ORGANIC LETTERS

2012
Vol. 14, No. 7
1846–1849

Synthesis of a Wide Range of Thioethers by Indium Triiodide Catalyzed Direct Coupling between Alkyl Acetates and Thiosilanes

Yoshihiro Nishimoto, Aya Okita, Makoto Yasuda, and Akio Baba*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

baba@chem.eng.osaka-u.ac.jp

Received February 23, 2012

ABSTRACT

An indium triiodide-catalyzed substitution of the acetoxy group in alkyl acetates with thiosilanes provides access to a variety of thioethers. The method is efficient for a wide scope of acetates such as primary alkyl, secondary alkyl, tertiary alkyl, allylic, benzylic, and propargylic acetates.

The development of the synthetic method for thioethers is a significant issue because various organosulfur compounds play important roles in organic synthesis, bioorganic, and medicinal chemistry.[1] The reaction between alkyl halides and metal thiolates is a classical route to thioethers.[2] However, these methods have drawbacks such as a requirement for a strong base and inherent byproduction of an equimolar amount of metal halides. To overcome these problems, the replacement of alkyl halides with other electrophiles, such as alkyl alcohols, ethers, or esters, is promising because of their availability and stability and the fact that they are environmentally benign.

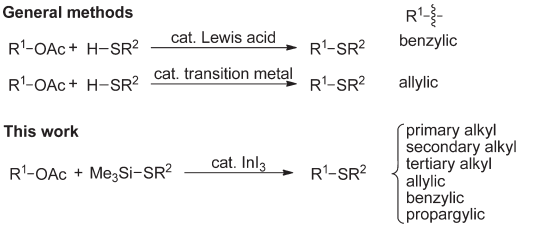


Figure 1. Syntheses of thioethers by direct coupling using alkyl acetates.

Several procedures have been presented, but they still have a limitation in the scope of applicable electrophiles.[3−7] In particular, the employment of alkyl acetates remains relatively undeveloped despite their high convenience for organic synthesis. Transition-metal-catalyzed reactions are limited to allylic acetates because of the generation of π-allylic metal intermediates.[4d−f] While some Lewis acid

(1) (a) Peach, M. E. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; John Wiley & Sons: London, 1979; pp 721−756. (b) Damani, L. A. In *Sulfur-Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology*; Ellis Horwood Ltd.: Chichester, UK, 1989; Vol. 1, Part B: Metabolism of Sulfur Functional Groups. (c) Oae, S., Ed. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press: Boca Raton, 1991. (d) Cremlyn, R. J. In *An Introduction to Organosulfur Chemistry*; Wiley & Sons: New York, 1996. (e) McReynolds, M. D.; Doughtery, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239.

(2) (a) Parham, W. E.; Wynberg, H. *Org. Synth.* **1963**, *4*, 295. (b) Boscato, J. F.; Catala, J. M.; Franta, E.; Brossas, J. *Tetrahedron Lett.* **1980**, *21*, 1519. (c) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. A. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073. (d) Malmstrom, J.; Gupta, V.; Engman, L. *J. Org. Chem.* **1998**, *63*, 3318. (e) Blanchard, P.; Jousselme, B.; Frere, P.; Roncali, J. *J. Org. Chem.* **2002**, *67*, 3961. (f) Ranu, B. C.; Jana, R. *Adv. Synth. Catal.* **2005**, 1811.

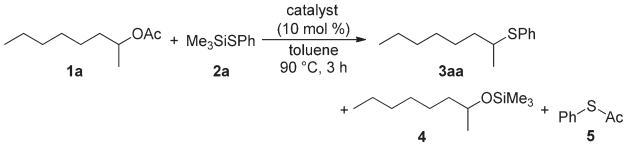
(3) Lewis acid catalyzed reactions: (a) Guindon, Y. R.; Frenette, R.; Fortin, J.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357. (b) Ouertani, M.; Collin, J.; Kagan, H. B. *Tetrahedron* **1985**, *41*, 3689. (c) Kawada, A.; Yasuda, K.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **2002**, *50*, 380. (d) Ohmori, K.; Ushimaru, N.; Suzuki, K. *Tetrahedron Lett.* **2002**, *43*, 7753. (e) Zhan, Z. P.; Yu, J. L.; Liu, H. J.; Cui, Y. Y.; Yang, R. F.; Yang, W. Z.; Li, J. P. *J. Org. Chem.* **2006**, *71*, 8298. (f) Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.

