

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

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Received May 30, 2013

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 pre-functionalized 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

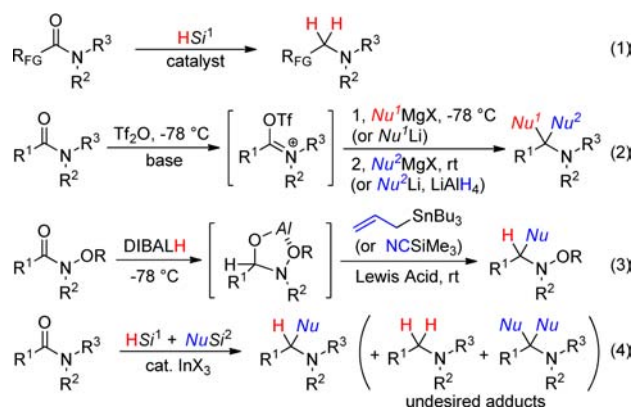
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nucleophiles, more than an equimolar amount of additional reagents, and respective control of reaction temperature, which continues to prevent the introduction of feasible functional groups.⁶

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 pre-functionalization 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	HSi (mmol)	InX ₃	yield (%) ^b	
				3	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)	$\text{In}(\text{OTf})_3$	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 ^c	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 HSi. 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 $\text{In}(\text{OTf})_3$.⁹ Solvent-free conditions also provided good results (Table 1, entry 13). The $\text{InBr}_3/\text{HSiEt}_3$ 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**

(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.

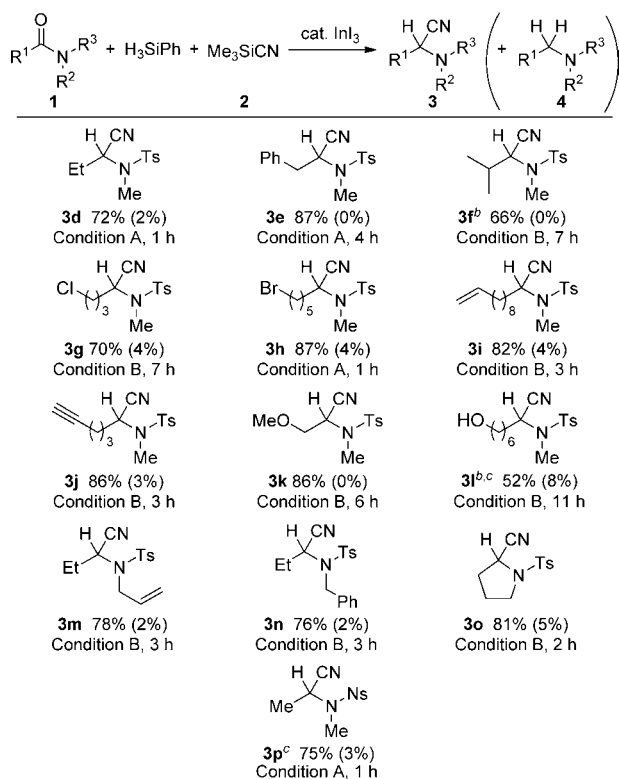
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Scheme 1. Reaction of *N*-Sulfonyl Amides **1** with H₃SiPh and Silyl Cyanide **2**^a



^aTo a solution of **1** (1 mmol), **2** (2 mmol), and InI₃ (0.05 mmol) in solvent (1 mL) was added H₃SiPh. Condition A: dichloromethane, rt. Condition B: 1,2-dichloroethane, 80 °C. Isolated yield of **3**. Values in parentheses indicate NMR yields of **4**. ^bH₃SiPh (1.5 mmol). ^cInI₃ (10 mol %).

