] dr = 52:48. [e] **5** (3 mmol). [f] H_3SiPh (2 mmol), **5** (3 mmol), InI_3 (0.1 mmol).

81% yield. Generally, a nosyl (*o*-nitrobenzenesulfonyl) group on the nitrogen atom can be more easily removed than a tosyl group under mild conditions.[12] To our delight, *N*-nosyl amide **1p** also reacted with H_3SiPh and silyl cyanide **2** in the presence of 10 mol % of InI_3 to give the corresponding product **3p** in 75% yield.

Next, we demonstrated a Mannich-type reaction by the application of silyl enolate **5** instead of silyl cyanide **2** (Scheme 2). To the best of our knowledge, there has been no study into the reductive functionalization of amides using an enolate as a nucleophile.[13] The single-stage treatment of an *N*-tosyl amide with H_3SiPh and a ketene silyl acetal **5a** successfully gave *β*-amino ester **6da** in a 93% yield.[14] The bromo and alkenyl groups were compatible with this system to produce amines **6ha** and **6ia**. Moreover, allyl, benzyl, and phenyl substituents on the nitrogen atom

(10) See the SI concerning the reaction of amide **1c** with silyl cyanide **2** in the presence of an InI_3 catalyst.

(11) A quantitative yield of **4c** indicated that two hydrogens of H_3SiPh were introduced.

(12) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

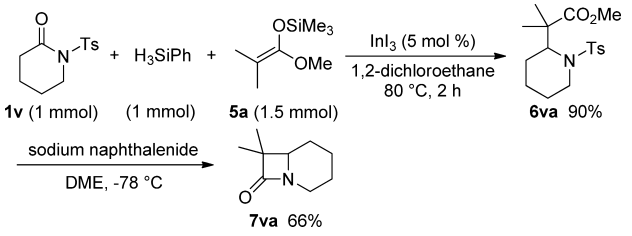
(13) The addition of an enolate into formamide followed by reduction using $NaBH(OAc)_3$ is reported in the literature. See ref 4a.

(14) See the SI concerning the opimization of reaction conditions.

did not suppress this reaction, furnishing **6ma**, **6na**, and **6qa**, respectively. The reaction of aromatic amides **1r** and **1s** gave the corresponding products **6ra** and **6sa**, respectively, under the usual conditions, whereas **1t** possessing an electron-donating group required solvent-free conditions to give the product **6ta**. When the treatments of dialkyl- and monoalkyl-ketene silyl acetals (**5b** and **5c**) were conducted, desired amines **6db** and **6dc** were obtained in high yields, respectively. Silyl enol ether **5d** had a nucleophilicity that was lower than ketene silyl acetal **5a**–**5c**[15] and also furnished adduct **6dd**, which was achieved by using the mild reducing reagent $HSiMePh_2$ instead of H_3SiPh or $HSiMe_2Ph$ to suppress the generation of byproduct **4d**. Interestingly, *N*-phenyl amide was applicable instead of *N*-tosyl amide to provide amine **6ua** under harsh conditions.

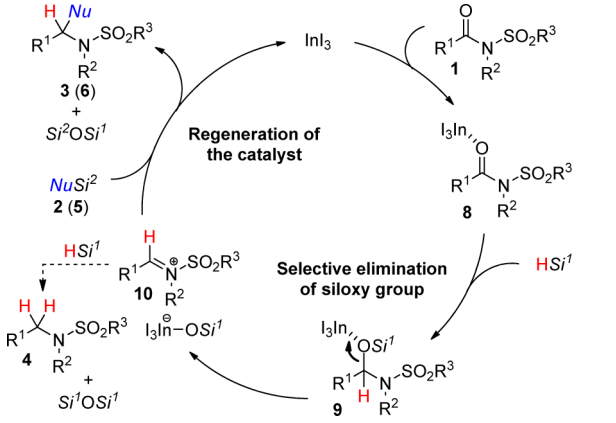
Six-membered lactam **1v** also gave the cyclic amine **6va** in a 90% yield, which was further transformed to fused bicyclic *β*-lactam **7va** via deprotection of the tosyl moiety by sodium naphthalenide (Scheme 3). This procedure is the first transformation from a lactam to a fused bicyclic *β*-lactam.[16]

Scheme 3. Transformation from Six-Membered Lactam **1v** to Fused Bicyclic *β*-Lactam **7va**



A plausible reaction mechanism is illustrated in Scheme 4. First, as noted in Table 1, entries 15 and 16, a completely exclusive hydrosilylation over the reaction with organosilicon nucleophile **2** (**5**) takes place to afford *N,O*-acetal intermediate **9**. Second, the selective elimination of the siloxy group generates iminium cation **10**. Finally, the resultant **10** predominantly reacts with **2** (**5**) over hydrosilane (HSi^1) to produce the functionalized amine **3** (**6**) along with the regeneration of the InI_3 catalyst. Besides the activation of amide **1** and iminium cation **10**, the sulfonyl group plays an important role in the selective release of a siloxy group from *N,O*-acetal **9** via a decrease in the interaction of the amine moiety with the indium(III) catalyst.[17] Although the cause of the predominant attack of silyl cyanide **2** and silyl enolate **5** over hydrosilylation is unclear, it may be the high reactivity of $NuSi^2$ **2** (**5**) toward the highly polarized iminium cation **10**.

Scheme 4. Plausible Reaction Mechanism



In conclusion, we have established the synthesis of functionalized amines from *N*-sulfonyl amides using hydrosilanes and organosilicon nucleophiles such as silyl cyanide and silyl enolates in the presence of an indium triiodide catalyst. In contrast to conventional methods, this step-economical system is a practical "single-stage" introduction of two kinds of nucleophiles into amides.

Acknowledgment. This work was supported by the Ministry of Education, Culture, Sports, Science and Technology (Japan).

Supporting Information Available. Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) For the reactivity order of organosilicon nucleophiles, see: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.

(16) For selected examples of the construction of fused bicyclic *β*-lactam **7va**, see: (a) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056–1059. (b) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761–1764.

(17) Our previous report, which conducted the indium(III)-catalyzed allylation of imines, shows that the introduction of a tosyl group gave good results; see: Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227–8235.

The authors declare no competing financial interest.