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Efficient asymmetric catalysis of chiral organoaluminum complex for enantioselective ene reactions of aldehydes

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This paper is dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—Chiral organoaluminum complex **1** efficiently catalyzed the asymmetric hetero-ene reaction of commercially available 2-methoxypropene (**2**) with aldehydes under mild conditions to give the corresponding β-hydroxymethyl ketones **3** in good to excellent chemical yields with high enantiomeric excesses. The asymmetric catalysis of **1** was further applied to the carbonyl addition of methallylsilanes, where exclusive formation of the optically active allylic silanes **5** was achieved.

The ene reaction involving a carbonyl compound as the enophile, carbonyl-ene reaction, has been widely utilized as an attractive tool for the stereocontrolled construction of a primary carbon framework of organic molecules.[1] The synthetic potential of this methodology has been further demonstrated by the recent extensive development of the asymmetric variants based on the use of chiral Lewis acid catalysts.[2] Among these, asymmetric hetero-ene reaction of aldehydes with 2-methoxypropene (**2**) appears as a convenient yet reliable bond-forming process, enabling the preparation of various enantiomerically enriched β-hydroxymethyl ketones from commercially available, easy-to-handle reaction partners. Unfortunately, however, previous studies on this subject have been strictly limited to two examples, that is, the pioneering work of Carreira et al. using NOBIN-derived chiral titanium Lewis acid,[3] and an optically active tridentate Schiff base chromium(III) complex-catalyzed reaction of **2** with mainly aromatic aldehydes elegantly invented by Ruck and Jacobsen.[4] Here we wish to report our own contribution uncovering the eminent catalytic activity of chiral organoaluminum complex **1**[5] in the hetero-ene reaction of aldehydes with **2**, giving rise to the corresponding β-hydroxymethyl ketones **3** with high enantiomeric purities (Scheme 1). Further application of the efficient asymmetric catalysis of **1** to the ene-type carbonyl addition of methallylsilanes is also reported.

The requisite chiral organoaluminum Lewis acid (*R*)-**1** can be readily prepared in situ by the treatment of (*R*)-2,2′-bis(trifluoromethanesulfonylamino)-1,1′-binaphthyl with 1 equiv of Me_3Al in CH_2Cl_2 at refluxing temperature for 1 h.[6] An initial attempt was then made by conducting the reaction of 3-phenylpropanal with **2** (2.1 equiv) in the presence of 5 mol % of (*R*)-**1** in CH_2Cl_2 at −78 °C; this revealed the complete consumption of the starting aldehyde within 30 min and that the subsequent acidic hydrolysis of the ene-product with 1 N HCl afforded the corresponding β-hydroxymethyl ketone **3** [R = $Ph(CH_2)_2$] in 95% isolated yield with 86% ee (entry 1 in Table 1). It is noteworthy that the catalyst loading can be reduced to 2 mol % without substantial loss of the enantioselectivity of the product **3** (entry 2).

Other selected examples summarized in Table 1 demonstrate the scope and limitations of the present chiral organoaluminum-catalyzed hetero-ene process. Generally, 5 mol % of (*R*)-**1** with 2.1 equiv of **2** was sufficient for the rapid bond formation. A high level of chiral efficiency was attained in the reactions of unbranched aliphatic aldehydes (entries 3 and 4), while certain decrease of the chemical yield and the enantiomeric excess was observed with the substrates having α-substituent (entries 5 and 6). The addition of **2** to various

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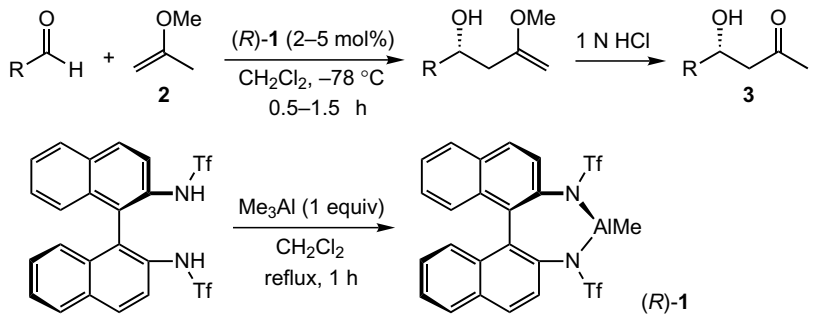
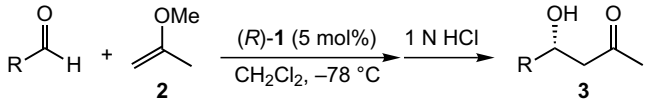


Scheme 1.

