TiCl$_4$-Zn Induced Reductive Acylation of Ketones with Acylsilanes

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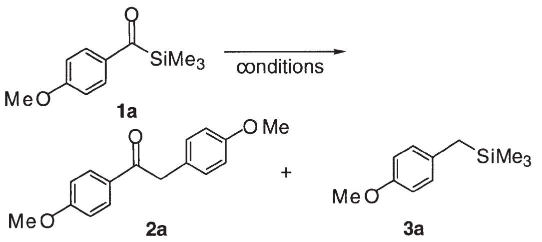
Acylsilanes were found to react with ketones in the presence of a low-valent titanium reagent generated from titanium(IV) chloride and zinc, giving the corresponding reductive acylated compounds.

Since the discovery by Mukaiyama,[1] Tyrlik,[2] and McMurry,[3] one- and/or two-electron reduction of carbonyl compounds induced by a low-valent titanium have provided a variety of important organic transformations such as symmetrical 1,2-diol formation (pinacol coupling) and alkene formation (McMurry coupling).[4] Recent reports from our laboratory have demonstrated highly diastereoselective pinacol coupling reactions using a catalytic amount of titanium or vanadium complex with chlorosilane and co-reductant metal such as Zn, Al, etc.[5–7]

Acylsilane is a stable main group-metal acyl compound and exhibits characteristic reactivities.[8] Because of its high energy level of n orbital, electrochemical behavior of acylsilanes has been extensively studied.[9,10] However, only few synthetic applications have been investigated involving one- and/or two-electron reduction of acylsilanes. As for the reductive self-coupling reactions, the following two examples have been reported. Metallic ytterbium promotes the double Peterson reaction of aroylsilane, giving the alkyne.[11] On the other hand, the reaction with low-valent titanium reagents affords a mixture of several products derived from McMurry, Brook, or Peterson reactions.[12] Such a complicated reaction process might prevent further application. In this paper we report that low-valent titanium generated by TiCl$_4$ and Zn induces a reductive (deoxygenative) acylation of ketones with acylsilanes.

First, self-coupling of 4-methoxybenzoyltrimethylsilane (**1a**) was attempted using a low-valent vanadium or titanium compound under an argon atmosphere (Table 1). Vanadium reagents did not promote any coupling reactions (entries 1 and 2), whereas the benzyl phenyl ketone (**2a**) was obtained with Ticl$_4$. The yield was increased to 38% in the presence of 4 molar amounts of metallic zinc in DME as shown in entry 5. Benzylsilane **3a** was also isolated in 19% yield. It should be noted that a trace amount of alkenic product *via* McMurry reaction, which is a major product of Fürstner's conditions,[12] was detected under these conditions.

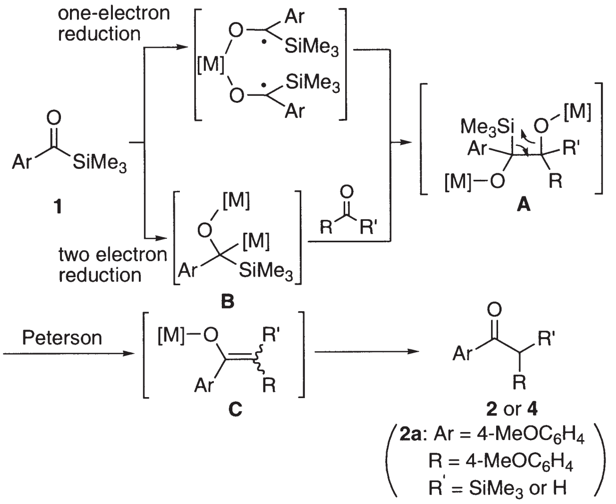
Table 1. Self-coupling reaction of **1a**



Entry	Conditions[a]	Yields / %	
		2a	**3a**
1	VOCl$_3$, 2Al / DME, reflux	0	0
2	VCl$_3$, 2Zn / THF, reflux	0	0
3	TiCl$_4$, 2Zn / DME, reflux	5	0
4	TiCl$_4$, 2Zn / THF, rt	28	0
5	TiCl$_4$, 4Zn / DME, rt	38	19

[a]Reaction time is 24 h.

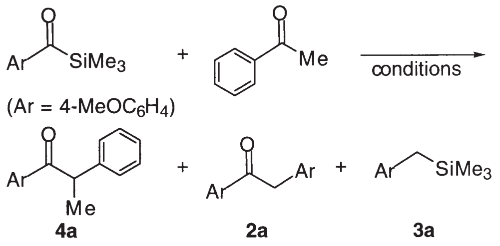
A possible pathway to **2a** is shown in Scheme 1. One-electron or further reduction of **1a** occurs to produce the pinacol coupling intermediate **A**. Peterson elimination of **A** affords the metal enolate **C**, which is then converted to the ketone **2a** after hydrolysis. If successive reduction process occurs predominantly and the thus-formed dianion equivalent **B** possesses enough nucleophilicity to other carbonyl compounds, reductive (deoxygenative) acylation can be developed. Since the reduction potential of acylsilanes usually ranges between those of aldehydes and ketones, the cross-coupling reaction with ketones was next examined.[13]



Scheme 1.

