Highly Selective Acetal Cleavage Using New Organoaluminum Reagents

Kazuaki Ishihara, Naoyuki Hanaki, and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University
Chikusa, Nagoya 464-01, Japan

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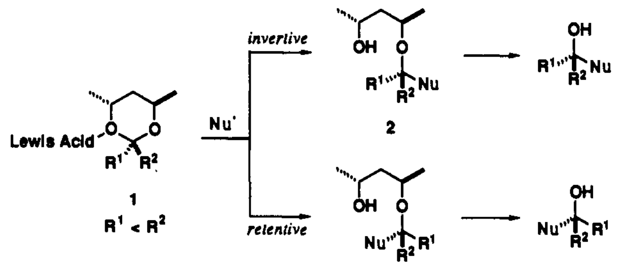
Controlling the stereochemistry of additions of nucleophiles to acetals is an increasingly important problem in organic synthesis.[1] The great synthetic value of this approach comes from the relative asymmetric induction with chiral acetals derived from optically active alcohols. Preferential complexation of one oxygen and invertive substitution takes place in these cases (**1** to **2**).[2] Our initial investigation of such a reaction, however, showed that when the nucleophile is aluminum hydride, reaction results in a retentive relationship between the coming hydride and the departing oxygen atom.[3] This retentive substitution of acetal was exceptional and may be explained by the tight ion pair between the aluminum ate complex and the oxocarbenium ion.[3b,4] However, similar retentive alkylation has not been reported, and the reaction of chiral acetals with trimethylaluminum is, for example, not stereoselective.[3b] It became of interest to search for an appropriate reaction system that could deliver the *alkyl* group enantioselectively to the *re* face of an oxocarbenium ion (**1** → **3**, Nu = alkyl), both as a test of the mechanistic hypothesis and as a step toward a more general synthetic methodology. The results that follow verify this possibility and thus close the methodological gap.



The lack of selectivity of trimethylaluminum may come from the low site selectivity in complexation of the aluminum reagent with two different acetal oxygens and/or the lower nucleophilicity of the resulting ate complex. To increase the selectivity of the reaction, therefore, we studied a variety of mono(aryloxy)aluminums, since the discriminating selectivity of a Lewis acid is significantly influenced by the size of the reagent.[5] Most of these reagents[6] gave exceedingly low yields of the alkylation products, which was not surprising because of the low nucleophilicity of the usual (aryloxy)aluminum reagents. We found, however, that the treatment of trialkylaluminum with 2,6-dihalo-substituted phenol derivatives produced sufficiently reactive aluminum reagent, which was more reactive than the corresponding trialkylaluminum and effective for the clean and stereoselective cleavage of chiral acetals.[7] Several examples of this transformation are given in Table I.

Table I. Alkylative Cleavage of Chiral Acetals Using R_2AlOAr[a]
$1\ (R^1 = H) \rightarrow 3\ (R^1 = H;\ Nu = R)$

R^2	R	ArOH[b]	yield, %	ret:inv[c]
C_6H_{13}	Me	A	70	>99:1 (70:30)
	Me	B	59	97:3
	Me	C	87	89:11
	Me	D	86	87:13
	Et[d]	A	70	93:7 (87:13)
	Et[e]	A	40	96:4
	Et	B	59	98:2
	Et[d]	C	87	89:11
	Et[d]	D	86	88:12
c-C_6H_{11}	Me	A	70	>99:1 (78:22)
	Et[d]	A	87	>99:1

[a] Unless otherwise specified, a mixture of trialkylaluminum (6 equiv) and phenol (6 equiv) in toluene was stirred at 25 °C for 1 h followed by treatment of acetal for 3–12 h. [b] A, pentafluorophenol; B, 2,4,6-trichlorophenol; C, 2,4,6-tri-*tert*-butylphenol; D, 2,6-di-*tert*-butyl-4-methylphenol. [c] The ratio was determined by capillary GC. The ratios in parentheses are from the trialkylaluminum in CH_2Cl_2. [d] Insufficient gas evolution (50–60%) was observed during the preparation of the reagent. [e] Et_2AlH was used in place of Et_3Al.

Table II. Reductive Cleavage of Acetals with $Et_2AlF–C_6F_5OH$[a]
$1 \rightarrow 4$

R^1	R^2	solvent	yield, %	ret:inv[b]
Me	C_5H_{11}	CH_2Cl_2	91	81:19
		toluene	61	86:14 (78:22)
Me	*i*-Pr	CH_2Cl_2	71	97:3
		toluene	62	98:2 (96:4)
Me	Ph	CH_2Cl_2	81	95:5
		toluene	68	99:1 (98:2)
Et	Ph	CH_2Cl_2	92	90:10
		toluene	84	93:7

[a] A mixture of diethylaluminum fluoride (1.2 equiv) and pentafluorophenol (2.4 equiv) in toluene was stirred at 0 °C for 10 min followed by treatment of acetal at 0 °C for 1 h. [b] The ratio was determined by capillary GC. The ratios in parentheses are from the dichloroaluminum hydride in ether followed by oxidation; see ref 3.

