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Coupling Reaction of Alkyl Chlorides with Silyl Enolates Catalyzed by Indium Trihalide

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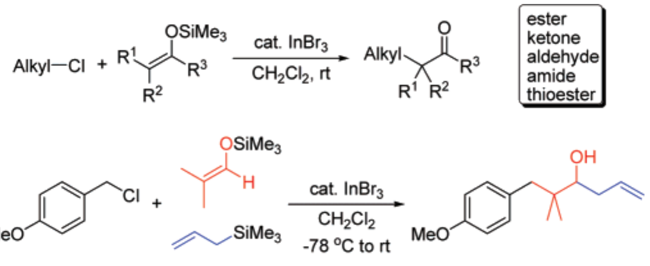
ABSTRACT



Three-component tandem reaction

Indium(III) halide catalyzed not only the coupling of alkyl chlorides with silyl enolates derived from esters, ketones, and aldehydes to give a variety of α-alkylated carbonyl compounds but also one-pot, three-component reactions of aldehyde enolate, alkyl chloride, and allylsilane or alkynylsilane.

A coupling reaction of organic halides with metal enolates is one of the most useful protocols for carbon−carbon bond formation in organic synthesis. A topic of current interest is the catalytic activation for coupling using less expensive organic chlorides. In particular, a reaction using unactivated organic chlorides remains to be a challenge. For this study, our group focused on the reaction of alkyl chlorides with silyl enolates, which are both stable and mild reagents, hence requiring activation by a Lewis acid. Although Reetz et al.[1,2] reported the coupling of alkyl chlorides with silyl enolates catalyzed by ZnCl$_2$ or ZnBr$_2$, the applicable substrates had strict limitations. Our group has recently demonstrated the catalytic ability of indium species using moderate Lewis acidity to effect Friedel−Crafts alkylation.[3] The present study deals the InBr$_3$-catalyzed coupling reaction of alkyl chlorides with aldehyde-, ketone-, and ester-derived silyl enolates.

First, the reaction of benzyl chloride **1a** with dimethylketene methyl trimethylsilyl acetal **2a** was investigated in the presence of various catalysts (Table 1). A 5 mol % loading of InBr$_3$ was found to give the coupling product **3aa** quantitatively in CH$_2$Cl$_2$ at room temperature (entry 2). By comparison, InCl$_3$ gave a low yield (entry 3). ZnBr$_2$ and ZnCl$_2$[4] had lower catalytic ability than InBr$_3$ and InCl$_3$, respectively (entries 4 and 5). Other typical Lewis acids such as BF$_3$·OEt$_2$, AlCl$_3$, and TiCl$_4$ were ineffective to afford the product **3aa** (entries 6−8). These results are perhaps because these catalysts might have highly oxophilic coordination with silyl enolate rather than activating the alkyl chloride. BiBr$_3$,

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[1] For review of reactions of alkyl chlorides with silyl enolates, see: Reetz, M. T. *Angew. Chem., Int. Ed.* **1982**, *21*, 96−108.

[2] (a) Reetz, M. T.; Maier, W. F. *Angew. Chem., Int. Ed.* **1978**, *17*, 48−49. (b) Reetz, M. T.; Schwellnus, K.; Hubner, F.; Massa, W.; Schmidt, R. E. *Chem. Ber.* **1983**, *116*, 3708−3724. (c) Reetz, M. T.; Walz, P.; Hubner, F.; Huttenhain, S. H.; Heimbach, H.; Schwellnus, K. *Chem. Ber.* **1984**, *117*, 322−325.

[3] Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227−8235.

[4] ZnCl$_2$ (98%) and ZnBr$_2$ (99.9%) were obtained from Wako Chemical Industries, Ltd., and used as received.

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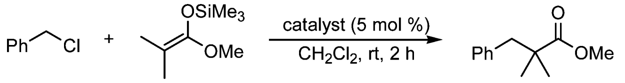
Table 1. Effect of Catalysts[a]



1a **2a** **3aa**

entry	catalyst	yield (%)
1	none	0
2	$InBr_3$	99
3	$InCl_3$	9
4	$ZnBr_2$	39
5	$ZnCl_2$	6
6	$BF_3·OEt_2$	0
7	$AlCl_3$	0
8	$TiCl_4$	0
9	$BiBr_3$	0

[a] Alkyl chloride **1a** (1 mmol), silyl enolate **2a** (1.5 mmol), catalyst (0.05 mmol), and CH_2Cl_2 (1 mL).