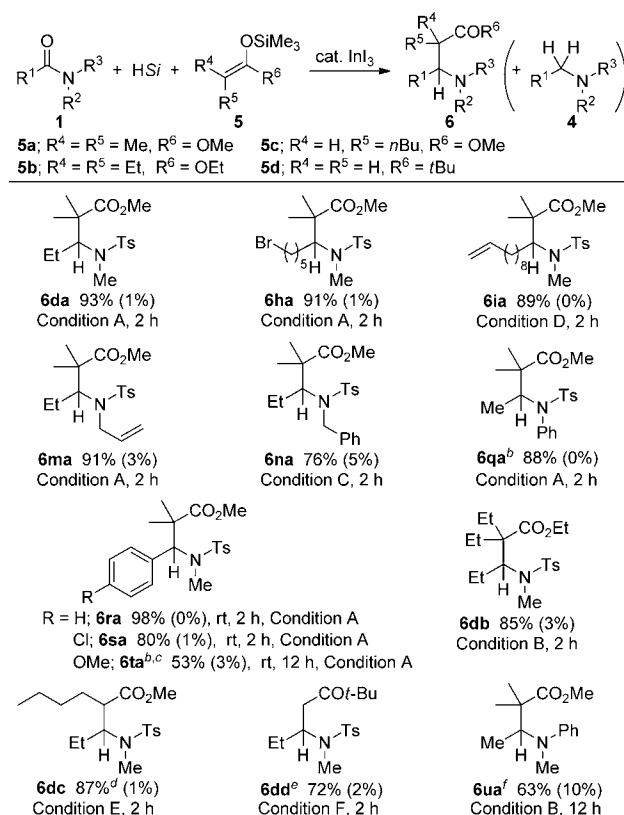
(Table 1, entries 15 and 16).¹¹ These results indicate that the reactivity of hydrosilanes toward amides **1c** was apparently higher than that of silyl cyanide **2**. Additionally, it was very strange and interesting that the second hydride attack was effectively suppressed to produce the desired cyanation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

(10) See the SI concerning the reaction of amide **1c** with silyl cyanide **2** in the presence of an InI₃ catalyst.

(11) A quantitative yield of **4c** indicated that two hydrogens of H₃SiPh were introduced.

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



^aTo a solution of **1** (1 mmol), **5** (1.5 mmol), and InI₃ (0.05 mmol) in solvent (1 mL) was added HSi. Isolated yield of **6**. Values in parentheses indicate NMR yields of **4**. Condition A: H₃SiPh (1 mmol), dichloromethane, rt. Condition B: H₃SiPh (1 mmol), 1,2-dichloroethane, 80 °C. Condition C: HSiMe₂Ph (1.5 mmol), dichloromethane, rt. Condition D: HSiMe₂Ph (1.5 mmol), 1,2-dichloroethane, 80 °C. Condition E: HSiMe₂Ph (1.5 mmol), 1,2-dichloroethane, 50 °C. Condition F: HSiMePh₂ (1.5 mmol), dichloromethane, rt. ^bH₃SiPh (1.5 mmol). ^cSolvent-free conditions. ^ddr = 52:48. ^e**5** (3 mmol). ^fH₃SiPh (2 mmol), **5** (3 mmol), InI₃ (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 H₃SiPh and silyl cyanide **2** in the presence of 10 mol % of InI₃ 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 H₃SiPh 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

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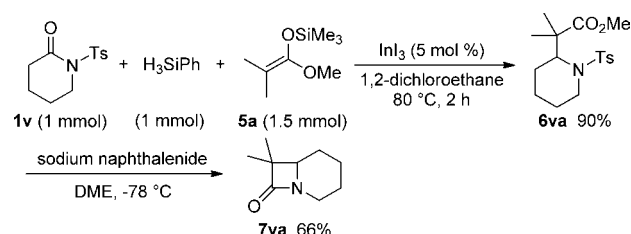
(13) The addition of an enolate into formamide followed by reduction using NaBH(OAc)₃ is reported in the literature. See ref 4a.

(14) See the SI concerning the optimization 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 HSiMePh₂ instead of H₃SiPh or HSiMe₂Ph 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

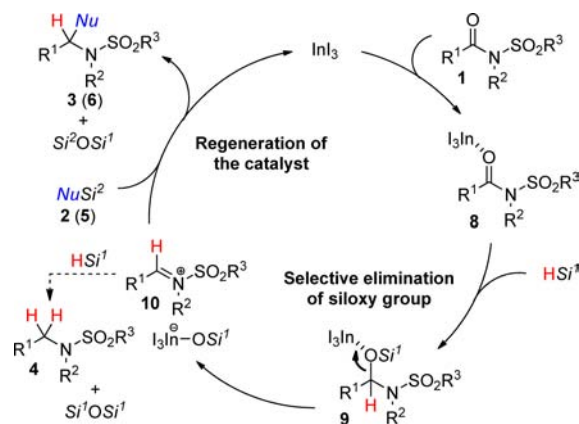
Scheme 3. Transformation from Six-Membered Lactam **1v** to Fused Bicyclic β -Lactam **7va**



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^{*i*}) to produce the functionalized amine **3** (**6**) along with the regeneration of the InI₃ 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 NuSi² **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>.

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The authors declare no competing financial interest.