## Ligand-Free Hydrosilylation of Aldehydes Mediated by Highly Active Zinc Metal

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The reduction of carbonyl compounds has been generally considered to be a fundamental protocol for the preparation of the corresponding alcohols. Catalytic hydrogenation of carbonyls has long been a traditional method for achieving this.<sup>1</sup> Aside from this protocol, metal-hydride,<sup>2</sup> boron-based reagents,<sup>3</sup> and bio-catalytic reduction<sup>4</sup> are also considered to be suitable methodologies. In addition, an emerging tool is reduction of the carbonyl group in the presence of a transition-metal catalyst. Numerous transition-metals have been extensively examined to successfully complete this transformation,<sup>5</sup> especially in transfer hydrogenation which is a safe and operationally simple protocol utilizing either element hydrogen or metal-hydrides.<sup>51, j</sup>

Along with these protocols, a zinc-based reduction process has been extensively applied for reduction of carbonyl compounds, mainly due to the environmental friendliness and economic benefits. Furthermore, the zinc-based reduction protocol could be readily extended to hydrosilylation of carbonyl compounds, thereby providing the corresponding alcohols. Since the first report by Caubere,<sup>6</sup> and pioneering work by Minoun,<sup>7</sup> it has emerged as an attractive synthetic method to reduce carbonyl compounds.<sup>8</sup>

When using this approach, zinc complexes such as zinc acetate and diethylzinc, which are particularly activated by nitrogen-chelating ligands, have frequently been used as pre-catalysts. In early studies of zinc-catalyzed hydrosilylation of aldehydes and ketones, both zinc(II) salt and zinc (0) powder worked well to obtain the corresponding alcohols in the presence of metal-hydride and chlorotrimethylsilane. In 2009, Nishiyama *et al.* reported a successful method for hydrosilylation of carbonyl compounds using zinc acetate as a catalyst without any assistance from ligands.<sup>9</sup>

From a synthetic point of view, reactions of carbonyl compounds with zinc metal also have value in novel applicability. A recent study by Len *et al.* used zinc metal and carbonyl compound for selective reductive pinacol coupling.<sup>10</sup> The reaction was carried out with zinc metal and NH<sub>4</sub>Cl in an aqueous media, yielding the diols as a major product along with small amounts of reduced alcohols. More recently, Dash's group has described a relatively simple process for selective reduction of carbonyls using a

combination of zinc metal-powder with an aqueous  $NH_4Cl$  solution as a proton source in THF. The corresponding product alcohols were exclusively produced along with a trace amount of the pinacol product diols (Scheme 1).<sup>11</sup>

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Inspired by the above results, we were interested in exploring the nature of highly active zinc (Zn\*) in the hydrosilylation of carbonyl compounds. To investigate the potential of our strategy, carbonyl compounds were treated with a mixture of highly active zinc and silane in the absence of any other ligands. Herein, we describe the successful development of Zn\*-mediated hydrosilylation of aldehydes and ketones, producing the corresponding alcohols as a major product.

To elucidate our strategy, the first step was to figure out the role of highly active zinc, especially for stoichiometric or catalytic use. As shown in Table 1, several different molar ratios of Zn\*/silane/aldehyde were examined under the conditions described below. When 1.0 equiv. of Zn\* with 1.0 equiv. of triethoxysilane was used, benzaldehyde (1a) was fully consumed at refluxing temperature in 39 h. After an appropriate workup was carried out, reduced benzyl alcohol (2a) was obtained with an isolated yield of 74% along with 18% pinacol-type coupling product (3a) (Table 1, entry 1). Surprisingly, by reducing the amount of Zn\* to 0.5 equiv., the reduction proceeded smoothly and lead to the exclusive formation of 2a (isolated yield of 89%, Table 1, entry 2). However, further reduction of the amount of Zn\* to 0.1 equiv. resulted in the formation of an unidentified mixture even though the conversion was fairly good with an extended reaction time. To clarify the influence of the amount of silane on the transformation, two more tests were carried out. Much less conversion occurred with the use of 0.5 equiv. of (EtO)<sub>3</sub>SiH compared to benzaldehyde (Table 1, entry 4). Excellent conversion was observed by use of an excess amount of silane, for which there was no improved selectivity of 2a to 3a (Table 1, entry 5). Additional examinations were performed to determine the role of each reagent, Zn\* and silane (Table 1, entries 6, 7, and 8), respectively. These indicated that the presence of each reagent was extremely critical for successful completion of the transformation.

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R	O R'	conditions		H + R'	P $R'$ $R'$ $R'$ $R'$
			A	D	D
	с	onditions	A	В	reference
	2.0 equi	v. Zn(0)/acids	minor	major	ref. 10
	5.0 equi	v. Zn(0)/NH <sub>4</sub> Cl	major	minor	ref. 11
_	0.5 equi	iv. Zn*/silane	major	minor	this work

Scheme 1. Development of carbonyl reduction with zinc metal.

