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# Construction of Contiguous Chiral Tertiary Carbon Centers by Enantioselective Michael Reaction of Ketone Lithium Enolates Using a Chiral Amine Ligand

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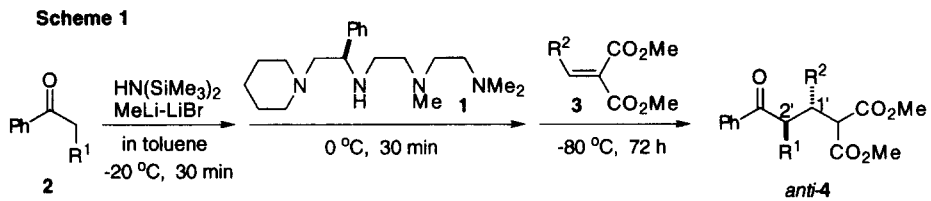
**Abstract:** The diastereo- and enantioselective Michael reaction of ketone lithium enolates using a chiral amine ligand (**1**) was examined. Michael adducts (**4**) were obtained in excellent chemical yields (95~99%) with high stereoselectivities (*syn*-**4**/*anti*-**4**: 16/84~1/99; ee of *anti*-**4**: 81~99%) by the reaction between alkyl phenyl ketones (**2**) and Michael acceptors (**3**) having an alkylidene group. © 1997 Elsevier Science Ltd.

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 catalytic enantioselective Michael reaction with active methylene compounds as Michael donors,[1] and some successful ones on the stoichiometric reactions with other donor species.[2] 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.[3,4] Furthermore, there has been no report on the construction of the contiguous chiral tertiary carbon centers in the open-chain systems.

Using a chiral tetradentate amine (**1**)[5] as an external ligand, we have recently reported enantioselective Michael reaction between the lithium enolates derived from methyl ketones as Michael donors and Michael acceptors having a benzylidene group. The Michael adducts of type **4** ($R^1$=H, $R^2$=Ph) having one chiral carbon center were obtained in up to 94% ee in high chemical yields.[6] We expected that if phenyl ketones (**2a~c**) having an alkyl group ($R^1$) on the carbon α to the carbonyl group were used as Michael donors and **3a~d** as Michael acceptors, the reaction could proceed diastereo- and enantioselectively to afford the Michael adducts (**4a~f**), and the stereoselective construction of the contiguous chiral tertiary carbon centers could be achieved in one stroke.

**Scheme 1**



The reaction is outlined in Scheme 1. The procedure is essentially the same as that reported previously for the enantioselective Michael reaction with methyl ketones.[6] Lithium enolate was generated from the corresponding alkyl phenyl ketone (**2a~c**) by using lithium hexamethyldisilazide in the presence of lithium bromide in toluene, and then chiral amine (**1**) was added. After aging of the resulting mixture at 0 °C for 30 min, Michael acceptor (**3a~d**) was added and the reaction was conducted at -80 °C for 72 h.

The reactions of a series of ketones (**2a~c**) and malonates (**3a~d**) were examined and the results are summarized in Table 1. In run 1, asymmetric Michael reaction between propiophenone (**2a**) and dimethyl benzylidenemalonate (**3a**) afforded the adduct (**4a**) almost quantitatively. The major diastereomer was *anti*-**4a**. Both the diastereo- and enantioselectivities were excellent (*syn*-**4a**/*anti*-**4a**: 1/99; ee of *anti*-**4a**: 99%). This remarkable outcome showed a striking contrast to the control experiments (runs 2 and 3). Thus, when the reaction between **2a** and **3a** was carried out in THF using LDA as a base, *dl*-**4a** was obtained only in a non-diastereoselective way (run 2). Moreover, when the reaction was carried out under the same conditions as those of run 1 except that the chiral amine (**1**) was not added, diastereoselectivity of the reaction was very low (run 3). These results suggest that the chiral amine (**1**) is essential not only to the enantioselectivity, but also to the diastereoselectivity of the reaction.

The Michael reaction using other combination of ketones (**2a~c**) and malonates (**3a~d**) proceeded also in excellent yields with high diastereo- and enantioselectivities (runs 4-8). The chemical yields ranged from 95 to 99%. The ratios of *syn*-**4b~e**/*anti*-**4b~e** and the ee values of *anti*-**4b~e** were 4/96~2/98 and 96~99%, respectively, except for run 8 in which somewhat lower selectivities were observed (*syn*-**4f**/*anti*-**4f**: 16/84; ee of *anti*-**4f**: 81%).