Table 1. Chiral organoaluminum Lewis acid (*R*)-**1**-catalyzed hetero-ene reaction of aldehydes with 2-methoxypropene (**2**)[a]

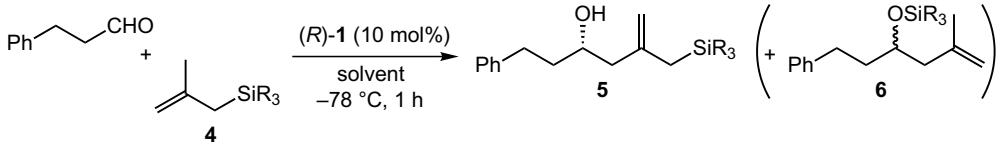


Entry	R	Reaction time (h)	% Yield[b]	% Ee[c] (config)[d]
1	$Ph(CH_2)_2$	0.5	95	86 (*S*)
2[e]	$Ph(CH_2)_2$	1.5	91	84 (*S*)
3	$Ph(CH_2)_4$	0.5	90	80
4	$CH_3(CH_2)_4$	0.5	83	81
5	C_6H_{11}	1	63	68 (*S*)
6	$(Et)_2CH$	1	78	70
7	Ph	0.5	95	74 (*S*)
8	*p*-F–C_6H_4	0.5	93	69
9	α-Naph	0.5	91	70
10	2-Furyl	0.5	84	72

[a] Unless otherwise specified, the reaction was carried out with 2.1 equiv of 2-methoxypropene (**2**) in the presence of 5 mol% of (*R*)-**1** in CH_2Cl_2 at −78 °C for the given reaction time.
[b] Isolated yield.
[c] Enantiomeric excess of **3** was determined by HPLC analysis using a chiral column with hexane–2-propanol as solvent.
[d] Absolute configuration was established by comparison of optical rotation to known literature value.[9]
[e] With 2 mol% of (*R*)-**1** and **2** was added over 1 h.

aromatic and hetero-aromatic aldehydes also proceeded smoothly with good enantioselectivity (entries 7–10).

The salient feature of the chiral organoaluminum catalyst **1** has been emphasized by its asymmetric catalysis in the ene-type carbonyl addition of methallylsilanes (Scheme 2 and Table 2). For instance, treatment of 3-phenylpropanal with *tert*-butyldimethylmethallylsilane (**4**, $R_3 = t\text{-}BuMe_2$) under the influence of (*R*)-**1** in toluene at −78 °C for 1 h resulted in the exclusive formation of the allylic silane **5** ($R_3 = t\text{-}BuMe_2$) in 78% yield, and the enantiomeric excess was determined to be 68% ee (entry 1 in Table 2). Particularly noteworthy is that the ene-type adduct **5** was obtained as a sole isolable product in good yield with similar enantioselectivity even in the reactions with triethyl- and trimethylmethallylsilanes, respectively (entries 2 and 3). This reaction profile is in contrast to the previously reported chiral titanium complex-catalyzed addition of trimethylmethallylsilane to methyl glyoxylate.[7] Although employment of the sterically more hindered silyl substituents ruined the stereoselectivity (entries 4 and 5), we found that the use of CH_2Cl_2 as solvent led to a significant enhancement of the catalytic efficiency, by which the desired **5** was obtained in excellent chemical yield regardless of the steric demand of the silyl group on **4**, and the optimal enantioselectivity reached 80% ee (entries 6–8).[8]



Scheme 2.

