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Direct Reductive Amination of Aldehydes and Ketones Using Phenylsilane: Catalysis by Dibutyltin Dichloride

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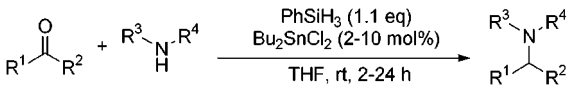
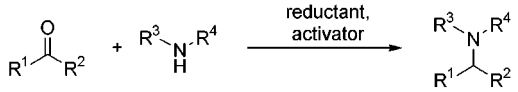
ABSTRACT



A procedure for direct reductive amination of aldehydes and ketones was developed which uses phenylsilane as a stoichiometric reductant and dibutyltin dichloride as a catalyst. Suitable amines included anilines and dialkylamines but not monoalkylamines.

The direct reductive amination of aldehydes and ketones is used extensively to prepare primary, secondary, and tertiary amines (Scheme 1).[1,2] This reaction offers compelling

Scheme 1



advantages over other amine syntheses, including brevity, wide commercial availability of substrates, generally mild reaction conditions, and in some cases exceptionally high functional group tolerance. Several reagents which effect direct reductive amination have been recently developed, including the following: $NaBH(OAc)_3$;[1a] $ZnCl_2-NaBH_4$;[3] $NiCl_2-NaBH_4$;[4] $Ti(O^iPr)_4$−polymethylhydrosiloxane;[5] $Ti(O^iPr)_4-NaBH_4$;[6] Bu_3SnH;[7] Bu_2SnClH and Bu_2SnIH;[8] decaborane;[9] silica gel−$ZnBH_4$;[10] Et_3SiH−trifluoroacetic acid;[11] pyridine−BH_3.[12] Reductive *N*-alkylation of amides with carbonyl compounds using Et_3SiH−trifluoroacetic acid has also been described.[13]

In connection with efforts to use direct reductive amination in multiple parallel solution phase synthesis, we desired a protocol that required no prechromatography product manipulation. Most published procedures call for filtration, aqueous workup, solvent evaporation, or combinations of these techniques prior to final purification. These manipulations typically serve to remove or decompose stoichiometric quantities of organic insoluble metal salts introduced as reductants or promoters. It therefore appeared reasonable that

(1) For a leading reference, see: (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. For a recent review, see: (b) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55.

(2) The term "direct reductive amination" describes a reaction in which an imine intermediate is not preformed or isolated and contrasts with "indirect reductive amination." See ref 1a.

(3) Bhattacharyya, S. *Synth. Commun.* **1997**, *27*, 4265.

(4) Saxena, I.; Borah, R.; Sarma, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 503.

(5) Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, 1655.

(6) Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781.

(7) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* **2000**, 556.

(8) (a) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 789. (b) Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* **1999**, *1*, 1579. (c) Shibata, I.; Moriuchi-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383. (d) Shibata, I.; Suwa, T.; Sugiyama, E.; Baba, A. *Synlett* **1998**, 1081.

(9) Bae, J. W.; Lee, S. H.; Cho, Y. J.; Yoon, C. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 145.

(10) Ranu, B. C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 370.

(11) Chen, B.-C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245.

(12) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995.

(13) Dubé, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295.

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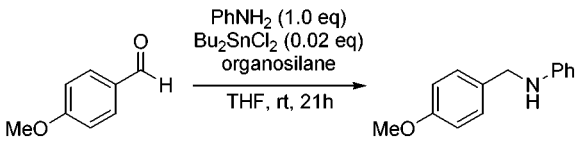
Table 1. Organosilane Reductants for Catalytic Reductive Amination



entry	organosilane (equiv)	yield, %[a]
1	Et_3SiH (1.1)	nr
2	Ph_3SiH (1.1)	nr
3	Ph_2SiH_2 (1.1)	88
4[b]	Ph_2SiH_2 (1.1)	*c*
5	$PhSiH_3$ (1.1)	82
6[b]	$PhSiH_3$ (1.1)	83
7	$PhSiH_3$ (0.50)	83
8	$PhSiH_3$ (0.33)	83
9	$PhSiH_3$ (0.20)	*c*
10[d]	PMHS (2.0[e])	82
11[f]	$PhSiH_3$ (1.1)	nr