The reaction conditions were optimized with acetophenone employed (Table 2). As shown in entry 1, TiCl$_4$ + 2Zn/DME gave the desired cross-coupling product **4a**, accompanied with the self-coupling product **2a** in 36% and 7% yields, respectively. Since the reaction temperature did not influence the yield drastically (entry 2), the following entries were carried out at room temperature. Titanium compounds were screened to find that TiCl$_4$ gave the best result (entries 2–5). Solvent effect was also studied (entries 6–8) to show that DME is a suitable solvent. It is noteworthy that no coupling product **4a** but self-coupling product **2a** was obtained using THF as a solvent. Addition of Me$_3$SiCl did not improve the yield. Finally, the yield of **2a** was increased to 51% when 2 molar amounts of acetophenone were

Table 2. The reaction of **1a** with acetophenone



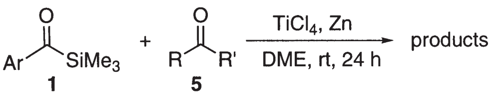
Entry	Conditions[a]	Yields / %		
		4a	**2a**	**3a**
1	2TiCl$_4$, 4Zn / DME, reflux	36	7	trace
2	2TiCl$_4$, 4Zn / DME, rt	35	8	6
3	2TiF$_4$, 4Zn / DME, rt	26	16	12
4	2TiBr$_4$, 4Zn / DME, rt	19	3	12
5	2TiI$_4$, 4Zn / DME, rt	0	0	27
6	2CpTiCl$_3$, 4Zn / DME, rt	15	23	3
7	2TiCl$_4$, 4Zn / THF, rt	0	24	13
8	2TiCl$_4$, 4Zn / CH$_2$Cl$_2$, rt	9	17	16
9	2TiCl$_4$, 4Zn / CH$_3$CN, rt	22	15	0
10	2TiCl$_4$, 4Zn / DME, rt[b]	51	5	3

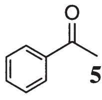
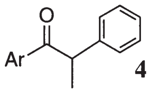
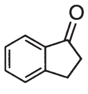
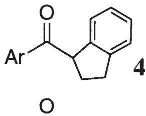
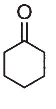
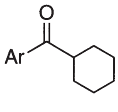
[a]Reaction time is 24 h. [b]Two molar amounts of acetophenone were used.

used as shown in entry 10.

Table 3 shows the representative results of the reaction of acylsilanes with various ketones.[14] Reductively acylated compounds **4** were yielded as a major product starting from both aromatic and aliphatic ketones. When excess amounts of ketone were used, **4** was obtained as a sole product (entry 4). The more electron-donating acylsilane was allowed to produce **4** in a better yield (entries 3, 5, and 6), suggesting the nucleophilicity of the dianion equivalent, generated from acylsilane, influences the reaction course.

Table 3. The reaction of **1** with ketones



Entry	1[a]	5[b]	Yields / %			
			4		**2**	**3**
1	**1a**	 **5a**	 **4a**	51	5	3
2	**1a**	 **5b**	 **4b**	38	trace	10
3	**1a**	 **5c**	 **4c**	49	8	trace
4	**1a**	**5c**[c]	**4c**	61	0	0
5	**1b**	**5c**	**4d**	31	4	0
6	**1c**	**5c**	**4e**	22	10	0

[a]**1a**: Ar = 4-MeOC$_6$H$_4$, **1b**: Ar = C$_6$H$_5$, **1c**: Ar = 4-CF$_3$C$_6$H$_4$.
[b]Two molar amounts of **5** were used. [c]Ten molar amounts of **5c** were used.

As described above, reductive cross-coupling of acylsilanes with ketones can be induced by TiCl$_4$ and Zn in DME, giving the reductive acylation products. The similar product has been reported in the reaction of dianion of benzophenone with acylsilane, which serves as a dianion accepter.[15] On the other hand, the present reaction demonstrated that acylsilanes possess a unique reactivity as dianion donors.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

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13 In the reaction with aldehydes, reduction of aldehydes proceeded predominantly, giving the pinacol coupling products.
14 Typical procedure: To a mixture of TiCl$_4$ (57 mg, 0.3 mmol) and zinc powder (78.5 mg, 1.2 mmol) in DME (5 mL) was added a ketone (0.6 mmol) then an acylsilane (0.3 mmol) at room temperature under an argon atmosphere. After stirring for 20 h, the reaction was quenched with ether (10 mL) and HCl aq (1 M, 10 mL). The organic layer was separated and then washed with saturated aqueous NaHCO$_3$ (10 mL), water (10 mL × 2), and brine (10 mL), dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography, giving the coupling product **4**.
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