With the results stated above, our next test was to identify a suitable silane reagent for use with our system. Various observations made in previous studies of metal-based hydrosilylation of carbonyl compounds clearly indicate that a suitable silane derivative is required for each reaction system to achieve successful functional group transformation. Therefore, we also examined several silane reagents in terms of the reduction of benzaldehyde under our conditions. Reaction with a readily available polymethylhydrosiloxane (PMHS) resulted in a mixture of unidentified products only (Table 1, entry 10). Similarly, both of the

Table 1. Screening of optimization conditions.

alkylsilanes Et<sub>3</sub>SiH and Me<sub>2</sub>PhSiH turned out to be inappropriate reagents for our system (Table 1, entries 11 and 12). Interestingly, another alkoxysilane,  $(EtO)_2MeSiH$ , yielded a similar result as  $(EtO)_3SiH$  (Table 1, entry 9). These observations strongly suggest that the presence of a polar bond such as the O—Si bond in silane substrates is required for effective reduction of carbonyls by highly active zinc. Several previous studies on zinc-based hydrosilylation of carbonyls have made similar observations.<sup>9,12</sup>

To undertake a brief mechanistic study, a control experiment was carried out as follows. Benzaldehyde was treated under the same conditions as used above (Table 1, entry 2) in the presence of a radical scavenger such as (3, 21-tetramethylpiperidine-1-yl)oxidanyl (TEMPO). As shown in Scheme 2, no reaction took place, which was the same result as a previous work.<sup>11</sup> This result is sufficient to infer that the electron transfer from Zn\* to the aldehyde generates a reactive alkoxy radical intermediate that subsequently cooperates with silane, and that then results in the corresponding reduced benzyl alcohol as the major product after an appropriate workup procedure. The inhibitory effect of TEMPO indicates that this reaction takes place by a single electron transfer (SET) pathway.

Based on these results, several representative benzaldehyde derivatives were hydrosilylated next to study the scope and the limitations of the reaction using the combination of active zinc and triethoxysilane. The results are summarized



Entry	Zn* (equiv.)	Silane	Time (h)	<b>2a</b> (%) <sup>a</sup>	<b>3a</b> $(\%)^a$
1	1.0	(EtO) <sub>3</sub> SiH (1.0 equiv.)	12	74	18
2	0.5	(EtO) <sub>3</sub> SiH (1.0 equiv.)	12	89	1
3	0.1	(EtO) <sub>3</sub> SiH (1.0 equiv.)	24	$(88)^{b}$	
4	1.0	(EtO) <sub>3</sub> SiH (0. 11 equiv.)	24	$(48)^{d}$	
5	1.0	(EtO) <sub>3</sub> SiH (3.0 equiv.)	18	79	14
6	_	(EtO) <sub>3</sub> SiH (1.0 equiv.)	24	e	e
7	0.5		24	e	e
8	1.0		24	e	e
9	0.5	(EtO) <sub>2</sub> MeSiH(1.0 equiv.)	12	82	
10	0.5	PMHS (1.0 equiv.)	12	f	f
11	0.5	Et <sub>3</sub> SiH (1.0 equiv.)	24	e	e
12	0.5	Me <sub>2</sub> PhSiH (1.0 equiv.)	24	e	e

<sup>a</sup> Isolated yield (based on benzaldehyde), otherwise mentioned.

<sup>b</sup> Conversion ratio of **2a** to benzaldehyde by G/C, along with unidentified mixture, no isolation.

<sup>c</sup> No diol formed by TLC.

<sup>d</sup> Conversion ratio of **2a** to benzaldehyde, no isolation.

<sup>e</sup> No reaction occurred.

<sup>f</sup> Unidentified products only.

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**Table 2.** The scope of Zn\*/silane combination in hydrosilylation of benzaldehydes.



Entry	FG	Product $(\%)^a$
1	7-Cl (1b)	<b>2b</b> (59)
2	7-NO <sub>2</sub> (1c)	<b>2c</b> (74)
3	7-CN (1d)	<b>2d</b> (63)
4	7-CO <sub>2</sub> Et ( <b>1e</b> )	<b>2e</b> (68)
5	7-OMe (1f)	<b>2f</b> (72)
6	7-CH <sub>3</sub> ( <b>1g</b> )	<b>2g</b> (75)
7	7-Ph ( <b>1h</b> )	<b>2h</b> (77)
8	7-NMe <sub>2</sub> (1i)	<b>2i</b> (66)
9	7-OMs (1j)	<b>2j</b> (59)
10	6-OMe (1k)	<b>2k</b> (64)
11	6-CF <sub>3</sub> (11)	<b>2l</b> (69)
12	6-Br ( <b>1m</b> )	<b>3b</b> $(39)^b$
13	3-Cl (1n)	<b>2m</b> (48)
14	3-OH (10)	No reaction