Table 2. Selective ene-type carbonyl addition of methallylsilanes to 3-phenylpropanal catalyzed by (*R*)-**1**[a]

Entry	R_3 (**4**)	Solvent	% Yield of **5**[b]	% Ee of **5**[c]
1	*t*-BuMe$_2$	Toluene	78	68
2	Et$_3$		83	69
3	Me$_3$		69	67
4	*t*-BuPh$_2$		79	54
5	*i*-Pr$_3$		63	61
6	*t*-BuMe$_2$	CH_2Cl_2	91	80
7	*t*-BuPh$_2$		99	63
8	*i*-Pr$_3$		90	74

[a] The reaction was performed with 2.1 equiv of methallylsilane **4** in the presence of 10 mol% of (*R*)-**1** in the given solvent at −78 °C for 1 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column with hexane–2-propanol as solvent, and absolute configuration was assigned by the correlation of the HPLC retention time with that reported after desilylation.[10]

In summary, chiral organoaluminum complex (*R*)-**1** derived from (*R*)-2,2′-bis(trifluoromethanesulfonylamino)-1,1′-binaphthyl and Me_3Al was found to display high catalytic and chiral efficiency in the asymmetric hetero-ene reaction of commercially available 2-methoxypropene (**2**) with aldehydes under mild conditions. Examination of the substrate generality revealed the scope and limitations of this system. The characteristic feature of the asymmetric catalysis of **1** has also been demonstrated by achieving the exclusive ene-type additions of methallylsilanes **4** to 3-phenylpropanal with good to high enantioselectivities. Further investigations of the unique reactivity and selectivity of this exceptionally Lewis acidic chiral organoaluminum catalyst are now underway in our laboratory.

Typical experimental procedure is as follows (entry 1 in Table 1): To a solution of (*R*)-2,2′-bis(trifluoromethanesulfonylamino)-1,1′-binaphthyl (27.4 mg, 0.05 mmol) in freshly distilled CH_2Cl_2 (5 mL) was added a 1 M hexane solution of trimethylaluminum (50 μL, 0.05 mmol) at room temperature under argon atmosphere and the mixture was refluxed for 1 h. The resulting solution was cooled to −78 °C and 3-phenylpropanal (132 μL, 1.0 mmol) was added followed by the dropwise introduction of 2-methoxypropene (**2**, 201 μL, 2.1 mmol). The reaction mixture was stirred at −78 °C for 0.5 h and then poured into 1 N HCl at 0 °C. After being stirred for 0.5 h at the same temperature, extractive workup was performed with ether. The organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (AcOEt/hexane = 1:5 as eluent) gave the corresponding β-hydroxymethyl ketone **3** [R = Ph(CH$_2$)$_2$][3] (183.3 mg, 0.95 mmol, 95% yield) as colorless oil. The enantiomeric excess was determined to be 86% ee by chiral HPLC analysis [Daicel Chiralpak AD-H, hexane/*i*-PrOH = 10:1, flow rate = 0.5 mL/min, λ = 254 nm, retention time: 17.6 min (*S*), 19.6 min (*R*)].

The ene-type addition of methallylsilanes to 3-phenylpropanal was conducted in a similar manner as described above. Characterization of allylic silane **5** (R_3 = *t*-BuMe$_2$) is representative; $[\alpha]_D^{30}$ −30.70 (*c* 1.05, $CHCl_3$, 80% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.33 (5H, m, Ph), 4.74 (2H, s, C=CH$_2$), 3.76 (1H, br s, C*H*OH), 2.66–2.76 (1H, m, PhCH$_2$), 2.78–2.88 (1H, m, PhCH$_2$), 2.18 (1H, dd, J = 14.0, 3.2 Hz, C(OH)C*H*$_2$C=C), 2.05 (1H, dd, J = 14.0, 9.5 Hz, C(OH)C*H*$_2$C=C), 1.92 (1H, s, OH), 1.75–1.85 (2H, m, PhCCH$_2$), 1.59 (1H, d, J = 13.3 Hz, C=CCH$_2$Si), 1.48 (1H, d, J = 13.3 Hz, C=CCH$_2$Si), 0.91 (9H, s, Si′Bu), −0.02 (6H, s, SiMe$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 142.0, 128.3, 128.2, 125.6, 110.7, 67.9, 46.5, 38.5, 32.0, 26.3, 22.0, 16.6, −5.9, −6.3; IR (neat) 3364, 2926, 2854, 1630, 1454, 1362, 1250, 1153, 1051, 835, 746, 698 cm^{-1}. HRMS (ESI-TOF) Calcd for $C_{19}H_{32}ONaSi$ ([M+Na]$^+$): 327.2110. Found: 327.2115. HPLC conditions: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 30:1, flow rate = 0.5 mL/min, λ = 254 nm, retention time: 12.8 min (major), 22.5 min (minor).

Acknowledgements

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