Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7403-7406, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01735-8

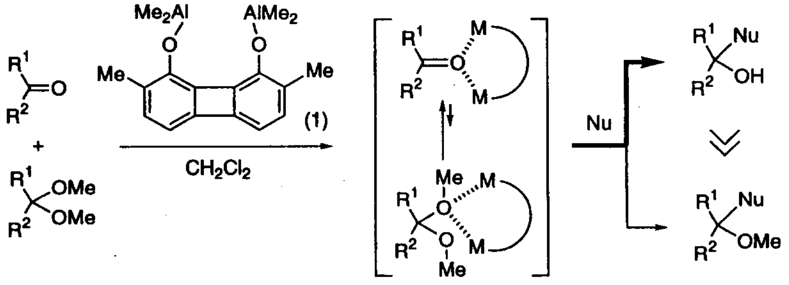
Bidentate Organoaluminum Lewis Acid for Selective Activation of Carbonyl over Acetal Functionality: Chemoselective Functionalization

Takashi Ooi, Eiji Tayama, Makoto Takahashi, and Keiji Maruoka*
Department of Chemistry, Graduate School of Science, Hokkaido University
Sapporo 060, Japan

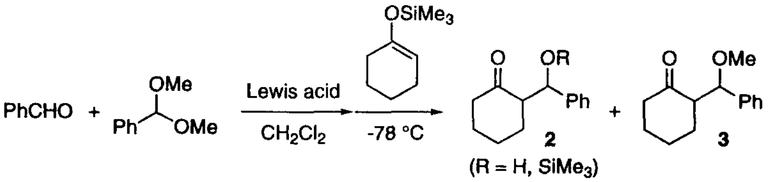
Abstract: Chemoselective functionalization of carbonyl compounds over acetals has been achieved by bidentate organoaluminum Lewis acid based on the selective double electrophilic activation of carbonyls. © 1997 Elsevier Science Ltd.

The chemoselective functionalization between carbonyls and their masked acetals is a synthetically useful operation, and is closely related to the chemistry of molecular recognition.[1] Most of the ordinary Lewis acid promoters activate both carbonyl and acetal functions.[2] The discrimination of acetals over carbonyls is commonly achievable using $TiCl_4$ and Me_3SiOTf, which induce selective activation of acetal functionality in the presence of carbonyl groups.[3] However, the opposite selectivity, *i.e.*, chemoselective functionalization of carbonyls seems quite difficult to attain in view of the high reactivity of acetal counterparts for Lewis acids, and hence it has not yet been fully realized in electrophilic reactions in spite of long-standing concern. Quite recently, Otera et. al. reported unprecedented preference for activation of aldehyde carbonyls over acetals in organotin Lewis acid-promoted Mukaiyama-Aldol reaction of ketene silyl acetals, which is unfortunately not applicable for selective activation of ketone carbonyls.[4] Here we wish to disclose our own results on this subject using our recently developed bidentate organoaluminum Lewis acid,[5] featuring a Lewis acid receptor for recognition and activation of carbonyls based on the selective Lewis acid-base complex formation (Scheme I).

Scheme I



First, we examined Mukaiyama aldol reaction of benzaldehyde and its dimethyl acetal with a silyl enol ether.[6] Reaction of a mixture of 1 equiv each of benzaldehyde and its dimethyl acetal with 1-(trimethylsiloxy)-1-cyclohexene under the influence of catalytic Me_3SiOTf (5 mol%) in CH_2Cl_2 at -78 °C for 3 h afforded aldol products **2** (R = H) and **3** (86% combined yield) in a ratio of 9:91, which indicates the higher reactivity of acetal functionality for Me_3SiOTf-catalyzed aldol reaction as reported by Noyori *et al.*[3b,3c] Switching a Lewis acid from Me_3SiOTf to $TiCl_4$ resulted in the loss of selectivity (ratio of **2**:**3** = 59:41), and both $SnCl_4$ and $BF_3{\bullet}OEt_2$ exhibited moderate and opposite chemoselectivity (73:27 and 74:26, respectively). In contrast, however, (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**1**) as a bidentate Lewis acid,[5] on treatment of an equimolar mixture of benzaldehyde and its dimethyl acetal, is capable of activating aldehyde carbonyl selectively as evident by the subsequent reaction with 1-(trimethylsiloxy)-1-cyclohexene, giving **2** (R = $SiMe_3$:71%; *erythro/threo* = 26:74 and R = H:10% yields) almost exclusively (97:3). It should be added that the aldol reaction with monodentate counterpart, dimethylaluminum 2,6-dimethylphenoxide resulted in very reluctant formation of **2** under similar reaction conditions (4.5% combined yield).