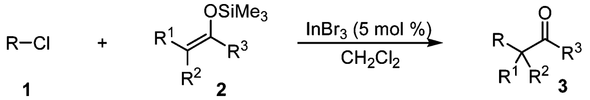
reported as a moderate Lewis acid, however, showed no effect (entry 9).[5]

Second, various alkyl chlorides and silyl enolates were treated, and the results are summarized in Table 2. Unactivated aliphatic chlorides **1b** and **1c** effectively produced the coupling products **3ba** and **3ca**, respectively (entries 1 and 2). It is an advantage of the indium catalyst that oxygen-containing functionalities are applicable (entries 3−5). The coupling with allylic chloride **1g** produced the corresponding ester **3ga** in high yield (entry 6). Both benzyl chlorides, bearing an electron-withdrawing or -donating group, gave satisfactory yields (entries 7 and 8). Silyl enolates **2b** and **2c**, derived from ketones, reacted with 1-chloro-1-phenylethane **1j** to yield the desired substituted ketones in high yields (entries 9 and 10). Interestingly, thioester and amide enolates **2d** and **2e** furnished the substituted thioester **3kd** and amide **3ke**, respectively (entries 11 and 12). This is the first example of coupling of alkyl chlorides with silyl enolates derived from thioesters and amides.

The alkyl chloride **1l** having a bromo moiety selectively provided the chloro-coupling product **3la** in 82% yield (Scheme 1). On the contrary, employment of Hiyama-coupling conditions using a palladium catalyst promoted an alternate coupling at the bromo moiety to furnish the dehydrochlorinated products **4** and **5**.[6]

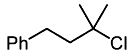
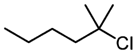
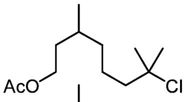
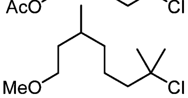
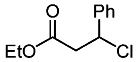
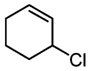
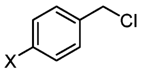
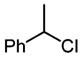
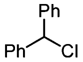
Most studies have focused on enolates derived from esters and ketones, while a few have been done using silyl enolates derived from aldehydes, in part due to a lower nucleophilicity.[7,8] In addition, the expected end products have a formyl moiety which reacts easily with the starting enolates and

Table 2. $InBr_3$-Catalyzed Reaction of Alkyl Halides with Silyl Enolates[a]



1 **2** **3**

	R^1	R^2	R^3
2a	Me	Me	OMe
2b	H	H	Ph
2c	H	-$(CH_2)_3$-	
2d	H	H	S^tBu
2e	Me	Me	NMe_2

entry	chloride		silyl enolate **2**	time (h)	product **3**	yield (%)
1		**1b**	**2a**	2	**3ba**	83
2		**1c**	**2a**	2	**3ca**	82
3[b]		**1d**	**2a**	2	**3da**	53
4[b]		**1e**	**2a**	6	**3ea**	75
5		**1f**	**2a**	3	**3fa**	82
6		**1g**	**2a**	1	**3ga**	91
7		**1h** X = Cl	**2a**	12	**3ha**	99
8		**1i** OMe	**2a**	2	**3ia**	86
9[c, d]		**1j**	**2b**	2	**3jb**	99
10[c]			**2c**	2	**3jc**	83[e]
11[d]		**1k**	**2d**	2	**3kd**	94
12[d]			**2e**	2	**3ke**	47

[a] Alkyl chloride **1** (1 mmol), silyl enolate **2** (1.5 mmol), $InBr_3$ (0.05 mmol), and CH_2Cl_2 (1 mL). [b] Silyl enolate **2** (3 mmol). [c] $InCl_3$ (0.05 mmol) was added instead of $InBr_3$. [d] Silyl enolate **2** (2 mmol). [e] Diastereomer ratio: 52:48.

leads to a complicated mixture. However, once the desired aldehyde products are effectively in hand, they make good synthetic building blocks. Our study examined various types of aldehyde enolates (Table 3). The reactions of enolate **2f** with unactivated alkyl chloride **1b** and benzylic chlorides **1a** and **1j** resulted in the corresponding aldehydes **3** (entries 1−5). Silyl enolates **2g** and **2h**, derived from butanal and acetaldehyde, were not applied to this reaction system (entries 6 and 7) because these enolates were decomposed by the indium(III) halide.[9] Silyl enolates derived from more hindered aldehydes **2i** and **2j** gave the desired aldehydes **3ji** and **3jj**, respectively.

