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$InCl_3/Me_3SiBr$-Catalyzed Direct Coupling between Silyl Ethers and Enol Acetates

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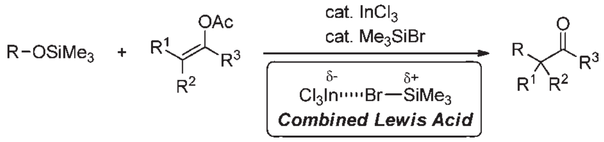
ABSTRACT



A combined Lewis acid catalyst of $InCl_3$ and Me_3SiBr promoted the direct use of enol acetates in the coupling with low-reactive silyl ethers, in which functional groups including ketones and aldehydes survived. Sterically hindered silyl ethers such as $ROSiEt_3$, $ROSiPh_3$, ROSi*t*-$BuMe_2$, and ROSi*i*-Pr_3 were also applicable.

The coupling reactions between metal enolates and alkylating electrophiles such as alkyl halides, alcohols, alkyl ethers, and alkyl carboxylates have been extensively investigated to produce α-alkylated carbonyl compounds.[1−3] The reaction system using silyl ethers as alkylating reagents, however, has not been sufficiently established,[4] because silyl ethers are used for the typical protection of alcohols and they have such a high tolerance to nucleophilic substitution. In fact, they do not react with even strong nucleophiles like Grignard reagents. Gevorgyan et al. also reported that no allylation using silyl ethers took place while other protected alcohols easily gave allylated products.[5] On the other hand, if the replacement of the metal enolates by metal-free enol acetates were achieved, it would be a great advantage in reducing metal waste. Moreover, enol acetates are easily available and handled, stable, and storable.[6] Thus, the coupling reaction between enol acetates and silyl ethers is a challenging and practical subject. Herein we report the direct coupling catalyzed by an $InCl_3/Me_3SiBr$ combined system.[7] To the best of our knowledge, this is the first successful direct substitution of bulkier siloxy groups rather than a trimethylsiloxy one. Furthermore, the direct coupling of silyl ethers enables skipping the deprotection process, which often requires a multistep synthesis.

We first screened various Lewis acids in the reaction of silyl ether **1a** with enol acetate **2a** (Table 1). Neither $InCl_3$ nor Me_3SiBr gave an adduct in their sole use (entries 1 and 2). Gratifyingly, when Me_3SiI or Me_3SiBr was combined with

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(1) For a review, see: Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Elsevier: Oxford, U.K., 1991; Vol. 9, pp 1−63.

(2) For reviews, see: (a) Reetz, M. T.; Maier, W. F.; Chatziiosifidis, I.; Giannis, A.; Heimbach, H.; Löwe, U. *Chem. Ber.* **1980**, *113*, 3734–3757. (b) Reetz, M. T. *Angew. Chem., Int. Ed.* **1982**, *21*, 96–108.

(3) For recent works on α-alkylation of carbonyl compounds using alcohols or protected alcohols, see: (a) Nishibayashi, Y.; Wakiji, I; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393–3394. (b) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340–9347. (c) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311–314. (d) Vicennati, P.; Cozzi, P. G. *Eur. J. Org. Chem.* **2007**, 2248–2253. (e) Rubenbauer, P.; Bach, T. *Tetrahedron Lett.* **2008**, *49*, 1305–1309. (f) Yoshimatsu, M.; Otani, T.; Matsuda, S.; Yamamoto, T.; Sawa, A. *Org. Lett.* **2008**, *10*, 4251–4254. (g) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313–1316. (h) Nishimoto, Y.; Onishi, Y.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9131–9134.

(4) For reports using silyl ethers as alkylating reagents, see: (a) Kira, M.; Hino, T.; Sakurai, H. *Chem. Lett.* **1992**, *21*, 555–558. (b) Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* **1995**, *36*, 5243–5246. (c) Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 514–517. (d) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, *72*, 8588–8590.