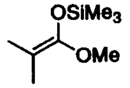


Lewis acid		
Me_3SiOTf	:	86% (9 : 91)
$TiCl_4$	:	77% (59 : 41)
$SnCl_4$	:	92% (73 : 27)
$BF_3{\bullet}OEt_2$	:	66% (74 : 26)
1	:	84% (97 : 3)

Other selected examples in Table 1 clearly demonstrate the effectiveness of bidentate organoaluminum Lewis acid **1** for recognition and activation of carbonyl functionality based on the double electrophilic activation, thereby allowing chemoselective functionalization of carbonyl compounds. Excellent chemoselective Mukaiyama aldol condensation of ketone carbonyl with ketene silyl acetals appears feasible by the use of **1**, while Me_3SiOTf resulted in a lack of selectivity depending upon the reactivity of the substrates (entries 1-11).[7] Notably, discriminative aldol reaction of acetophenone and its dimethyl acetal with ketene silyl acetal in the presence of catalytic dibutyltin bis(triflate) (DBTT) (10 mol%),[4] which is quite useful for activation of aldehyde carbonyls over acetals, gave unsatisfactory results, producing β-methoxy ester preferentially (entry 10). In the Lewis acid-promoted allylation of aldehydes with allyltributyltin, virtually complete chemoselective functionalization of aldehyde carbonyls is also observable and the opposite chemoselectivity is easily accessible using $TiCl_4$ as promoter (entries 12-15).[8]

A typical experimental procedure follows. To a suspension of 2,7-dimethyl-1,8-biphenylenediol (117 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) was added 2 M hexane solution of Me_3Al (0.55 mL, 1.1 mmol) at room temperature and the resulting solution was stirred at room temperature for 30 min. Benzaldehyde (51 μL, 0.5 mmol) and its dimethyl acetal (75 μL, 0.5 mmol) were then added at -78 °C. After 5 min of stirring, 1-(trimethylsiloxy)-1-cyclohexene (97 μL, 0.5 mmol) was added dropwise to the solution. The reaction mixture was stirred at -78 °C for 3 h, poured into 1 N HCl solution, and extracted with ether. The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$, brine, and then dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (dichloromethane to hexane/ethyl acetate = 20:1 to 5:1 as eluants) gave aldol adducts **2** and **3** as pale yellow oil (84% combined yields; ratio of **2**:**3** = 97:3).

Table 1. Discrimination reaction between carbonyl compounds and their acetals [a]

entry	nucleophile	carbonyl	acetal	Lewis acid	yield (%) [b]	ratio [c]
1		$C_6H_{11}CHO$	$C_6H_{11}CH(OMe)_2$	Me_3SiOTf	89	26 : 74
2				**1**	89	90 : 10
3		$C_7H_{15}CHO$	$C_7H_{15}CH(OMe)_2$	Me_3SiOTf	76	58 : 42
4				**1**	82	87 : 13
5		PhCHO	$PhCH(OMe)_2$	Me_3SiOTf	92	79 : 21
6				**1**	97	90 : 10
7		$C_9H_{19}COCH_3$	$C_9H_{19}C(OMe)_2CH_3$	Me_3SiOTf	81	11 : 89
8				**1**	86	>99 : <1
9		$PhCOCH_3$	$PhC(OMe)_2CH_3$	Me_3SiOTf	81	57 : 43
10				$Bu_2Sn(OTf)_2$ [d]	75	16 : 84
11				**1**	88	>99 : <1
12		$C_6H_{11}CHO$	$C_6H_{11}CH(OMe)_2$	$TiCl_4$ [e]	87	14 : 86
13				**1**	80	>99 : <1
14		PhCHO	$PhCH(OMe)_2$	$TiCl_4$ [e]	81	12 : 88
15				**1**	86	>99 : <1

[a] The electrophilic reaction of carbonyl compounds and acetals (1 equiv each) was carried out in CH_2Cl_2 at -78 °C for 2-3 h with nucleophiles (1 equiv) in the presence of either a catalytic amount of Me_3SiOTf (0.05 equiv) or 1.1 equiv of (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**1**). [b] Isolated yield. [c] The ratio of carbonyl and acetal adducts was determined by 300 MHz ^1H NMR analysis. [d] Dibutyltin bis(triflate) (DBTT) (0.1 equiv) was used as catalyst. [e] Use of 1 equiv of $TiCl_4$.

Acknowledgment. This work was partially supported by the Asahi Glass Foundation, the Akiyama Foundation, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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(7) The aldol reaction of cyclohexanecarboxaldehyde dimethyl acetal with ketene silyl acetal, $Me_2C{=}C(OMe)OSiMe_3$ by **1** was attempted at -78 °C to evaluate intrinsic reactivity of the acetal itself, which resulted in the formation of aldol product in 37% yield (*cf.* entries 1 and 2 in Table 1). Therefore, the high chemoselectivity observed herein is ascribed to the rate difference between the aldol reaction of carbonyl compounds and that of their corresponding acetals based on the double electrophilic activation of carbonyls.

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(*Received in Japan* 17 *July* 1997; *revised* 21 *August* 1997; *accepted* 22 *August* 1997)