<sup>*a*</sup> Isolated yield (based on benzaldehyde), otherwise mentioned. <sup>*b*</sup> No reduced product obtained. Instead, diol (**3b**) and unreacted

aldehyde obtained under the conditions used.

in Table 2. Irrespective of the electron-withdrawing group present within the para-substituted benzaldehydes (1b-1e), moderate to good conversions to the corresponding benzyl alcohols were obtained (Table 2, entries 1-4). With stronger electron-donating substituents such as methoxy and dimethylamino groups, no profound difference was observed in terms of the isolated yield (2f, 72%, 2i, 66%, respectively). The position of the substituent on the arene ring was not a determinant factor for successful execution of our system, resulting in the alcohols (2k and 2l) in good yields (entries 10 and 11). Interestingly, when 6-bromobenzaldehyde was treated under the same conditions, no complete reduction was observed, furnishing a 39% isolated yield of homocoupling product of aldehyde, 3, 6-di-(6'-bromophenyl) butane-3, 6-diol (3b), along with a substantial amount of unreacted 6-bromobenzaldehyde. A moderate yield (Table 2, entry 13) was also obtained from the reaction of 3-chlorobenzaldehyde (1n). No hydrosilylation took place with salicylaldehyde (Table 2, entry 14).

In order to examine the generality of this catalytic system, we applied the optimized conditions with various aldehydes, and the results are displayed in Table 3. The reaction yield with 3-thiophenecarboxaldehyde (1p) was satisfactory (60%) whereas the reaction with 3-furaldehyde (1q) resulted in the formation of a mixture of unidentified by-products along with only 22% of the desired product (Table 3, entries 1 and 2). 3-Pyridinecarboxaldehyde (1r) was shown to be a suitable substrate for our system (Table 3, entry 3). Cinnamaldehyde (1s), as well as 3-naphthaldehyde (1t), worked well with the combination of Zn\* and silane, affording the corresponding reduced alcohols (2q and 2r, respectively) in high yields (Table 3, entries 4 and 5). Even though a somewhat reduced yield was obtained, the protocol proved to be suitable for the reduction of alkyl aldehyde (1u) to alcohol 2s (Table 3, entry 6).

It is of interest that the current conditions work selectively for the reduction of ketones. As summarized in Scheme 3 below, acetophenone was not compatible with the system used in this study, while benzophenone resulted in the corresponding alcohol (2t) in a moderate yield. This result prompted further investigation of the general applicability of our system for the reduction of various unsaturated molecules, the results of which will be reported in due course.

**Table 3.** Expansion to various aldehydes<sup>a</sup>.



<sup>&</sup>lt;sup>*a*</sup> All reactions were carried out using 1.0 equiv. of aldehyde, 0.5 equiv. of Zn\*, and 1.0 equiv. of  $(EtO)_3SiH$  in THF at refluxing temperature for 39 h.

<sup>b</sup> Number in parenthesis is isolated yield.



Scheme 3. Reduction of ketones.

In conclusion, we have developed a novel applicability of highly active zinc as a reducing agent in hydrosilylation of carbonyl compounds. This study was performed by combining active zinc metal and alkoxysilane to reduce aldehydes in the absence of any extra ligand under mild conditions. The corresponding reduced alcohols were obtained as major products in most cases along with minor amounts of pinacol-type products. Importantly, a brief mechanistic study strongly indicates that the reduction process under our reaction system takes place by a single electron transfer (SET) pathway. Improving the reactivity toward ketones and applications to C—N multiple bonds are currently being tested in our laboratory.

## Experiment

General procedure for reduction of carbonyl compounds to alcohols; Into a 25 mL round-bottomed flask was placed 0.065 g of active zinc (Zn\*, 1.0 mmol) in 7 mL of THF under an argon atmosphere. Next, 0.37 mL of triethoxysilane (0.328)g, 2.0 mmol) and 0.19 mL of 3-thiophenecarboxaldehyde (0.224 g, 2.0 mmol) was cannulated at room temperature. The resulting mixture was stirred for 39 h at refluxing temperature. The reaction mixture was cooled down to room temperature. Quenched with 6 M HCl solution, then extracted with diethyl ether (6  $\times$  35 mL). Combined organic layers were washed with NaHCO3 solution and brine, then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Purification by flash column chromatography on silica gel (35% ethyl acetate/90% hexanes) afforded 0.137 g of thiophen-3-yl-methanol (2m) in 60% isolated yield as an orange liquid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  22.16 (t, J = 7.0 Hz, 1 H), 21.87 (d, J = 6.24 Hz, 3 H), 7.62 (s, 3 H), 6.01 (br s, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 144.04, 126.90, 125.57, 125.52, 59.68 ppm. HRMS (EI<sup>+</sup>): m/z calcd. For C<sub>5</sub>H<sub>6</sub>OS 115.0217, found 115.0221.

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