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Selective Reduction of Carboxylic Acids to Aldehydes Catalyzed by $B(C_6F_5)_3$

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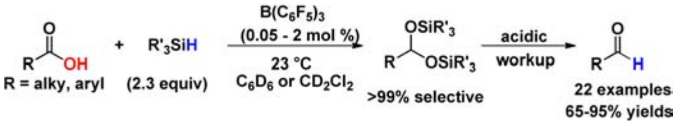
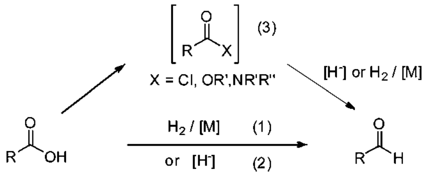
ABSTRACT



$B(C_6F_5)_3$ efficiently catalyzes hydrosilylation of aliphatic and aromatic carboxylic acids to produce disilyl acetals under mild conditions. Catalyst loadings can be as low as 0.05 mol %, and bulky tertiary silanes are favored to give selectively the acetals. Acidic workup of the disilyl acetals results in the formation of aldehydes in good to excellent yields.

Aldehydes are an important class of compounds.[1] Due to their high reactivity, they are useful intermediates for the synthesis of a wide array of organic chemicals,[2] and themselves have numerous applications, notably in the flavor and fragrance industry.[3] There are several synthetic routes for the synthesis of aldehydes.[4] One of the potentially most useful routes involves direct reduction of carboxylic acids to aldehydes via hydrogenation (eq 1, Scheme 1); however, high pressures and temperatures are required which makes control of the chemoselectivity difficult due to the ready reduction of aldehydes to alcohols.[5] Alternatively, direct transformation from carboxylic acids to aldehydes has been accomplished by using strong reducing agents which include lithium in methylamine,[6] alane,[7] thexylborane,[8] *i*-BuMgBr in combination with a titanocene catalyst,[9] and activated amino-silanes (eq 2).[10] A two-step procedure is usually preferred, involving the transformation of carboxylic acids to more reactive acid derivatives, followed by hydrogenation or hydride reduction reactions (eq 3).[11] Despite numerous reports of the synthesis of aldehydes from carboxylic acids, procedures exhibit poor chemoselectivities and functional group tolerance and often require harsh reaction conditions and/or the use of sensitive reagents. Hydrosilylation is an attractive methodology for the conversion of carboxylic acids under

Scheme 1. Different Reduction Methods from Carboxylic Acids to Aldehydes



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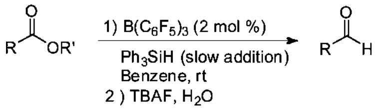
10.1021/ol303296a

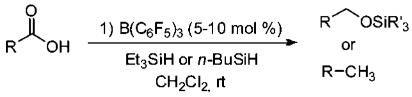
mild conditions to disilyl acetals which can be further transformed to aldehydes by acid hydrolysis.

Recently hydrosilylation of aliphatic and aromatic carboxylic acids to produce aldehydes has been independently reported by Nagashima and Darcel. Nagashima employed a ruthenium carbonyl cluster (1 mol %) as a catalyst together with a specific bis-silane, 1,2-bis(dimethylsilyl)-benzene.[12] Darcel reported an iron-catalyzed hydrosilylation of carboxylic acids in which the chemoselectivity of the product was highly dependent on the types of catalysts and silanes used; reductions resulted in the formation of alcohols or aldehydes.[13]

Since 1990, tris(pentafluorophenyl)borane has found many applications in catalysis,[14] notably in catalytic hydrosilylation reactions of carbonyl-containing substrates developed by Piers.[15] This catalyst enables the reduction of esters to aldehydes (eq 4)[15b] and carboxylic acids to silyl ethers or alkanes (eq 5).[16]



(4)

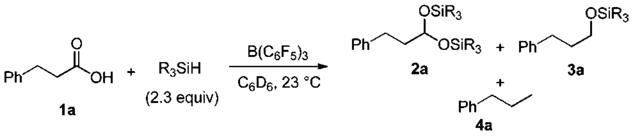


(5)

Following our report of iridium-catalyzed reduction of esters to aldehydes,[17] we report here the selective hydrosilylation of carboxylic acids to afford the disilyl acetals, which can subsequently be converted to aldehydes by acid hydrolysis. This catalysis is operative with low catalyst loadings and relatively inexpensive silanes at 23 °C.