10.1021/ol300450j
Published on Web 03/19/2012

catalyzed S_N1 reactions were also reported, only benzylic acetates, which easily generate the corresponding carbocations, were used.[3d,6j,6k] There are only S_N2 reactions using specifically activated acetates such as β-nitro acetates,[6b,c] β-acetoxy α-diazo carbonyl compounds,[6h] and α-amide α-acetoxy esters.[6g] In these reaction systems, the scope of applicable alkyl acetates was strictly limited by the reaction mechanism. In addition, the substitution of simple alkyl acetates, which requires harsh conditions, has not been much developed because of the risk of undesired transformation of esters into thioesters. Herein, we present a general route to thioethers in which a direct coupling between alkyl acetates and thiosilanes was effectively catalyzed by InI_3. Various types of acetates such as primary, secondary, tertiary, allylic, benzylic, and propargylic acetates were readily applicable. As far as we could ascertain, the present reaction system has the widest scope of alkyl acetates among reported procedures (Figure 1).

First, the screening of catalysts was carried out in the model reaction of 2-acetoxyoctane **1a** with trimethyl(phenylthio)silane **2a** (Table 1). InI_3 was found to promote most effectively the direct substitution of the acetoxy group by **2a** at 90 °C in toluene, furnishing the desired thioether **3aa** in 77% yield (entry 1). $InBr_3$ also showed a moderate catalytic effect (entry 2).[8] The use of $InCl_3$ and $In(OTf)_3$ resulted in no reaction (entries 3 and 4). The representative oxophilic Lewis acids such as $BF_3\cdot OEt_2$ and $AlCl_3$ afforded no desired thioether (entries 5 and 7). Interestingly, a stoichiometric amount of $BF_3\cdot OEt_2$ or $AlCl_3$ promoted a type of transesterification to produce silyl ether **4** and thioester **5** (entries 6 and 8). These results strongly indicated a sharp contrast in activation mode of acetoxy moiety between indium triiodide and the representative Lewis acids. Moreover, the employment of ZnI_2, which was reported to be effective in the synthesis of thioethers by the reaction between thiols and alcohols,[3a] resulted in only 8% yield (entry 9). $B(C_6F_5)_3$ and $Bi(OTf)_3$ were ineffective, although they accelerated coupling reactions of alkyl acetates with allylic silanes and silyl enolates, respectively (entries 10 and 11).[9,10] $Sc(OTf)_3$ also gave no product (entry 12). $ClCH_2CH_2Cl$ and hexane were also found to be suitable solvents (entries 13 and 14). In contrast, coordinative solvents like acetonitrile and DMF did not furnish the desired reaction (entries 15 and 16).

Table 1. Screening of Catalysts and Solvents[a]



		yield[b] (%)		
entry	catalyst	**3aa**	**4**[c]	**5**
1	InI_3	77	0	0
2	$InBr_3$	49	0	0
3	$InCl_3$	0	0	0
4	$In(OTf)_3$	0	0	0
5	$BF_3\cdot OEt_2$	0	0	5
6[d]	$BF_3\cdot OEt_2$	0	34	35
7	$AlCl_3$	0	0	0
8[d]	$AlCl_3$	0	30	20
9	ZnI_2	8	0	0
10	$B(C_6F_5)_3$	0	0	0
11	$Bi(OTf)_3$	0	0	0
12	$Sc(OTf)_3$	0	0	0
13[e]	InI_3	66	0	0
14[f]	InI_3	64	0	0
15[g]	InI_3	0	0	0
16[h]	InI_3	0	0	0

[a] **1a** (1 mmol), **2a** (2 mmol), catalyst (0.1 mmol), toluene (1 mL), 90 °C, 3 h. [b] Yields were determined by analysis of ^1H NMR spectra of product mixtures prior to purification. [c] The yield of **4** was determined after the hydrolysis of **4** to 2-octanol with 1 M HCl aq. [d] Catalyst (1 mmol). [e] 1,2-DCE solvent. [f] Hexane solvent. [g] CH_3CN solvent. [h] DMF solvent.

We next surveyed the scope of applicable thioethers. As Table 2 shows, a variety of alkyl acetates were employed smoothly. Primary and tertiary alkyl acetates (**1b** and **1d**)

(4) Transition-metal-catalyzed reactions: (a) Inomata, K.; Yamamoto, T.; Kotake, H. *Chem. Lett.* **1981**, 1357. (b) Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141. (c) Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 8099. (d) Kondo, T.; Morisaki, Y.; Uenoyama, S.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 8657. (e) Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 3474. (f) Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2007**, *9*, 4603. (g) Tanaka, S.; Pradhan, P. K.; Maegawa, Y.; Kitamura, M. *Chem. Commun.* **2010**, *46*, 3996.