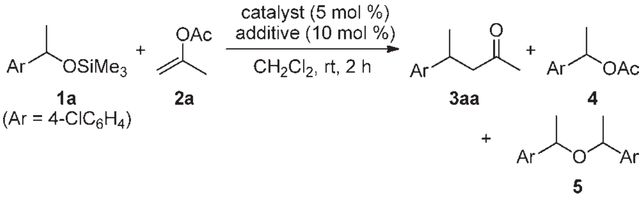
(5) (a) Schwier, T; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999–2001. (b) Rubin, M; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705–2707.

(6) (a) Mukaiyama, T.; Izawa, T.; Saigo, K. *Chem. Lett.* **1974**, 323–326. (b) Shono, T.; Nishiguchi, I.; Komamura, T.; Sasaki, M. *J. Am. Chem. Soc.* **1979**, *101*, 984–987. (c) Yanagisawa, M.; Shimamura, T.; Iida, D.; Matsuo, J.; Mukaiyama, T. *Chem. Pharm. Bull.* **2000**, *48*, 1838–1840. (d) See ref 3h. (e) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002–6004. (f) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069–3072.

(7) (a) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578–1581. (b) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737–1739. (c) Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516–8522. (d) See ref 4d.

10.1021/ol200875m

Table 1. Screening of Catalytic System[a]



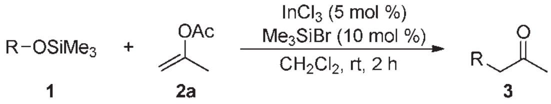
entry	catalyst	additive	yield/ %[b]		
			3aa	**4**	**5**
1[c]	$InCl_3$	–	0	0	0
2[c]	–	Me_3SiBr	0	0	0
3	$InCl_3$	Me_3SiI	68	22	10
4	$InCl_3$	Me_3SiBr	65	20	15
5	$InCl_3$	Me_3SiCl	22	18	14
6	$InBr_3$	Me_3SiBr	27	6	64
7	InI_3	Me_3SiBr	11	0	65
8	$FeBr_3$	Me_3SiBr	13	0	76
9	$GaBr_3$	Me_3SiBr	35	14	43
10	$Sc(OTf)_3$	Me_3SiBr	0	10	90
11[c]	$ZnCl_2$	Me_3SiBr	0	8	8
12[c]	$BF_3 \cdot OEt_2$	Me_3SiBr	0	7	0
13[c]	$AlCl_3$	Me_3SiBr	0	0	21
14[c,d]	$InCl_3$	Me_3SiBr	0	9	7
15[c,e]	$InCl_3$	Me_3SiBr	0	12	26
16[f]	$InCl_3$	Me_3SiBr	12	26	50
17[c,g]	$InCl_3$	Me_3SiBr	0	5	0

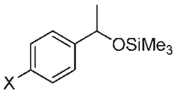
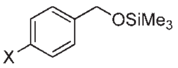
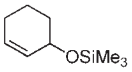
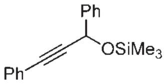
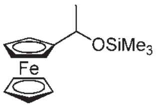
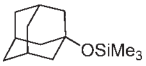
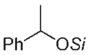
[a] Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), catalyst (0.05 mmol), additive (0.1 mmol), CH_2Cl_2 (2 mL), rt, 2 h. [b] ^1H NMR yield. [c] **1a** and the corresponding alcohol were considerably recovered. [d] Hexane (2 mL). [e] Toluene (2 mL). [f] MeCN (2 mL). [g] THF (2 mL).

$InCl_3$, the desired α-alkylated ketone **3aa** was furnished at room temperature in 68 or 65% yields, respectively, while the combination with Me_3SiCl was less effective (entries 3–5).[8] $InBr_3$ and InI_3 were decidedly inferior to $InCl_3$ to produce dimerized ether **5** as a major product (entries 6 and 7). These results indicate that the subtle control of Lewis acidity by the combined ingenuity is essential. $FeBr_3$ and $GaBr_3$ provided unsatisfactory results even in the presence of Me_3SiBr while they were reported to be effective catalysts in the direct coupling between alcohols and enol acetates (entries 8 and 9).[9] Representative Lewis acids such as $Sc(OTf)_3$, $ZnCl_2$, $BF_3 \cdot OEt_2$, and $AlCl_3$ gave no desired ketone (entries 10–13). CH_2Cl_2 was found to be the choice of solvent because both noncoordinative solvents such as hexane and coordinative ones (e.g., THF) were ineffective (entries 14–17). The combination of $InCl_3$ and Me_3SiBr at room temperature in CH_2Cl_2 was employed as practically optimal conditions because of the instability of Me_3SiI.