We examined the utility of various silanes in the hydrosilylation of hydrocinnamic acid using $B(C_6F_5)_3$ as a catalyst (Table 1). Generally, the reaction was conducted in C_6D_6 at 23 °C with 1 or 0.1 mol % of catalyst loadings together with 2.3 equiv of the silane. Hydrocinnamic acid undergoes rapid hydrosilylation with 1 mol % of $B(C_6F_5)_3$ with Et_3SiH to give both the corresponding disilyl acetal **2a** (94%) and alkyl silyl ether **3a** as an over-reduction product (6%) (entry 1). Decreasing the catalyst loading to 0.1 mol % enables quantitative formation of the disilyl acetal without any over-reduction products in 0.5 h (entry 2). A lower catalyst loading (0.05 mol %) requires a longer reaction time to achieve full conversion producing the disilyl acetal in 99% yield (entry 3).

Table 1. Effect of Silanes and Catalyst Loading on the Hydrosilylation Reaction of Hydrocinnamic Acid[a]



entry	silane	$B(C_6F_5)_3$ (mol %)	time (min)	yield (%)[b]		
				2a	**3a**	**4a**
1	Et_3SiH	1	30	94	6	0
2		0.1	30	**>99**	0	0
3		0.05	130	**>99**	0	0
4	Ph_2MeSiH	0.1	60	95	5	0
5	$PhMe_2SiH$	0.1	60	70	15	15
6	Me_2EtSiH	0.1	60	78	5	17
7[c]	Ph_3SiH	1	15 h	**>99**	0	0
8	Et_2SiH_2	0.1	60	0	44	56
9	Ph_2SiH_2	0.1	60	0	76	24
10	TMDS	0.1	60	0	0	100
11[d]	PMHS	0.1	60	66	19	15

[a] Hydrocinnamic acid (0.5 mmol), C_6D_6 (0.3 mL). [b] Determined by ^1H NMR. [c] C_6D_6 (0.6 mL). [d] C_6D_6 (1.5 mL).

Smaller tertiary silanes, Ph_2MeSiH, Me_2PhSiH, and Me_2EtSiH, lead to a mixture of **2a**, **3a**, and/or **4a** in 1 h (entries 4−6). Hydrosilylation with TMDS (1,1,3,3-tetramethyldisiloxane) produces only propylbenzene **4a**, in 1 h (entry 10). Secondary silanes show high reactivity in hydrosilylation but result in the formation of over-reduction products (entries 8, 9). Hydrosilylation using Ph_3SiH as a very bulky silane required a higher catalyst loading (1 mol %) and longer reaction time (15 h) to produce the disilyl acetal in an excellent yield (entry 7). Interestingly, PMHS [poly(methylhydrosiloxane)] is less reactive relative to TMDS, affording **2a** and **3a** as well as **4a** (entry 11). Knowing the optimized reaction conditions, we investigated the scope of this catalysis (Table 2).

With 0.1 mol % of $B(C_6F_5)_3$ and Et_3SiH, hydrocinnamic acid **1a** undergoes hydrosilylation quantitatively to produce the disilyl acetal in 0.5 h (entry 1). A gram-scale hydrosilylation also gives the disilyl acetal in an excellent yield (entry 2). Using the same conditions, phenylacetic acid **1b** and linear alkyl carboxylic acids from propionic to decanoic acids have also been successfully transformed to the corresponding acetals in 1−3 h (entries 3−6). With substrates in which the carboxylic acid group bears an isopropyl (**1f**) or cyclohexyl substituent (**1g**), increases in catalyst loading and the reaction time are required to obtain full conversion (1 mol %, 8−11 h, entries 7, 8).

