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Enantioselective Michael Reaction of Ketone Lithium Enolates Using a Chiral Amine Ligand

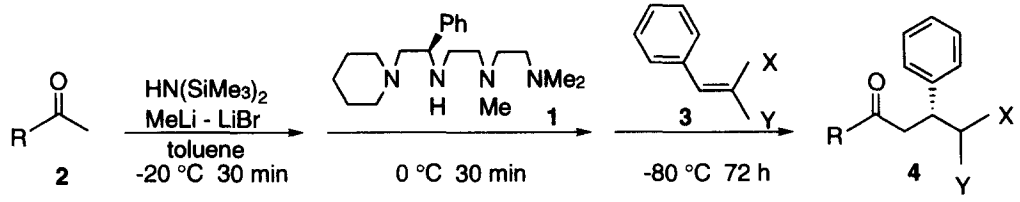
Kōsuke Yasuda,[1] Mitsuru Shindo, and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: The enantioselective Michael reaction of ketone lithium enolates using a chiral amine ligand (**1**) was studied. Michael adducts (**4**) of up to 94% ee were obtained by the reaction between methyl ketones (**2**) and Michael acceptors (**3**) having a benzylidene group.

The enantioselective Michael reaction has been one of the most intensively studied fields in synthetic organic chemistry. There have been a number of reports on the enantioselective Michael reaction with chiral catalysts in which active methylene compounds such as malonic acid esters,[2a] β-keto esters,[2b] cyanoacetic acid esters,[2c] phenylacetic acid esters,[2d] and nitroalkanes[2e] etc., were utilized as Michael donors. There are some successful examples of stoichiometric reactions with other donor species as well.[3] On the other hand, although ketone lithium enolate is a versatile and widely used carbon nucleophile, it has been used as a Michael donor in an enantioselective Michael reaction in only one report so far.[4]

We have previously reported an enantioselective alkylation of ketones using chiral amine (**1**)[5] as an external ligand[6], where **1** proved itself to be a powerful tool for enantioface differentiation *via* complex formation with ketone lithium enolate. We expected that **1** could be also efficient in the enantioselective Michael reaction utilizing ketone as the Michael donor.



Scheme 1.

The reaction is outlined in **Scheme 1**. Lithium enolate was generated from the corresponding ketone (**2a-f**) by using lithium hexamethyldisilazide in the presence of lithium bromide (LiBr) in toluene. Next, **1** was added to form the ternary complex composed of the lithium enolate, LiBr, and chiral amine (**1**), that was previously postulated to be essential to efficient asymmetric induction in enantioselective alkylation of cyclic ketones.[6] Aging of the complex at 0 °C for 30 min was necessary for the higher enantiomeric excess (ee). Without this process, the values of ee were somewhat lower than those obtained with aging.

The reaction with a series of methyl ketones and Michael acceptors was examined and the results are summarized in **Table 1**. In runs 1-4, Michael reaction between aryl methyl ketones and dimethyl benzylidenemalonate (**3a**) afforded the adducts (**4a-d**) in 52 to 93% yields, and the values of ee were equal to or more than 90%. In runs 5 and 6, almost no asymmetric induction was observed. The severe steric hindrance around the carbonyl group of such ketones should prevent the formation of the complex necessary for stereoselection. With acetophenone as the Michael donor, diethyl benzylidenemalonate (**3b**) gave **4g** in 94% ee, and benzylidene-Meldrum's acid (**3c**) afforded **4a** in 87% ee after conversion of the primary adduct to **4a** in 94% overall yield (runs 7 and 8). Malononitrile derivative (**3d**) gave an adduct of lower ee; however, relatively high enantioselectivity (69%) was obtained using *trans*-nitrostyrene (**3e**). This suggests that nitro-olefins as well as benzylidenemalonic acid esters would be good acceptors for this enantioselective Michael reaction.

Table 1. Enantioselective Michael Reaction of Ketones using Chiral Amine **1**[a]

Run		R		X	Y		Yield (%)	ee (%)[b]	$[\alpha]_D$[c]	Config.
1	**2a**	Ph	**3a**	CO_2Me	CO_2Me	**4a**[d]	93	92	+10.0°[e]	(*S*)[f]
2	**2b**	4-Me-Ph	**3a**	CO_2Me	CO_2Me	**4b**	80	94[g]	+25.4°	(*S*)[h]
3	**2c**	4-MeO-Ph	**3a**	CO_2Me	CO_2Me	**4c**	52[i]	93[g]	+22.7°[j]	(*S*)[h]
4	**2d**	2-Naphthyl	**3a**	CO_2Me	CO_2Me	**4d**	76	90	+47.4°	(*S*)[h]
5	**2e**	1-Naphthyl	**3a**	CO_2Me	CO_2Me	**4e**	69	2	+1.6°[k]	
6	**2f**	Bu^t	**3a**	CO_2Me	CO_2Me	**4f**	82	0	0.0°	
7	**2a**	Ph	**3b**	CO_2Et	CO_2Et	**4g**	67	94	+6.0°[l]	(*S*)[m]
8	**2a**	Ph	**3c**[n]	$-CO_2C(Me)_2OCO-$		**4a**	94[o]	87[o]	+9.4°	(*S*)
9	**2a**	Ph	**3d**	CN	CN	**4h**	83	10	-2.0°	(*S*)[p]
10	**2a**	Ph	**3e**	H	NO_2	**4i**	100	69	+25.4°[q]	(*R*)[r]