**Table 1.** Enantio- and Diastereoselective Michael Reaction of Ketones using Chiral Amine (**1**)[a]

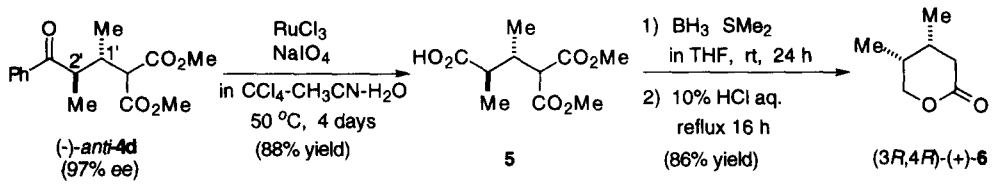
| | Ketone | | Alkylidenemalonate | | Product | | | *anti*-**4** | |
|---|---|---|---|---|---|---|---|---|---|
| Run | **2** | $R^1$ | **3** | $R^2$ | **4** | Isolated y. (%) | *syn*/*anti*[b] | E.e. (%)[c] | Confign.[d] |
| 1 | **2a** | Me | **3a** | Ph | **4a** | 99 | 1/99 | 99 | (1'*R*,2'*R*) |
| 2[e] | **2a** | Me | **3a** | Ph | *dl*-**4a** | 73 | 40/60 | - | |
| 3[f] | **2a** | Me | **3a** | Ph | *dl*-**4a** | 95 | 35/65 | - | |
| 4 | **2b** | Pr | **3a** | Ph | **4b** | 99 | 2/98 | 99[g] | (1'*R*,2'*R*) |
| 5 | **2c** | Bzl | **3a** | Ph | **4c** | 95 | 4/96 | 96 | (1'*R*,2'*R*) |
| 6 | **2a** | Me | **3b** | Me | **4d** | 98 | 4/96 | 97[h] | (1'*R*,2'*R*) |
| 7 | **2a** | Me | **3c** | Et | **4e** | 97 | 3/97 | 98[i] | (1'*R*,2'*R*) |
| 8 | **2a** | Me | **3d** | $^i$Pr | **4f** | 96 | 16/84 | 81[i] | (1'*R*,2'*R*) |

a) For procedure, see Typical Procedure in the text. b) Determined by $^1$H-NMR of the curde product. c) Determined by HPLC under the conditions in ref. 11, unless otherwise specified. d) See ref. 7. e) The reaction was carried out using LDA (1.1 eq.) in THF at -78 °C for 18 h. f) The conditions were identical to those of the Typical Procedure, except that the reaction was carried out in the absence of **1**. g) Hexane-isopropanol (45:1) as eluent. h) Hexane-isopropanol (80:1) as eluent. i) Hexane-ethanol (150:1) as eluent.

The relative and absolute configurations of *anti*-**4d** were determined as follows (Scheme 2).[7] Diastereomerically pure (-)-*anti*-**4d** (97% ee, $[\alpha]_D^{25}$ -34.2 (*c* = 1.00, $CHCl_3$)) was converted[8] to the acid (**5**) ($[\alpha]_D^{25}$ +4.8 (*c* = 1.00, $CHCl_3$)), and then to the known lactone ((3*R*,4*R*)-(+)-**6**) ($[\alpha]_D^{22}$ +46.6 (*c* = 1.85, MeOH)), which Mori's group had already synthesized *via* resolution ($[\alpha]_D^{22}$ +46.3 (*c* = 1.85, MeOH)).[9] The relative and absolute configurations of this compound was determined chemically, and was used as a key

intermediate for the total synthesis of (3*S*,4*R*)-(+)-faranal, the natural trail pheromone of *Monomorium pharaonis* (Pharaoh's ant).[9] The relative configuration of this compound was further confirmed by the comparison of the chemical shifts of the $^{13}$C-NMR spectrum with those reported by Nakai's group.[10]

**Scheme 2**




Typical procedure (Table 1, run 1) is as follows. Under argon atmosphere, a solution of MeLi-LiBr in ether (0.99 *M* for MeLi, 1.16 *M* for LiBr) (1.05 mL, 1.04 mmol for MeLi, 1.20 mmol for LiBr) was added to a solution of hexamethyldisilazane (323 mg, 2.0 mmol) in toluene (44 mL) at 0 °C. After 20 min, the mixture was cooled to -20 °C and a solution of propiophenone (**2a**) (134 mg, 1.0 mmol) in toluene (2 mL) was added. After stirring at -20 °C for 30 min, a solution of a chiral amine (**1**) (366 mg, 1.1 mmol) in toluene (2 mL) was added. The mixture was stirred at -20 °C for 10 min, at 0 °C for 30 min, and then cooled to -78 °C. A solution of dimethyl benzylidenemalonate (**3a**) (147 mg, 0.67 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% aqueous HCl (10 mL) and the whole was extracted with ethyl acetate twice. The organic extracts were combined and worked up as usual. The ratio of *syn*-**4a**/*anti*-**4a** was determined by $^1$H-NMR of the crude mixture (1/99), which was then purified by silica gel column chromatography to afford a mixture of *syn*-**4a**/*anti*-**4a** as a colorless solid (234 mg, 99% yield based on **3a**) of mp 91-92 °C. Ee of *anti*-**4a** was determined to be 99% by HPLC using a chiral column.[11]

It is thus shown that diastereo- and enanatioselective Michael reaction of lithium enolates derived from phenyl ketones (**2a~c**) as Michael donors with Michael acceptors (**3a~d**) having an alkylidene group can be carried out highly efficiently by using a chiral tetradentate amine (**1**) as an external ligand, giving the adducts (**4a~f**) in excellent yields (95~99%), in high diastereoselectivities (*syn*-**4**/*anti*-**4**: 16/84~1/99), and in high enantioselectivities (81~99% for *anti*-**4**). This is the first successful example of the construction of two contiguous chiral tertiary carbon centers in the open-chain systems by Michael reaction with ketone lithium enolate as the Michael donor. The usefulness of the present asymmetric Michael reaction is demonstrated by the efficient formal total synthesis of (3*S*,4*R*)-faranal. Further investigation of the reaction mechanism is now under way.

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