The scope of silyl ethers was investigated (Table 2). Secondary benzylic silyl ethers bearing electron-withdrawing and -donating groups provided excellent yields while primary ones gave lower yields (entries 1–6). Allylic and propargylic silyl ethers effectively produced the ketones **3ga** and **3ha**, respectively (entries 7 and 8). Silyl ether **1i** with a ferrocene moiety produced **3ia** in 82% yield (entry 9). The reaction using 1-adamantyl trimethylsilyl ether **1j** proceeded effectively (entry 10). These results indicate the incorporation of a cationic mechanism.[10] Gratifyingly, even the siloxy groups such as $OSiEt_3$, $OSiPh_3$, OSi*t*-

Table 2. Reactions of Various Silyl Ethers with Enol Acetate **2a**[a]



entry	silyl ether			product	yield / %[b]
1[c]		X = Cl	**1a**	**3aa**	99 (66)
2		H	**1b**	**3ba**	91 (57)
3		Me	**1c**	**3ca**	99 (93)
4[d]		OMe	**1d**	**3da**	89 (68)
5[c]		X = H	**1e**	**3ea**	23 (14)
6[c]		Me	**1f**	**3fa**	54 (31)
7[e]			**1g**	**3ga**	84 (80)
8[f]			**1h**	**3ha**	77 (70)
9[g]			**1i**	**3ia**	82 (74)
10[c]			**1j**	**3ja**	99 (90)
11		*Si* = $SiEt_3$	**1k**	**3ba**	93 (77)
12		$SiPh_3$	**1l**	**3ba**	84 (67)
13		Si*t*-$BuMe_2$	**1m**	**3ba**	82 (68)
14		Si*i*-Pr_3	**1n**	**3ba**	99 (79)

[a] Reaction conditions: **1** (1 mmol), **2a** (2 mmol), $InCl_3$ (0.05 mmol), Me_3SiBr (0.1 mmol), CH_2Cl_2 (2 mL), rt, 2 h. [b] ^1H NMR yield. Values in parentheses are isolated yields. [c] $ClCH_2CH_2Cl$ (2 mL), 83 °C, 2 h. [d] CH_2Cl_2 (2 mL), 0 °C, 2 h. [e] Me_3SiBr (0.2 mmol), CH_2Cl_2 (2 mL), 0 °C, 2 h. [f] MeCN (2 mL), 2 h. [g] **2a** (5 mmol), MeCN (2 mL), 81 °C, 2 h

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(8) Other combinations of indium halides and trimethylsilyl halides were investigated; see Supporting Information.

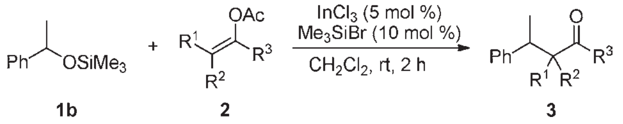
(9) See ref 3h.

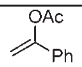
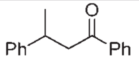
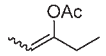
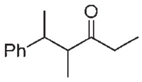
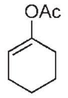
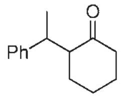
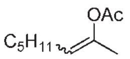
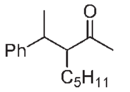
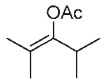
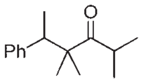
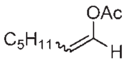
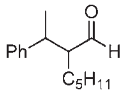
(10) Several reports suggest the generation of a adamantyl cation as an intermediate; see: (a) Sasaki, T.; Usuki, A.; Ohno, M. *J. Org. Chem.* **1980**, *45*, 3559–3564. (b) Laali, K. K.; Sacra, V. D.; Okazaki, T.; Brock, A.; Der, P. *Org. Biomol. Chem.* **2005**, *3*, 1034–1042. (c) Nishimoto, Y.; Kajioka, M.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Commun.* **2008**, 6396–6398.