In most of these reactions, a small amount (~5%) of unexpected β-alkoxy ketone of type **4** was produced, which would be derived from a unique intramolecular Meerwein–Ponndorf–Verley–Oppenauer reaction. Our interests then focused on the exclusive preparation of β-alkoxy ketones from chiral acetals, since

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(1) For a recent review, see: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Mash, A. E. In *Studies in Natural Product Synthesis*; Atta-Ur Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 577. (c) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, p 125.

(2) Trialkylsilanes: (a) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987. (b) Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755. Allylsilanes: (c) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951. Silyl enol ethers: (d) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. (e) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7372. (f) Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588. (g) Silverman, I. R.; Edington, C.; Elliott, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180. Alkynylsilane: (h) Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904. Silyl cyanide: (i) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (j) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. Ketene silyl acetal: (k) Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, *26*, 2535. Alkylzinc, alkylmagnesium, or alkyllithium: (l) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947. (m) Mori, A.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 4421. Alkylcopper: (n) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3083. (o) Normant, J. F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* **1989**, *45*, 507.

(3) (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83. (c) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *26*, 983.

(4) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. See also: Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595. Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

(5) Maruoka, K.; Nagahara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 6115.

(6) Other phenols that revealed no reactions are 2-fluorophenol, 2,4,6-trimethylphenol, and 2,6-diisopropylphenol. The complex of pentachlorophenol and trimethylaluminum was not soluble in toluene or dichloromethane.

(7) The following experiment is typical: To a solution of trimethylaluminum (1.50 mL of a 2.0 M solution in hexane, 3.0 mmol) in toluene (10 mL) was added pentafluorophenol (1.50 mL of a 2.0 M solution in toluene, 3.0 mmol) at 25 °C under argon. The reaction mixture was stirred for 1 h at that temperature, during which period the evolution of methane gas ceased. To this was introduced (4*R*,6*R*)-4,6-dimethyl-2-hexyl-1,3-dioxane (100 mg, 0.5 mmol) in toluene (1 mL) at 25 °C. After stirring for 12 h, the solution was poured into dilute sodium hydroxide and the product was extracted with hexane. The solvent was evaporated, and the residue was purified by column chromatography on silica gel to give the methylation product as a colorless oil (76 mg, 70% yield).

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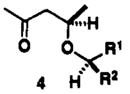
the direct formation of the β-alkoxy ketone is practically quite useful. It was soon realized that the combined use of diethylaluminum fluoride (1.2 equiv) and pentafluorophenol (2.4 equiv) was the most effective for a diastereoselective reductive cleavage reaction. The major isomer afforded a retentive product, and the observed high diastereoselectivity was similar to or better than that of reductive cleavages of acetals with aluminum hydride. As shown in Table II, several chiral acetals derived from aliphatic or aromatic ketones are applicable in good yields and with high diastereoselectivities.



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In summary, this paper describes a new methodology for cationic *retentive* alkylation and reduction of acetals. The results reflect the unusual effect of a halophenol ligand on the reactivity of organoaluminum reagents. We also found that pentafluorophenol is an effective accelerator for Meerwein–Ponndorf–Verley reduction. Reduction of 4-*tert*-butylcyclohexanone with aluminum isopropoxide (3 equiv) in dichloromethane, for example, was very slow at 0 °C (<5% for 5 h), but in the presence of pentafluorophenol (1 equiv), the reduction was cleanly completed within 4 h at 0 °C. The question of why these reagents retain sufficient nucleophilicity is still open. It is possible that the *o*-halo-substituents of the phenoxide ligand may coordinate with the aluminum atom, thus increasing the nucleophilicity of the reagent. Whatever the reason, the combination of halophenol and organoaluminum reagent offers unique opportunities in organometallic reactions.[8]

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γ-Selective Cross-Coupling Reaction of Allyltrifluorosilanes: A New Approach to Regiochemical Control in Allylic Systems

Yasuo Hatanaka, Yasuo Ebina, and Tamejiro Hiyama*

Sagami Chemical Research Center
4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

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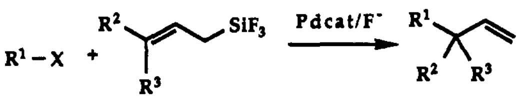
Although the cross-coupling reaction of allylmetals with vinylic, allylic, and aromatic electrophiles is a straightforward route to 1,4-dienes,[1] 1,5-dienes,[2] and allylic arenes,[3] low regioselectivity regarding organometallics has severely limited their synthetic application. Especially, no reliable allylmetal reagents with high γ-selectivity have been realized yet. We report herein that allyltrifluorosilanes,[4] when promoted by fluoride ion and a palladium catalyst,[5] undergo cross-coupling reactions with various electrophiles exclusively at the γ-carbon to give allylated products *in regiochemically pure forms* (Scheme I).[6]

