

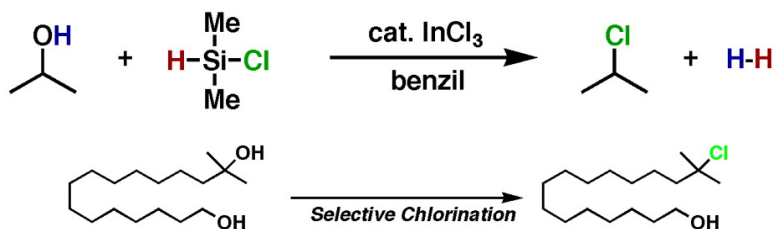
Communication

Indium-Catalyzed Direct Chlorination of Alcohols Using Chlorodimethylsilane–Benzil as a Selective and Mild System

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Indium-Catalyzed Direct Chlorination of Alcohols Using Chlorodimethylsilane–Benzil as a Selective and Mild System

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Alcohols are one of the most common and versatile compounds for transformation into other classes of chemicals. However, due to the lower leaving ability, the hydroxyl moieties are hardly substituted under mild conditions.¹ Chlorodehydroxylation of alcohols into organic chlorides has been accepted as a general and basic transformation pathway in organic synthesis by using HCl gas, PCl₃, SOCl₂, Vilsmeier–Haack reagent, Viehe salt.² However, the co-generation of HCl often causes undesired side reactions. The system using Ph₃P–CCl₄ serves as a useful reagent for converting primary alcohols into the corresponding chlorides under neutral conditions in which triphenylphosphine oxide and CHCl₃ are byproducts. In this context, further development of a direct chlorination method under neutral conditions would be greatly desired. This communication describes a novel methodology for chlorination of alcohols with HSiMe₂Cl in the presence of benzil under mild and neutral conditions.

We have previously reported that 1-phenyl-2-propanol (**1a**) was reduced to 1-phenylpropane (**2a**) in the presence of 1.1 equiv of HSiPh₂Cl with an InCl₃ catalyst (Table 1, entry 1).^{1a} The reaction course includes the step of removal of HCl, giving the corresponding silyl ether, which then transforms to **2a**. Surprisingly, the addition of benzil (PhCOCOPh) significantly changed the reaction course to give 47% of 2-chloro-1-phenylpropane (**3a**) exclusively without formation of **2a** (entry 2).³ The yield was improved to 68% by using HSiMe₂Cl at room temperature (entry 3). Apparently, this yield suggests that an equimolar amount of HSiMe₂Cl is stoichiometric in this chlorination and no elimination of HCl is involved. When InCl₃ was not loaded, almost no formation of **3a** was observed. This result prompted us to investigate a HSiMe₂Cl/InCl₃/benzil system that would contribute to a useful chlorination reaction of alcohols under neutral conditions.

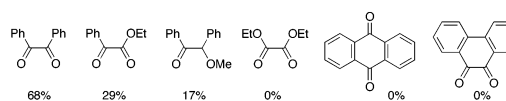
The choice of additive is very important (Chart 1). The α -ketoester and α -alkoxyketone in place of benzil gave the product in lower yields. The reaction using α -diester afforded no product at all. The use of phenanthraquinone or anthraquinone also gave no product. It was surprising that most of the benzil was recovered unchanged after the reaction although we have reported that usual carbonyl compounds suffered reductive chlorination by HSiMe₂Cl with an InCl₃ catalyst.⁴ The choice of the catalyst (InCl₃) is also crucial for this chlorination. Other typical Lewis acids such as AlCl₃ and Sc(OTf)₃ hardly catalyzed the reaction.⁵

The chlorination was monitored by ¹H NMR to examine the reaction mechanism (Scheme 1). When the mixture of **1a** and HSiMe₂Cl in dichloromethane was stirred at room temperature for 1 h and the solvent removed under reduced pressure, the signal of hydrosilyl ether **4** was observed.^{1a} On the other hand, the loading of benzil and InCl₃ catalyst caused the appearance of the signal of chlorosilyl ether **5**, whereas no signal of **4** was detected. The

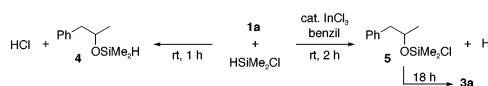
Table 1. Effect of Benzil on Selective Formation of Chloride

entry	additive	H–Si–Cl	conditions	yield %	
				2a	3a
1	–	HSiPh ₂ Cl	80 °C, 1.7 h	40	0
2	benzil	HSiPh ₂ Cl	80 °C, 1.7 h	0	47
3	benzil	HSiMe ₂ Cl	rt, 15 h	0	68

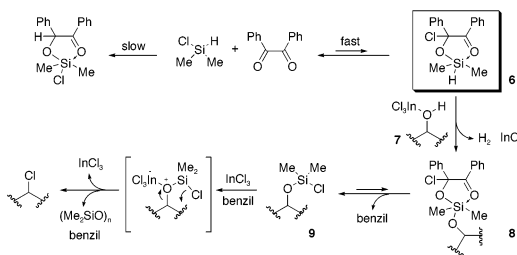
Chart 1. Additive Effects on Yields in the Reaction of **1a** with HSiMe₂Cl



Scheme 1. NMR Study



Scheme 2. Plausible Reaction Course



generation of H₂ was also confirmed during this reaction step.⁶ After stirring for 18 h, transformation from **5** to the chloride **3a** was completed.