(5) Ruthenium-catalyzed propargylic substitution reaction:Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172.

(6) S_N2-type reaction using a strong base: (a) Carroll, F. I.; White, J. D.; Wall, M. *J. Org. Chem.* **1963**, *28*, 1236. (b) Lehr, H.; Karlan, S.; Goldberg, M. W. *J. Med. Chem.* **1963**, *6*, 136. (c) Carroll, F. I.; White, J. D.; Wall, M. E. *J. Org. Chem.* **1963**, *28*, 1240. (d) Ono, N.; Kamimura, A.; Kaji, A. *Tetrahedron Lett.* **1986**, *27*, 1595. (e) Selva, M.; Trotta, F.; Tundo, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 519. (f) Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633. (g) Paulitz, C.; Steglich, W. *J. Org. Chem.* **1997**, *62*, 8474. (h) Xu, F.; Shi, W.; Wang, J. *J. Org. Chem.* **2005**, *70*, 4191. (i) Kuroda, K.; Maruyama, Y.; Hayashi, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 381. (j) Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 6480. (k) Saha, A.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 1902.

(7) (a) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *17*, 1409. (b) Mukaiyama, T.; Ikegai, K. *Chem. Lett.* **2004**, 1522.

(8) (a) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414. (b) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737. (c) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516. (d) Huang, J.-M.; Wong, C.-M.; Xub, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375. (e) Baba, A.; Yasuda, M.; Nishimoto, Y.; Saito, T.; Onishi, Y. *Pure Appl. Chem.* **2008**, *80*, 845. (f) Nishimoto, Y.; Kajioka, M.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Commun.* **2008**, 6396. (g) Nishimoto, Y.; Onishi, Y.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9131. (h) Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2009**, *65*, 5462. (i) Nishimoto, Y.; Moritoh, R.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4577. (j) Nishimoto, Y.; Inamoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2010**, 3382. (k) Nishimoto, Y.; Ueda, H.; Inamoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2010**, *12*, 3390. (l) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2011**, *13*, 2762. (m) Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8623. (n) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Chem. Lett.* **2011**, *40*, 1223.

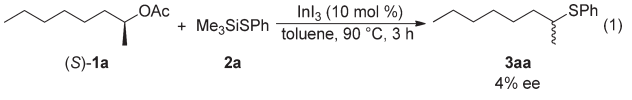
(9) (a) Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705. (b) Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999.

(10) (a) Rubenbauer, P.; Bach, T. *Tetrahedron Lett.* **2008**, *49*, 1305. (b) Rubenbauer, P.; Herdtweck, E.; Strassner, T.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 10106.

as well as a secondary substrate **1c** were utilized to give the corresponding thioethers in high yields (entries 1−3). The reaction of 1-adamantyl acetate **1e** proceeded in excellent yield despite possessing significant steric hindrance (entry 4). Benzylic acetates bearing both electron-donating and -withdrawing groups were found to be reactive electrophiles (entries 5−9). This reaction system was applicable for large-scale synthesis (entry 6). (2-Thienyl)methyl acetate **1j** furnished the desired product **3ja** in 87% yield (entry 10). The substitutions of allylic and propargylic acetoxy groups (**1k** and **1l**) were achieved (entries 11 and 12). α-Acetoxy ketone **1m** was also applicable to furnish the corresponding α-thio ketone **3ma** in 67% yield (entry 13). Ferrocene, alkene, and phthalimide moieties tolerated the reaction conditions (entries 14−16).[11] It was notable that the acetoxy group was substituted in preference to the chloro group to give 5-chloropentyl phenyl thioether **3qa** in 49% yield in the reaction using 5-chloropentyl acetate **1q**, although a 10% yield of 1,5-bis(phenylthio)pentane **6** was observed (entry 17). The intramolecular competitive reaction using compound **1r** showed that the tertiary alkyl acetate has a higher reactivity than the primary counterpart (entry 18).

Scheme 1 shows the effect of substituents in thiosilanes **2**. In the reaction with benzylic acetate **1f**, both arylthiosilanes bearing electron-donating and withdrawing groups gave satisfying results at room temperature (**3fb** and **3fc**). Primary- and secondary alkyl thiosilanes also furnished the corresponding thioethers in high yields, respectively, at 90 °C (**3fd** and **3fe**). The difference in reaction temperature indicated the higher reactivity of arylthiosilanes as compared to alkylthiosilanes.