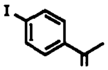
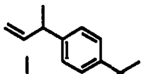
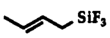
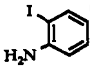
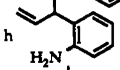
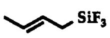
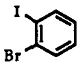
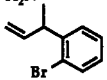
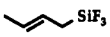
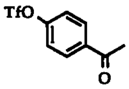
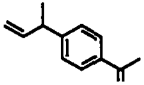
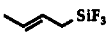
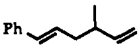
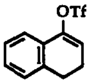
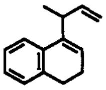
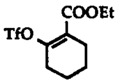
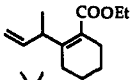
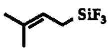
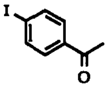
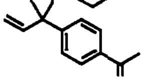
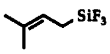
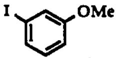
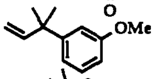
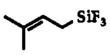
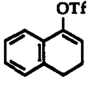
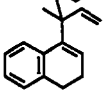
Our results summarized in Table I clearly demonstrate that a wide range of electrophiles such as organic halides, triflates, and an acetate can effectively take part in this coupling reaction. For example, the cross coupling of (*E*)-crotyltrifluorosilane with 4-iodoacetophenone in the presence of 1 equiv of tetrabutylammonium fluoride (TBAF) and 5 mol % of $Pd(PPh_3)_4$ in tetrahydrofuran (THF) at 80 °C (in a sealed tube) proceeded with complete γ-attack, giving 3-(4-acetylphenyl)-1-butene in 95% yield (entry 1).[7] With an appropriate Pd catalyst, fluoride ion, and reaction conditions (see footnotes of Table I), (*E*)-crotyltri-

Scheme I[a]



[a] R^1 = aryl, alkenyl, allyl; X = Br, I, OTf, OAc; R^2 = Me, R^3 = H; R^2 = Me, R^3 = Me.

Table I. Cross-Coupling Reactions of Allyltrifluorosilanes with Various Electrophiles Mediated by Palladium Catalyst and Fluoride Ion in THF

Entry	Allylsilane	Substrate	Conditions[a]	Product	Yield(%)[b]
1			A 80 °C, 19 h		95
2			B 100 °C, 25 h		53
3			B 100 °C, 37 h		78
4			C 100 °C, 12 h		96
5			A 60 °C, 5 h		54
6			C 100 °C, 12 h		85
7			C 120 °C, 24 h		98
8			B 100 °C, 46 h		70
9			B 100 °C, 33 h		51
10			C 120 °C, 46 h		83

[a] Reactions were carried out in sealed tubes under the following conditions. A: $Pd(PPh_3)_4$ (2–5 mol %) and TBAF (1.0 equiv) were used. B: $Pd(PPh_3)_4$ (5 mol %) was used. After the addition of TBAF (1.0 equiv), additional TBAF (0.5 equiv) was introduced at intervals of 10 h. C: $Pd(OAc)_2$ (5 mol %), dppb (10 mol %), and TASF (1.0 equiv) were used. [b] Isolated.

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[1] (a) Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695 and references cited therein. For the cross coupling of higher order allylic cuprates with alkyl halides, see: (b) Lipshutz, B. H.; Crow, R.; Dimock, S. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4063.

[2] (a) Godschlax, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599. (b) **1983**, *24*, 1905. (c) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969. (d) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

[3] Kosugi, M.; Sasaki, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.

[4] Various types of allyltrifluorosilanes are conveniently prepared via a copper-catalyzed coupling of trichlorosilane with the corresponding allyl chlorides and fluorination of the resulting allyltrichlorosilanes using SbF_3: (a) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099. (b) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1.

[5] For the cross-coupling reaction of organosilicon compounds promoted by palladium catalyst and fluoride ion, see: (a) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. (b) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719 and references cited therein.

[6] With the aid of a Lewis acid catalyst, allyltrimethylsilane couples with tertiary chlorides only: (a) Fleming, I.; Paterson, I. *Synthesis* **1979**, 446. (b) Sasaki, T.; Usuki, A.; Ohno, M. *Tetrahedron Lett.* **1978**, 4925.

[7] The following procedure is representative (Table I, entry 1). A tetrahydrofuran (THF) solution of tetrabutylammonium fluoride (1.0 M, 3.0 mL, 3.0 mmol, purchased from Aldrich Chemical Co.) was added to 4-iodoacetophenone (490 mg, 2.0 mmol), (*E*)-crotyltrifluorosilane (420 mg, 3.0 mmol), and $Pd(PPh_3)_4$ (62 mg, 0.05 mmol) dissolved in THF (10 mL) at room temperature under an argon atmosphere. The reaction mixture was then heated to 80 °C for 19 h. Concentration and purification by column chromatography (silica gel) using ethyl acetate/hexane (1:10) gave 3-(4-acetylphenyl)-1-butene (341 mg, 95%).

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