A plausible reaction course is proposed as shown in Scheme 2. The chlorosilylation of benzil by HSiMe₂Cl takes place at the first step and gives the intermediate **6**, whose Si–H bond must be activated by the intramolecular carbonyl coordination. This path is faster than the reduction (hydrosilylation) of benzil with HSiMe₂Cl. The formed species **6** is kinetically unstable and reacts with the indium-activated alcohol **7** to generate H₂ and **8**. The formed alkoxyethyl ether **8** transforms to **9** that corresponds to **5** in Scheme 1. The silyl ether **9** gives the product mediated by InCl₃.^{1,7} The following points in Scheme 2 can explain the results in Chart 1: the additive requires (i) a ketone moiety to be added by chlorosilane at the first step, (ii) chelation ability in the intermediate, and (iii) a flexible carbon framework to generate the highly coordinated hydrosilane. Therefore, benzil gave the best results among the additives examined.

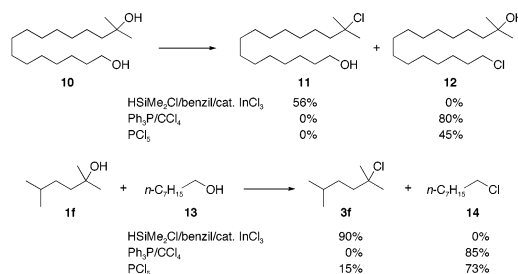
Table 2. Chlorination of Various Alcohols^a

entry	alcohol	time/h	product	yield/%
1		8		74 ^c
2		15		59
3		91		98
4		6		100
5		9		100
6		23		71
7		82		93
8		1		25 ^d
9		24		0
10		1		80
11		2.5		92
12		0.7		83
13		24		97
14		1.5		77
15		2.5		91 ^e
16		0.1		96
17		3		0 ^f
18 ^g		0.1		98

^a All entries were carried out at room temperature in CH₂Cl₂ with 5 mol % of InCl₃, 1.1 equiv of HSiMe₂Cl and 1.0 equiv of benzil. ^b Rearrangement products (regio isomers) were observed in 23% yield. ^c dr = 1:1. ^d <2% ee. ^e 2-Phenylpropane was obtained in 49% yield. ^f Premixing of HSiMe₂Cl and MeOH (1.0 equiv) followed by the addition of **1r**.

The generality of this chlorination methodology is summarized in Table 2.⁸ Various secondary and tertiary alcohols were converted into chlorides in high yields (entries 1–7). The rearranged product **3i** was obtained in the reaction with **1i** (entry 8). This result supports the carbocation mechanism in the chlorination. The primary alcohol **1j** did not give the desired product (entry 9). However, effective transformation was observed in the reaction with benzyl alcohols **1k–m** which bear electron-withdrawing or -donating substituents (entries 10–12). Nitro and ester moieties tolerated these reaction conditions to furnish the corresponding chlorides **3n** and **3o** in 97% and 77% yields, respectively (entries 13 and 14). When the optically pure alcohol **1p** was used (entry 15), racemization was observed. This result also suggests the carbocation mechanism. The reaction with hydroxyester **1q** gave the desired product **3q** in high yield (entry 16). Those good results using acid-sensitive substrates clearly confirm the advantage of this reaction system. In fact, the reaction of **1q** with PCl₃ gave a complicated mixture. The chlorination with PCl₅ gave **3q** in lower yield (66%) along with ethyl 3-phenyl-2-propenoate (5%) through HCl elimination.⁹ The alcohol **1r** did not give the desired chloride **3s** but a reduced product (2-phenylpropane) in 49% (entry 17). We found that premixing of methanol (1 equiv) and HSiMe₂Cl/benzil/cat. InCl₃ followed by the loading of **1r** successfully gave a high yield of **3r** (entry 18). It is assumed that methanol readily reacts with HSiMe₂Cl with the generating H₂, that was actually confirmed, and affords the methoxysilane like **8**. The silyl transfer between methoxysilane and the added alcohol generates the desired alkoxy silane **8**. The premixing with methanol avoids the undesired process releasing HCl.

The methanol method (Table 2, entry 18) including silyl transfer prompted us to examine the diol which bears both primary and tertiary hydroxyl sites (Scheme 3). Gratifyingly, selective chlorina-

Scheme 3. Competitive Reaction between Tertiary and Primary Alcohols

tion only at the tertiary site proceeded in the reaction of diol **10** to give **11**. It is noted that one equivalent of hydrosilane is enough for the selective reaction for diol, while our previous systems involving reduction^{1a} or alkylation^{1b} require an excess amount of reagents. Even if the primary OH site reacts with hydrosilane faster than the tertiary site, silyl transfer finally affords the silyl tertiary alkoxide, which leads to the tertiary chloride. On the contrary, conventional chlorination systems such as PPh₃/CCl₄ or PCl₅ gave the primary chloride **12**. Similar selectivity in an intermolecular version was also observed between **1f** and **13**. These results show the unique and interesting selectivity of this chlorination system.

In conclusion, we have demonstrated a novel method for chlorination of alcohols using HSiMe₂Cl/benzil/InCl₃ system under neutral conditions. This system can be used for acid-sensitive substrates. High selectivity for tertiary alcohols over primary alcohol was observed. Further utility of this novel system is currently under investigation.

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Supporting Information Available: Reaction procedure and spectroscopic details of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (3) During our trial for competitive reaction between alcohols and carbonyls, we unexpectedly found this interesting outcome.
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- (6) Detected by GC (packed with porapak-Q).
- (7) The chlorosilyl ether **5** transformed to the chloride **3a** (82% yield) in the presence of InCl₃ and benzil (See Supporting Information).
- (8) Although Scheme 2 shows that a catalytic amount of benzil could work, lower yields were, in fact, obtained in the catalytic reactions using alcohols in Table 2. Much less generation of **6** in catalytic conditions does not give a practical reaction rate to chlorides.
- (9) Even the PPh₃/CCl₄ system that is considered as a neutral reagent also gave the lower yield of the product **3r** (62%) and the enoate (8%).

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