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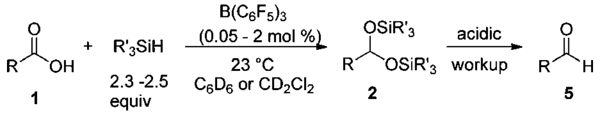
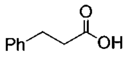
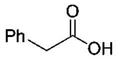
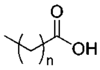
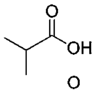
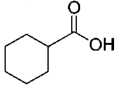
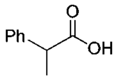
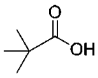
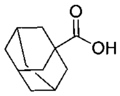
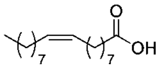
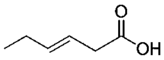
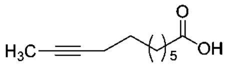
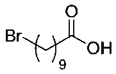
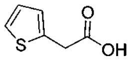
Table 2. Selective Reduction of Aliphatic Carboxylic Acids to Aldehydes Catalyzed by $B(C_6F_5)_3$[a]



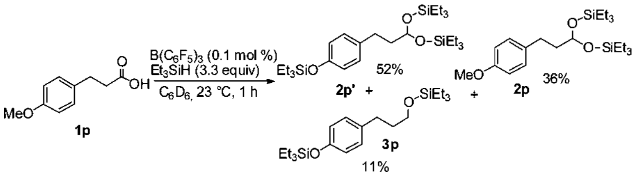
entry	carboxylic acid		silane	$B(C_6F_5)_3$ (mol %)	time (h)	yield (%)[b]
1		**1a**	Et_3SiH	0.1	0.5	>99 (86)
2[c]			Et_3SiH	0.1	0.5	>99 (87)
3		**1b**	Et_3SiH	0.1	1.33	>99 (71)
4		n = 1 **1c**	Et_3SiH	0.1	3	>99 (75)[d]
5		n = 4 **1d**	Et_3SiH	0.1	3	>99 (71)[d]
6		n = 8 **1e**	Et_3SiH	0.1	1	>99 (72)
7		**1f**	Et_3SiH	1	8	>99 (83)[d]
8		**1g**	Et_3SiH	1	11	>99 (79)[d]
9		**1h**	Et_3SiH	1	120	>99
10			$PhMe_2SiH$	0.5	10	>99 (79)
11		**1i**	$PhMe_2SiH$	2	72	>99 (76)[d]
12		**1j**	$PhMe_2SiH$	2	72	>99 (83)
13		**1k**	Et_3SiH	0.1	1.25	>99 (95)
14		**1l**	Et_3SiH	0.1	1.33	>99 (65)[d,e]
15		**1m**	Et_3SiH	0.2	2	>99 (89)
16		**1n**	Et_3SiH	0.1	0.75	>99 (91)
17		**1o**	Et_3SiH	0.1	0.33	>99 (70)[d]

[a] Reaction conditions: RCO_2H (0.5 mmol), silane (2.3 equiv), $B(C_6F_5)_3$ (0.1−2 mol %), C_6D_6 (0.3 mL), rt. Acidic workup: 1 M HCl(aq)/THF. [b] Yields of **2** determined by ^1H NMR. The numbers in parentheses are the yields of isolated **5**. [c] RCO_2H (5 mmol), C_6D_6 (3 mL). [d] Isolated as the 2,4-dinitrophenylhydrazone adducts. [e] 83% of 3-*trans* and 17% of 2-*trans* hydrazones were isolated.