a) Reaction was carried out according to Scheme 1 (see Typical Procedure). b) Enantiomeric excess was determined by HPLC with CHIRALPAK AD® and hexane-isopropanol (9:1) as eluent unless otherwise noted. c) The specific rotation was measured at 25 °C (c =1.0, $CHCl_3$) unless otherwise noted. d) See ref. 7. e) At 25 °C (c =1.0, benzene). f) See notes 8 and 9. g) Hexane-isopropanol (7:3) as eluent. h) See note 11. i) The reaction was carried out for 500 h. j) At 25 °C (c =0.37, $CHCl_3$). k) At 25 °C (c =2.67, $CHCl_3$). l) At 25 °C (c =2.3, benzene). m) See note 13. n) See ref. 14. o) Overall yield and ee after conversion of the primary adduct to **4a** (MeOH, reflux, 12h; Me_3SiCHN_2, CH_2Cl_2-MeOH). p) See note 15. q) $[\alpha]_{577}^{20}$ (c =1.0, CH_2Cl_2). r) See ref. 16.

In conclusion, we have studied the enantioselective Michael reaction of ketone lithium enolate as the Michael donor using a chiral amine (**1**) as an external ligand. The adducts (**4a-i**) were obtained in 52-100% yield and the values of ee were up to 94% ee. Further studies on the reaction mechanism and application are now under way.

Typical Procedure (run 1 in Table 1) To a solution of hexamethyldisilazane in toluene (44 ml) was added methyllithium-lithium bromide in ether (methyllithium 0.99 M, lithium bromide 1.16 M; 1.05 ml, methyllithium 1.04 mmol, lithium bromide 1.20 mmol) at 0 °C. After 30 min, the mixture was cooled to -20 °C and a solution of acetophenone (120 mg, 1.0 mmol) in toluene (2 ml) was added. After stirring at -20 °C for 30 min, a solution of **1** (366 mg, 1.1 mmol) in toluene (2 ml) was added. The turbid solution thus obtained was stirred at -20 °C for 10 min and 0 °C for 30 min. A solution of dimethyl benzylidenemalonate **3a** (110 mg, 0.50 mmol) in toluene (2 ml) was added at -78 °C and the mixture was stirred at -80 °C for 72 h. The reaction was quenched with 10% HCl (10 ml) and the mixture was worked up as usual. The crude product was purified by silica gel column chromatography to afford **4a** as a colorless solid (158 mg, 0.46 mmol, mp 82-83 °C, 93% based on **3a**; ee was determined to be 92% by chiral HPLC: CHIRALPAK AD®, hexane-isopropanol (9:1), 1.0 ml/min, UV 254 nm).

References and Notes

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8. (*S*)-**4a** ($[\alpha]_D^{25}$+9.4° (c=1.0, benzene), 88% ee) showed $[\alpha]_D^{20}$+23.7° (c=1.0, $CHCl_3$).
9. The absolute configuration of (*S*)-**4a** was further confirmed as follows: (*S*)-**4a** ($[\alpha]_D^{25}$+7.1° (c=1.0, benzene), 81% ee) was converted to methyl (*S*)-5-oxo-3-phenylhexanoate[10] of $[\alpha]_D^{20}$-17.0° (c=1.14, benzene), (*m*-chloroperbenzoic acid, CH_2Cl_2, reflux, 38 h, 56%; NaCN, DMSO, aq. $NaHCO_3$, rt, 4h, 54%; $(COCl)_2$, cat. DMF, benzene, rt, 10 h; MeLi, CuI, ether, -78 °C, 0.5 h, 85% in 2 steps; 10% aq. HCl, AcOH, reflux, 7 h; CH_2N_2, 93% in 2 steps).
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11. The absolute configuration of **4b-4d** was determined by synthesizing these compounds from (*S*)-**4a**; (*S*)-**4a** ($[\alpha]_D^{25}$+8.1° (c=1.0, benzene), 83% ee) led to (*S*)-2-phenyl-1,1,3-propanetricarboxylic acid 1,1-dimethyl ester ($[\alpha]_D^{25}$+9.7° (c=2.0, $CHCl_3$)) by the same procedure described in note 9 (43% in 2 steps), which was converted into the corresponding acid chloride (quant.). Treatment of the acid chloride with the appropriate arylstannane in the presence of Pd catalyst ($PdCl_2(PPh_3)_2$, $RSnBu_3$, dioxane, reflux, overnight)[12] gave **4b-4d**; (*S*)-**4b** (51%), $[\alpha]_D^{25}$+21.6° (c=1.0, $CHCl_3$), 81% ee, (R=4-Me-Ph); (*S*)-**4c** (48%), $[\alpha]_D^{25}$+20.0° (c=0.37, $CHCl_3$), 80% ee, (R=4-MeO-Ph); (*S*)-**4d** (46%), $[\alpha]_D^{25}$+41.0° (c=1.0, $CHCl_3$), 77% ee, (Ar=2-naphthyl). Enantiomeric excess was determined by HPLC using the conditions described in the footnotes to Table 1.
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