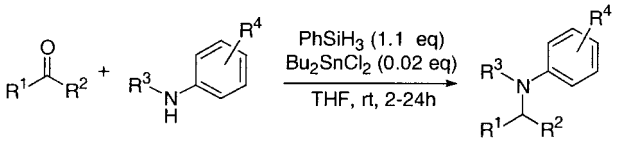
[a] Isolated yield of chromatographed product. Reactions were monitored for completion by ^1H NMR of the crude mixture: nr = less than 5% conversion. [b] Reaction time was 2 h. [c] Not determined due to incomplete conversion. [d] Reaction produced a filterable gel-like precipitate. [e] Stoichiometry was based on a hydride content of 16.7 mmol per gram of polymer (ref 20). [f] Reaction was performed in the absence of Bu_2SnCl_2.

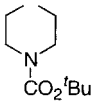
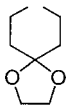
using highly organic soluble reductants such as organosilanes with activation by efficient catalysts could significantly streamline the direct reductive amination reaction.[14,15]

Recent literature reports suggested the possibility that diorganotin dihalides could catalyze direct reductive aminations in the presence of organosilane reductants.[16] In particular, catalysis of both imine formation[17] and imine reduction with organosilanes[15e] have been separately described. If these two processes occurred in the same reaction medium, development of a catalytic silane-based direct reductive amination procedure would be feasible.

This idea was tested in a model study involving the direct reductive amination of 4-methoxybenzaldehyde with aniline in the presence of 2 mol % of dibutyltin dichloride (Table 1).[18,19] Reductive amination was promoted by diphenylsilane, phenylsilane, and polymethylhydrosiloxane (PMHS). Of these three reductants, phenylsilane was most suitable because it was more active than diphenylsilane (entries 4 and 6) and because PMHS produced an insoluble precipitate which required filtration (entry 10). Reactions performed with substoichiometric phenylsilane suggest that all three hydrogen atoms are transferable (entries 5, 7, 8, and 9). No reductive amination was observed with phenylsilane in the absence of dibutyltin dichloride (entry 11), demonstrating a catalytic role for the organotin.

Table 2. Direct Reductive Aminations of Carbonyl Compounds with Anilines



entry	R^1	R^2	R^3	R^4	yield, %[a]
1	Ph	H	H	H	80
2	4-$(NO_2)C_6H_4$	H	H	H	85
3	4-I-C_6H_4	H	H	H	86
4[b]	PhCH=CH	H	H	H	70[c]
5	2-(BnO)C_6H_4	H	H	H	82
6	4-(MeO)C_6H_4	H	Me	H	83
7[d]	4-(MeO)C_6H_4	H	H	4-OMe	82
8	4-(MeO)C_6H_4	H	H	4-NO_2	85
9	4-(MeO)C_6H_4	H	H	2-$C(Me)_3$	77
10	*n*-C_6H_{13}	Me	H	4-NO_2	87
11			H	4-NO_2	86
12			H	H	91
13[e]	Ph	Me	H	H	70

[a] Isolated yield of chromatographed, analytically pure product. [b] Reaction was exothermic. [c] Traces of bis-cinnamyl aniline were also isolated. [d] Reaction solidified. Additional THF (0.3 mL) was added to aid mixing. [e] 0.10 equiv of Bu_2SnCl_2 was used.

To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with anilines using phenylsilane as a stoichiometric reductant and dibutyltin dichloride as a catalyst (Table 2). Reactions with substrates bearing potentially reducible functional groups including aryl iodide (entry 3), cinnamyl (entry 4), nitro (entries 2, 8, 10, and 11), and benzyloxy (entry 5) gave the anticipated products, without detectable reduction side products. Potentially acid-labile groups were also well tolerated (entries 11 and 12). Reactions involving sterically demanding or electron poor anilines proceeded in good yields, although at noticeably reduced rates (entries 6, 8, 9, 10, and 11). Although acetophenone is a difficult case for some reductive amination protocols, the use of 10 mol % of

(14) Laboratory automation of existing protocols is another approach to this problem. See: Bhattacharyya, S.; Fan, L.; Vo, L.; Labadie, J. *Comb. Chem. High Throughput Screening* **2000**, *3*, 117.