In our study, a tentative mechanism in which alkyl chloride was activated by $InBr_3$ to produce a carbocation was

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(5) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 8345−8350.

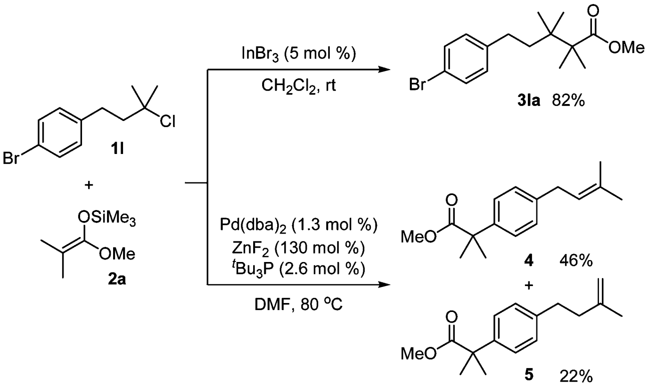
(6) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176−11177.

(7) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

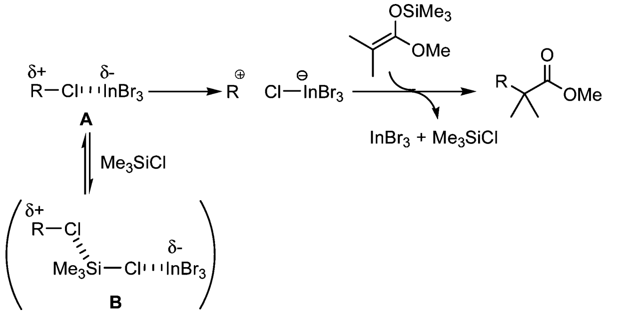
(8) (a) Reetz, M. T.; Maier, W. F. *Angew. Chem., Int. Ed.* **1978**, *17*, 48−49. (b) Sasaki, T.; Usuki, A.; Ohno, M. *J. Org. Chem.* **1980**, *45*, 3559−3564. (c) Mayr, H.; Hellmann, W.; Lammers, R. *Tetrahedron* **1986**, *42*, 6663−6668. (d) Bentley, T. W.; Irrgang, B.; Mayr, H.; Schleyer, P. v. R. *J. Org. Chem.* **1988**, *53*, 3492−3498.

(9) When $InBr_3$ and an aldehyde enolate were mixed, the formation of a complicated mixture was observed. Probably the enolate easily changed to α-silyl aldehyde under the conditions, and the enolate reacted with the formed α-silyl aldehyde.

Scheme 1. Chemoselective Reaction by Choice of Catalyst Systems

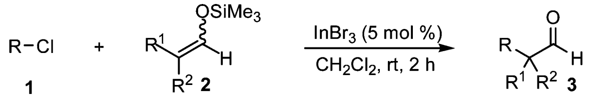


Scheme 2. Plausible Mechanism

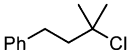
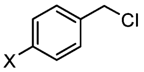
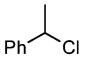


proposed (Scheme 2, type **A**). The reaction with silyl enolate gave the desired ester and Me$_3$SiCl with a regeneration of InBr$_3$. An indium(III) halide activated alkyl halide selectively and weakly interacted with silyl enolate because of its high halophilicity.[10] In contrast, a high oxophilicity was the reason the strong Lewis acids such as AlCl$_3$ and BF$_3$·OEt$_2$ showed no activity. The reaction may accelerate with the combined Lewis acid of InBr$_3$ and Me$_3$SiCl (type **B**) generated in situ because in the combined form it acted as a strong Lewis acid.[3] The coupling reaction was catalyzed by both systems.

Table 3. InBr$_3$-Catalyzed Reaction of Alkyl Halides with Aldehyde-Derived Silyl Enolates[a]