The reaction using optically active alkyl acetate, (*S*)-2-acetoxyoctane (*S*)-**1a**, proceeded with racemization to give the thioether **3aa** in only 4% ee, which suggested that the reaction is likely proceeding through an S_N1 mechanism via a carbocation intermediate (eq 1). However, the effective reaction using primary alkyl acetates and α-acetoxy ketone, which cannot be expected to generate a stable carbocation, is consistent with the reaction proceeding through an S_N2 mechanism. Therefore, the reaction mechanism would depend on the type of alkyl acetates.



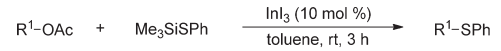
The mixture of InI_3, *n*-hexyl acetate **1s**, and thiosilane **2a** in toluene-d_8 solvent was monitored by ^{13}C NMR at room temperature, in which these conditions caused no substitution reaction of **1s** with **2a**. The considerable change of signals of both acetate **1s** and thiosilane **2a** were observed, which indicated that InI_3 interacts with both alkyl acetate and thiosilane.[12] In addition, no transmetalation between thiosilane **2a** and InI_3 was detected.[13] In contrast, $AlCl_3$

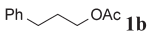
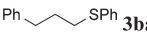
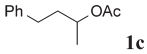
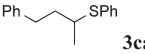
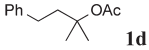
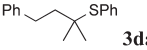
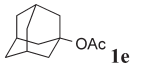
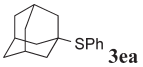
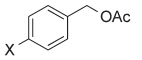
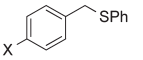
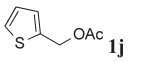
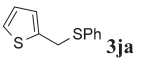
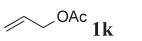
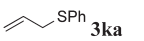
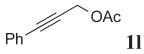
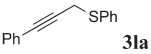
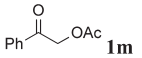
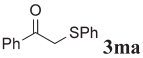
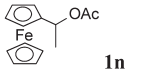
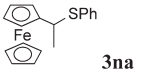
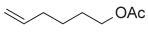
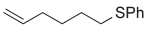
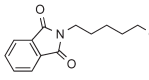
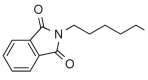
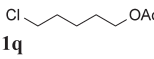
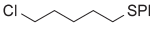
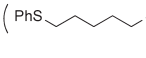
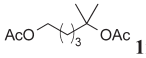
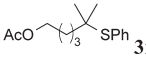
(11) The difference between an NMR yield and an isolated yield was caused by the difficult separation of the product from byproduct, PhSSPh.

(12) See the Supporting Information for details of the NMR study.

(13) When an equivalent amount of InI_3 and thiosilane **2a** was mixed in toluene-d_8, no transmetalation was observed by ^{13}C NMR.

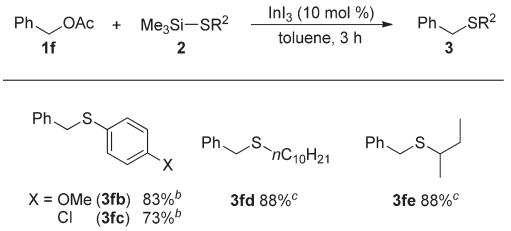
Table 2. Substitution of OAc Group in Various Alkyl Acetates **1** with Thiosilane **2a**[a]



entry	alkyl acetate **1**	product **2**	yield (%)[b]
1[c]	 **1b**	 **3ba**	99 (67)
2[c]	 **1c**	 **3ca**	88 (66)
3	 **1d**	 **3da**	69 (56)
4[c]	 **1e**	 **3ea**	99 (82)
			
5	X = H (**1f**)	X = H (**3fa**)	95 (86)
6[d]	H (**1f**)	H (**3fa**)	74
7	OMe (**1g**)	OMe (**3ga**)	99 (81)
8	Cl (**1h**)	Cl (**3ha**)	96 (90)
9	CO_2Et (**1i**)	CO_2Et (**3ia**)	99 (89)
10	 **1j**	 **3ja**	87 (75)
11	 **1k**	 **3ka**	94 (43)
12[c]	 **1l**	 **3la**	55 (41)
13[e]	 **1m**	 **3ma**	67 (57)
14	 **1n**	 **3na**	85 (28)
15[c]	 **1o**	 **3oa**	99 (75)
16[c]	 **1p**	 **3pa**	95 (57)
17[f]	 **1q**	 **3qa**	49 (44)
		 **6**	10
18	 **1r**	 **3ra**	69 (58)