(15) To our knowledge, only three direct reductive aminations using organosilane reductants have been described, and all employ stoichiometric promoters. See refs 5, 11, and 13. For recent examples of imine reductions by organosilanes, see: (a) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921. (b) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (c) Takaki, K.; Kamata, T.; Miura, Y.; Shishido, T.; Takehira, K. *J. Org. Chem.* **1999**, *64*, 3891. (d) Chandrasekhar, S.; Reddy, M. V.; Chandraiah, L. *Synth. Commun.* **1999**, *29*, 3981. (e) Lopez, R. M.; Fu, G. C. *Tetrahedron* **1997**, *53*, 16349. (f) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.

dibutyltin dichloride enabled reductive amination of this ketone at a rate comparable to that of the other substrates (entry 13).

Reductive amination of 4-methoxybenzaldehyde with primary and secondary alkylamines was also examined (Table 3). Reactions with both cyclic and acyclic secondary amines gave the anticipated products in moderate yields (entries 1−4). Interestingly, reductive amination with piperidine also proceeded in the absence of dibutyltin dichloride, although in significantly lower yield (entries 1 and 5). In contrast, reactions with primary alkylamines gave the corresponding imines with complete consumption of phenylsilane, as determined by ^{1}H NMR of the crude reaction mixtures (entries 6 and 7).

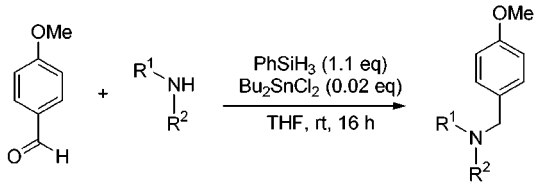
Unlike reductive aminations with anilines, exothermicity and vigorous gas evolution were consistently observed upon adding phenylsilane to reaction mixtures containing either primary or secondary alkylamines. To determine the origin of this behavior, control reactions were performed in the absence of catalyst and carbonyl compound. Addition of phenylsilane to a solution of cyclohexylamine in THF resulted in mild gas evolution and some phenylsilane decomposition. This effect was much more pronounced when phenylsilane was added to a solution of cyclohexylamine and 1 equiv of water in THF. Alkylamine-promoted oxidation of phenylsilane with the water produced from imine condensation may play a role in the lack of reductive amination observed with cyclohexylamine and benzylamine.[21]

Imines are in some cases reduced by the same reductants used in direct reductive aminations.[22] To examine this possibility, *N*-benzylidineaniline was treated with phenylsilane under various conditions (Table 4). In the presence of 2 mol % of dibutyltin dichloride, only trace reduction, with no detectable decomposition of phenylsilane, was observed (entry 1). In an attempt to duplicate the exact conditions of the direct reductive amination reaction, imine reduction was performed in the presence of both dibutyltin dichloride and 1 equiv of water (entry 2). Complete consumption of the imine was observed, and the secondary amine product was isolated in good yield. No reaction occurred in the absence of dibutyltin dichloride, either in the presence or absence of water (entries 3 and 4).

Other species have been found which behave as reductive amination catalysts, although none were as effective as dibutyltin dichloride. For example, metal salts (scandium triflate and zinc iodide), a Bronsted acid (hydrogen chloride), and another diorganotin (dibutyltin oxide) catalyzed the reductive amination of 4-methoxybenzaldehyde with aniline in the presence of phenylsilane. Efforts are underway to evaluate the mechanistic implications of these observations and to identify more active catalysts.[23]

The direct reductive amination protocol reported here offers some advantages over other methods. Because little,

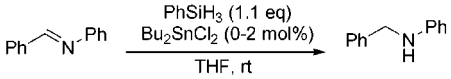
Table 3. Direct Reductive Amination Using Alkylamines[a]



entry	amine	yield, %[b]
1	piperidine	70
2	morpholine	78
3	*N*-phenylpiperazine	67
4	diethylamine	49
5[c]	piperidine	13[d]
6	cyclohexylamine	*e*
7	benzylamine	*e*

[a] Because of exothermicity, reactions were performed with cooling from a room temperature water bath and dropwise phenylsilane addition. [b] Isolated yield of chromatographed, analytically pure product. [c] Reaction was performed in the absence of Bu_2SnCl_2. [d] ^{1}H NMR of the crude reaction mixture revealed remaining aldehyde and fully decomposed phenylsilane. [e] ^{1}H NMR of the crude reaction mixture showed imine formation and phenylsilane decomposition.