BuMe$_2$, and OSi*i*-Pr$_3$, which are bulkier than OSiMe$_3$, could be easily substituted without deprotection (entries 11−14).

Various enol acetates effectively reacted with silyl ether **1b** as summarized in Table 3. Enol acetates derived from aromatic and aliphatic ketones gave the corresponding α-alkylated ketones in excellent yields (entries 1−3). Also, unsymmetrical ketone-derived **2e** was applicable without isomerization (entry 4). Sterically hindered **2f** furnished the product **3bf** in a moderate yield (entry 5). The production of an α-alkylated aldehyde without overreaction demonstrates the mildness of our system (entry 6). This result prompted us to examine a competitive reaction between aldehyde **6** and silyl ether **1c**, as illustrated in Scheme 1. As expected, silyl ether **1c** was exclusively consumed irrespective of the aldehyde to furnish α-alkylated ketone **3ca** in 99% yield. It is apparent that the combined catalyst predominantly activates a silyl ether more than it does an aldehyde.[11] On the other hand, the addition of tri-*n*-butyltin methoxide **8** leads to a generation of a tin enolate *in situ* to give only the aldol adduct **7** in 65% yield.[12]

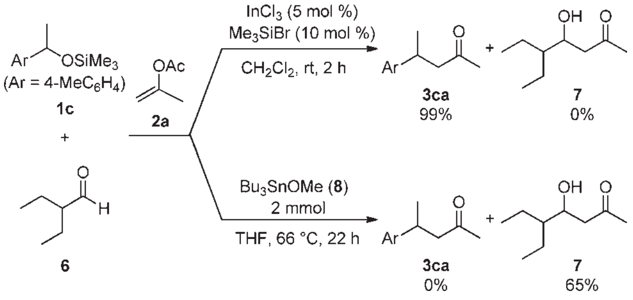
Table 3. Reactions of Various Enol Acetates with Silyl Ether **1b**[a]



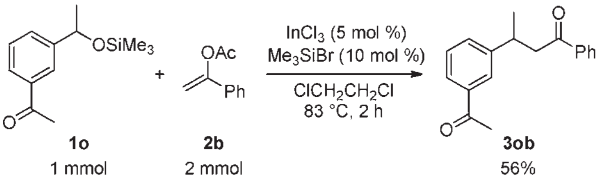
entry	enol acetate		product		yield / %[b]
1		2b		3bb	99 (59)
2	 (*E*/*Z* = 69:31)	2c		3bc	97 (66)
3		2d		3bd	78[c] (82)
4	 (*E*/*Z* = 67:33)	2e		3be	93[d] (74)
5[e]		2f		3bf	51 (33)
6[f]	 (*E*/*Z* = 63:37)	2g		3bg	78[g] (37)

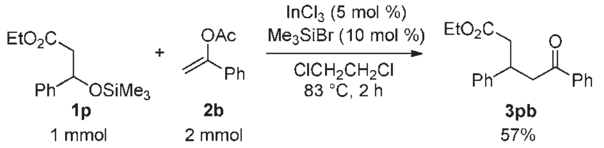
[a] Reaction conditions: **1b** (1 mmol), **2** (2 mmol), InCl$_3$ (0.05 mmol), Me$_3$SiBr (0.1 mmol), CH$_2$Cl$_2$ (2 mL), rt, 2 h. [b] ^{1}H NMR yield. Values in parentheses are isolated yields. [c] dr = 63:37. [d] dr = 54:46. [e] ClCH$_2$CH$_2$Cl (2 mL), 83 °C, 2 h. [f] **2g** (5 mmol), Me$_3$SiCl (0.1 mmol), ClCH$_2$CH$_2$Cl (2 mL), 83 °C, 1 h. [g] dr = 63:37.