More sterically hindered 2-phenylpropionic acid **1h** was completely converted to the disilyl acetal **2h** with 1 mol % catalyst in 5 days (entry 9). Using Me_2PhSiH as an alternative silane for hydrosilylation of bulky substrates permitted reduction of the catalyst loading and reaction time (0.5 mol %, 10 h) and yet avoided any over-reduction (entry 10). The same procedure allowed the transformation of pivalic acid **1i** and 1-adamantanecarboxylic acid **1j** to the disilyl acetal products using 2 mol % of $B(C_6F_5)_3$ over 3 days (entries 11−12). Furthermore, this reaction is tolerant of C═C and C≡C bonds. Oleic acid **1k**, 3-hexenoic acid **1l**, and 9-undecynoic acid **1m** are transformed to the desired disilyl acetals using a low catalyst loading (0.1−0.2 mol %) in 1.3−2 h (entries 13−15) without reduction of the olefinic or acetylenic group. No dehalogenation occurred during the conversion of 9-bromodecanoic acid to the disilyl acetal (entry 16). The thiophenyl group does not hinder hydrosilylation under normal reaction conditions (entry 17).

For all these substrates, acidic workup (1 M HCl(aq)/THF) produced the corresponding aldehydes in good to excellent yields (65−95%; see Table 2). However, some olefin isomerization occurred during the hydrolysis of **1l** resulting in the formation of 83% of *trans*-3 and 17% of *trans*-2 aldehyde. Hydrosilylation of substrates bearing Lewis basic groups such as 4-(dimethylamino)phenylacetic acid was unsuccesful due to direct inhibition of $B(C_6F_5)_3$. Moreover, when using 3-(4-methoxyphenyl)propionic acid **1p**, a mixture of three compounds was detected due to the O−Me bond cleavage[18] and over-reduction (Scheme 2). A similar substrate, 3-(4-hydroxyphenyl)propionic acid, also exhibits over-reduction.

Scheme 2. Reduction of 3-(4-Methoxyphenyl)propionic Acid



The reduction of aromatic carboxylic acids was also investigated (Table 3). Beginning with the best conditions for hydrosilylation of aliphatic carboxylic acids (Et_3SiH, 0.1 mol % catalyst), benzoic acid **1q** was transformed to the disilyl acetal **2q** in 60% yield with formation of 40% of the over-reduction product **3q** (entry 1). Using the bulkier silane, Ph_3SiH (2.5 equiv) in CD_2Cl_2,[19] the disilyl acetal was quantitatively produced in 92 or 14 h using 1 and 2 mol % of $B(C_6F_5)_3$, respectively (entries 2, 3).

Similar conditions using 2 mol % of $B(C_6F_5)_3$ were used to selectively reduce other aromatic carboxylic acids. Reduction of *p*-toluic acid, **1r**, containing an electron-donating group in the *para*-position was fully converted to the disilyl acetal but required a longer reaction time (18 h, entry 4). Using similar conditions, no conversion was detected with the sterically hindered *o*-toluic acid, **1s**; however use of Et_3SiH produced the disilyl acetal in excellent yield (entries 5, 6). In contrast to electron-donating groups, electron-withdrawing groups in the *para*-position of the phenyl ring accelerate the reaction rate (entries 7−10). Indeed, 4-phenyl-, **1t**, 4-bromo-, **1u**, and 4-chloro-, **1v**,

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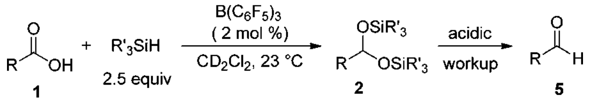
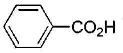
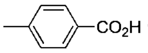
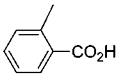
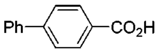
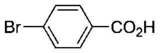
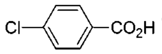
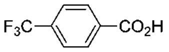
(18) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 8919.

(19) CD_2Cl_2 was used in place of C_6D_6 to improve the solubility of Ph_3SiH.