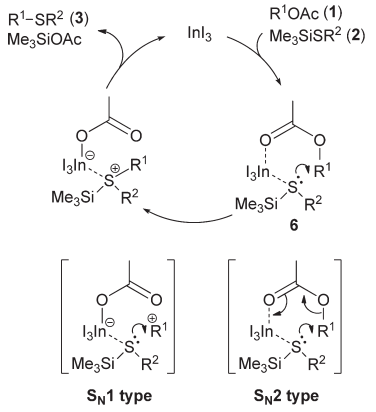
[a] **1** (1 mmol), **2a** (2 mmol), InI_3 (0.1 mmol), toluene (1 mL), room temperature, 3 h. [b] Yields of crude products determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. Values in parentheses are yields of isolated products. [c] The reaction was carried out at 90 °C. [d] Large-scale synthesis **1** (20 mmol), **2a** (40 mmol), InI_3 (2 mmol), toluene (20 mL). Isolated yield is shown. [e] The reaction was carried out from 0 °C to room temperature. [f] InI_3 (0.2 mmol).

Scheme 1. Examination for Scope of Thiosilane **2**.[a]



[a] Reaction conditions: **1f** (1 mmol), **2** (2 mmol), InI_3 (0.1 mmol), toluene (1 mL), 3 h. Yield of products after purification. [b] At room temperature. [c] At 90 °C.

Scheme 2. Tentative Mechanism

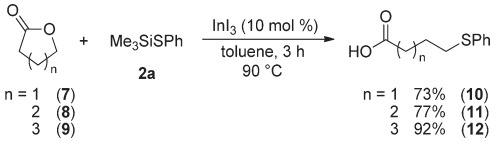


and $BF_3 \cdot OEt_2$ easily transmetalated with **2a** to generate thioaliminum and thioborane, respectively.[14] These metal thiolates may cause a type of transesterification to give thioesters (Table 1, entries 6 and 8).

On the basis of the above controlled studies, a tentative mechanism is presented in Scheme 2. InI_3 is coordinated by both the carbonyl oxygen of alkyl acetate **1** and the sulfur atom of thiosilane **2** to form complex **6**. In the case of secondary alkyl, tertiary alkyl, benzylic, propargylic, and allylic acetates, an S_N1-type substitution proceeds. On the other hand, reactions of primary alkyl acetates and α-acetoxy carbonyl compounds occur in S_N2-type mechanisms because of instability of the corresponding carbocation. Finally, thioether **3** and trimethylsilyl acetate are produced with regeneration of InI_3. InI_3 brings alkyl acetate **1** close to thiosilane **2** in complex **7**, which would contribute to the widespread scope of alkyl acetates. The Lewis acidity of the indium center is not decreased due to no transmetalation between InI_3 and thiosilane to activate alkyl acetate **2** effectively.

To expand the present procedure, the reaction of lactones with thiosilane **2** was examined (Scheme 3).[15] γ-Butyrolactone **7** smoothly underwent the ring-opening reaction to give the corresponding thiocarboxylic acid **10** in 73% yield. δ-Valerolactone **8** and ε-caprolactone **9** also furnished the desired products **11** and **12** in excellent yields, respectively.

Scheme 3. Ring-Opening Reactions of Lactones with Thiosilane **2a**[a]



[a] Yield of products after purification.

In conclusion, we have developed an effective and practical synthesis of thioethers by the InI_3-catalyzed substitution reaction between alkyl acetates and thiosilanes. The generality of alkyl acetates is remarkably widespread: primary alkyl, secondary alkyl, tertiary alkyl, allylic, benzylic, and propargylic acetates, and α-acetoxy ketones were all applicable. This reaction system was compatible with a diverse range of functional groups including alkene, alkyne, ferrocene, phthalimide, and ketone groups. Mechanistic studies revealed the interesting feature of InI_3 that accelerates both mechanisms of S_N1 and S_N2 types.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (No. 22106527 and No. 23105525) and Challenging Exploratory Research (No. 23655083) from the Ministry of Education, Culture, Sports, Science and Technology (Japan).

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

(14) NMR studies showed that $AlCl_3$ and $BF_3 \cdot OEt_2$ transmetalated with **2a** to generate Me_3SiCl and Me_3SiF, respectively. See the Supporting Information for details.

(15) Node, M.; Nishide, K.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 5163.

The authors declare no competing financial interest.