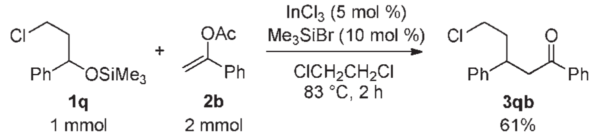
Scheme 1. Competitive Reaction between Silyl Ether **1c** and Aldehyde **6**



Equations 1−3 demonstrate a high chemoselective promotion toward a siloxy moiety. Ketone, ester, and halogen moieties survived the dichloroethane refluxing conditions for direct coupling at siloxy moieties. In particular, it was noteworthy that silyl ether **1q** provided a relatively higher yield of the desired product **3qb** than our previous InI$_3$-catalyzed coupling reaction between alcohols and enol acetates [eq 4].[3h,13] This example shows the practical advantage of the direct substitution of silyl ethers without deprotection.

 (1)

 (2)

 (3)

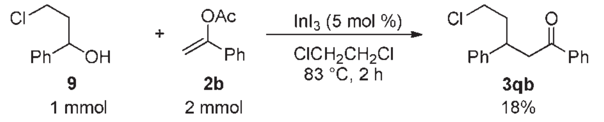
 (4)

Figure 1 shows a plausible mechanism. First, the generation of a combined Lewis acid **10** is followed by the interaction between the silicon center of **10** and silyl ether **1** as illustrated. Then, the carbocation species **11** is generated along with the elimination of Me$_3$SiOSiMe$_3$ **12**.[14] Enol

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[11] Lewis acid catalyzed aldol-type reaction of aldehydes with enol acetates; see ref 6a.

[12] For recent works, see: (a) Yasuda, M.; Chiba, K.; Baba, A. *J. Am. Chem. Soc.* **2000**, *122*, 7549–7555. (b) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8331–8339. (c) Yanagisawa, A.; Sekiguchi, T. *Tetrahedron Lett.* **2003**, *44*, 7163–7166.

[13] The results using other alcohols are shown in the Supporting Information.

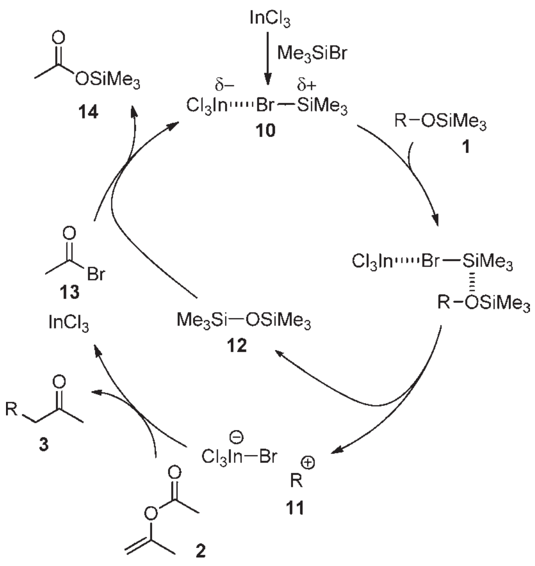

Figure 1. Tentative mechanism.

acetate **2** reacts with the generated cation to produce the α-alkylated carbonyl compound **3**. Finally, acid bromide **13** reacts with **12** to regenerate the combined Lewis acid $InCl_3/Me_3SiBr$ with the formation of byproduct **14**. The elimination of stable **12** may be a driving force of this catalytic cycle, and the weak interaction between $InCl_3$ and oxygen have caused the selective activation of silyl ether.

In conclusion, we have reported the direct coupling between enol acetates and silyl ethers, which is achieved by chemoselective activation of siloxy moieties by the combined Lewis acids of $InCl_3$ and Me_3SiBr.

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Supporting Information Available. Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The reaction of optically active silyl ether **1b** with enol acetate **2a** gave the racemized product **3ba**. The details are shown in the Supporting Information.