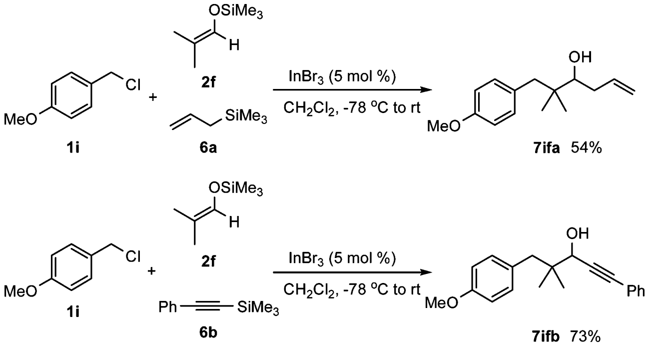


	R^1	R^2
2f	Me	Me
2g	H	H
2h	H	Et
2i	H	^{i}Pr
2j	H	^{t}Bu

entry	R-Cl		silyl enolate **2**	product **3**	yield (%)
1		**1b**	**2f**	**3bf**	54
2[b]			**2f**	**3bf**	72
3		**1a** X = H	**2f**	**3af**	68
4[c]		**1i** OMe	**2f**	**3if**	83
5		**1j**	**2f**	**3jf**	77
6			**2g**	**3jg**	0
7			**2h**	**3jh**	0
8			**2i**	**3ji**	83[e]
9[d]			**2j**	**3jj**	83[f]

[a] Alkyl chloride **1** (1 mmol), silyl enolate **2** (2 mmol), InBr$_3$ (0.05 mmol), and CH$_2$Cl$_2$ (1 mL). [b] Silyl enolate **2** (3 mmol). [c] The reaction was run at −78 °C. [d] InCl$_3$ (0.05 mmol) was added instead of InBr$_3$. [e] Diastereomer ratio: 59:41. [f] Diastereomer ratio: 65:35.

Scheme 3. Three-Component Tandem Reaction



Next, we envisioned a three-component reaction in which the generated aldehyde was to immediately react with allylsilane. This idea was based on our previous report of a Hosomi−Sakurai reaction catalyzed by the combined Lewis acid of InCl$_3$ and Me$_3$SiCl.[11] After the reaction of alkyl chloride **1i** with silyl enolate **2f** was complete, allylsilane **6a** was added to the resulting mixture at room temperature. This step-by-step process yielded the homoallyl alcohol **7ifa** in 76% yield (see the Supporting Information). Next, the three components **1i**, **2f**, and **6a** in the presence of InBr$_3$ were mixed (Scheme 3). Surprisingly, when the mixture was gradually warmed from −78 °C to room temperature, the desired selective tandem reactions took place prior to the coupling of **1i** and **6a**. The addition of alkynylsilane **6b** instead of **6a** gave propargyl alcohol **7ifb** in 73% yield. InBr$_3$ is a good catalyst that promotes both coupling and addition reactions and also controls the reaction order.

Finally, our system had another advantage with respect to solvents. Most of the previous Lewis acid-catalyzed reactions of organic chlorides with silyl enolates have been conducted in a halogenated solvent such as CH$_2$Cl$_2$,[12] while a reaction in non-halogenated solvents is essential for green

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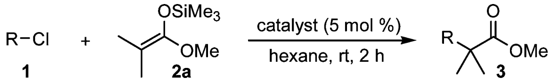
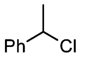
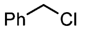
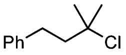
(10) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516−8522.

(11) (a) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578−1581. (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227−8235. (c) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737−1739. (d) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516−8522. (e) Babu, S. A.; Yasuda, M.; Baba, A. *Org. Lett.* **2007**, *9*, 405−408.

(12) See refs 10, 11, and 17.

Table 4. Reactions in Non-Halogenated Solvent[a]



entry	R−Cl	catalyst	product **3**	yield (%)
1	 **1j**	$InBr_3$	**3ja**	100
2		$ZnBr_2$	**3ja**	0
3	 **1a**	$InBr_3$	**3aa**	51
4		$ZnBr_2$	**3aa**	0
5	 **1b**	$InBr_3$	**3ba**	31
6		$ZnBr_2$	**3ba**	0

[a] Alkyl chloride **1** (1 mmol), silyl enolate **2a** (1.5 mmol), catalyst (0.05 mmol), hexane (1 mL).

chemistry. Our system using $InBr_3$ was effective in hexane solvent (Table 4). These results were inferior to those in CH_2Cl_2, but satisfactory yields were secured (entries 1, 3, and 5). Under the same conditions, $ZnBr_2$ was ineffective (entries 2, 4, and 6), but $InBr_3$-catalyzed systems removed the restrictions of the solvent.

In conclusion, our study demonstrated the coupling reactions of alkyl chlorides with silyl enolates catalyzed by $InBr_3$ or $InCl_3$. This reaction system was applied to aldehyde enolates and the three-component sequential carbon−carbon bond formation between alkyl chloride, aldehyde enolate, and other silyl nucleophiles. In addition, the coupling reaction effectively occurred in a non-halogenated solvent such as hexane. Further detailed studies are in progress.

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

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