Table 4. Reduction of *N*-Benzylidineaniline with Phenylsilane



entry	Bu_2SnCl_2, mol %	additive (equiv)	time, h	yield, %[a]
1	2	none	19	nr
2	2	water (1)	4	89
3	0	none	19	nr
4	0	water (1)	19	nr

[a] Isolated yield of chromatographed product. Reactions were monitored for completion by ^{1}H NMR of the crude mixture: nr = less than 5% conversion.

(16) Catalysis of a variety of organic reactions by diorganotins has been reported. For some recent examples, see: (a) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996. (b) Orita, A.; Sakamoto, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899. (c) Whitesell, J. K.; Apodaca, R. *Tetrahedron Lett.* **1996**, *37*, 2525. (d) Whitesell, J. K.; Apodaca, R. *Tetrahedron Lett.* **1996**, *37*, 3955.

(17) Stetin, C.; de Jeso, B.; Pommier, J. C. *Synth. Commun.* **1982**, *12*, 495.

(18) **General experimental procedure**: A solution of carbonyl compound (1.5 mmol, 1 equiv) in tetrahydrofuran (0.3 mL) was treated with an amine (1.5 mmol, 1 equiv), followed by dibutyltin dichloride (9 mg, 0.03 mmol, 0.02 equiv). After 1−2 min at room temperature, the resulting mixture was treated with organosilane (1.7 mmol, 1.1 equiv). Upon completion, the reaction was diluted with chromatography solvent (with added dichloromethane or ethyl acetate to dissolve solid material) and chromatographed.

(19) THF was selected as a solvent because of its ability to form concentrated solutions with a variety of potential substrates.

(20) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.

(21) Dehydrogenative coupling of hydroxylic compounds with silicon hydrides in the presence of amine bases is a known process. For a review, see: Lukevics, E.; Dzinatara, M. *J. Organomet. Chem.* **1985**, *295*, 265.

(22) For examples, see refs 1a and 8a.

if any, competitive carbonyl reduction was observed in these reactions, the use of excess aldehyde or ketone is unnecessary. Because of its catalytic nature, reaction rates can be increased by simply adding more catalyst or through the potential development of more active catalysts. Finally, product isolation is streamlined by the use of small solvent volumes and by the elimination of aqueous workup, filtration, and solvent removal steps prior to chromatography.[24]

In summary, we have developed a simple direct reductive amination procedure which employs phenylsilane as a stoichiometric reductant and dibutyltin dichloride as a catalyst. Both aldehydes and ketones were reductively aminated with anilines and secondary alkylamines, although the reaction failed with primary alkylamines. Studies aimed at broadening the scope of this reaction and understanding its mechanism are currently in progress.

Acknowledgment. We thank Professor Scott Denmark (University of Illinois at Urbana−Champaign), Curt Dvorak, and Nicholas Carruthers for helpful discussions.

Supporting Information Available: Experimental details and characterization for the compounds in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Direct reductive aminations are known to be promoted by Bu_2SnClH under conditions similar to those we report here (ref 8). Although our results are not inconsistent with the catalytic intermediacy of such a species, other possibilities, including simple acid catalysis either by Bu_2SnCl_2 itself or a hydrolysis product, cannot be ruled out.

(24) The fate of organosilicon and organotin byproducts in these reactions has not been examined in detail. Highly nonpolar UV-active species were detected chromatographically, but these species did not usually interfere with product isolation. Final products contained no detectable organosilicon- or organotin-derived impurities, as determined by ^1H and ^{13}C NMR.