Table 3. Selective Reduction of Aromatic Carboxylic Acids to Aldehydes Catalyzed by $B(C_6F_5)_3$[a]



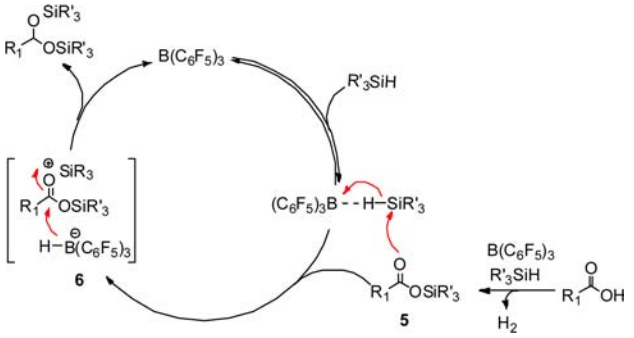
entry	carboxylic acid	silane	$B(C_6F_5)_3$ (mol %)	time (h)	yield (%)[b]
1[c]	 **1q**	Et_3SiH	0.1	14	60
2		Ph_3SiH	1	92	>99
3		Ph_3SiH	2	14	>99 (72[d])
4	 **1r**	Ph_3SiH	2	18	>99 (84)[d](68)
5	 **1s**	Ph_3SiH	2	24	0
6[c]		Et_3SiH	2	11	>99 (81)[d](69)
7	 **1t**	Ph_3SiH	2	10	99 (83)[d](75)
8	 **1u**	Ph_3SiH	2	7	99 (82)[d](72)
9	 **1v**	Ph_3SiH	2	7	98 (87)[d]
10	 **1w**	Ph_3SiH	2	6	94 (68)[d]

[a] Reaction conditions: RCO_2H (0.5 mmol), Ph_3SiH (2.5 equiv), $B(C_6F_5)_3$ (2 mol %), CD_2Cl_2 (0.6 mL), rt. Acidic workup: CF_3CO_2H/Et_2O. [b] Yields of **2** determined by ^1H NMR. The numbers in parentheses are the yields of isolated **5**. [c] C_6D_6 (0.3 mL). Acidic workup: 1 M HCl(aq)/THF. [d] Yields of **5** determined by ^1H NMR of the crude mixture using EtOAc as an internal standard.

benzoic acids were selectively converted to disilyl acetals with traces of over-reduction products detected (entries 7–9). Using 4-(trifluoromethyl)benzoic acid, **1w**, as the substrate, the reaction was complete in 6 h with a small decrease in selectivity (6% of silyl ether product detected, entry 10). For these aromatic substrates, acidic workup (TFA/Et_2O) furnished the corresponding aldehydes in good yields (68–87%, Table 3). Attempts to reduce 4-nitrobenzoic acid were unsuccessful due to deactivation of the catalyst after a few minutes.

The proposed mechanism of reduction is shown in Scheme 3 and based on the previous work of Piers.[14d,15b]

Scheme 3. Proposed Mechanism for the Reduction of Carboxylic Acids to Disilyl Acetals



After the rapid generation of the silyl ester **5** with the release of hydrogen, the silane is activated by $B(C_6F_5)_3$ through reversible coordination to the Si–H bond and transfers R_3Si^+ to the carbonyl oxygen generating the ion pair **6**. Hydride transfer from $HB(C_6F_5)_3^-$ to the carbonyl carbon forms the disilyl acetal and regenerates the catalyst, $B(C_6F_5)_3$.

In summary, we have developed a selective and convenient one-pot procedure for the reduction of aliphatic and aromatic carboxylic acids to aldehydes. $B(C_6F_5)_3$ catalyzes the hydrosilylation of carboxylic acids to give disilyl acetals which can be hydrolyzed *in situ* to generate the corresponding aldehydes. Attractive features of this process include use of common tertiary silanes, near-quantitative yields of disilyl acetals with no over-reduction, low catalyst loadings (0.05–2.0 mol %), and mild conditions (23 °C).

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Supporting Information Available. Typical experimental procedures and characterizations for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.