Pergamon

Tetrahedron 58 (2002) 2585–2588

TETRAHEDRON

A practical large-scale synthesis of enantiomerically pure 3-[bis(methoxycarbonyl)methyl]cyclohexanone via catalytic asymmetric Michael reaction

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Received 28 December 2001; accepted 4 February 2002

Abstract—A highly practical and efficient procedure for the large-scale (up to 6 mol) synthesis of enantiomerically pure (*R*)-3-[bis(methoxycarbonyl)methyl]cyclohexanone using an (*R*)-AlLibis(binaphthoxide) complex ((*R*)-ALB)-catalyzed asymmetric Michael reaction was developed. The reaction was successfully accelerated under highly concentrated conditions without lowering chemical yield or the high enantiomeric excess. Under these conditions, only 0.05 mol% of the catalyst forced the reaction to completion in 48 h. The work-up procedure was also improved and the enantiomerically pure compound was obtained as a white crystal in up to 95% yield without chromatographic separation. Finally, pre-manufacturing scale synthesis was performed. Using 0.1 mol% of the catalyst with 0.09 mol% of KO-*t*-Bu and MS 4 Å, the Michael reaction of 2-cyclohexenone (6.0 mol, 581 mL) with dimethyl malonate (6.0 mol, 686 mL) was completed in 24 h at ambient temperature to afford more than a kilogram of the enantiomerically pure product in 91% yield after three successive crystallizations. The described method renders the enantiomerically pure Michael adduct readily available on greater than kilo scale.

1. Introduction

The use of catalytic asymmetric reactions for the synthesis of highly enantiomerically enriched chiral compounds is of growing importance in organic chemistry and in industrial production in terms of atom economy.[1] A number of asymmetric catalyses have been reported, some of which have industrial applications, such as Rh(I)-catalyzed hydrogenation of olefins,[2] Ru(II)-catalyzed hydrogenation of ketones,[3] Ti(IV)-catalyzed epoxidation of allylic alcohols,[4] Cu-catalyzed cyclopropanation of olefins,[5] and Rh(I)-catalyzed isomerization of allylic amines,[6] just to name a few. Most catalytic asymmetric carbon–carbon bond formations, however, often are difficult to produce on a manufacturing scale in terms of catalyst efficiency, enantioselectivity, or chemical yield. To address this issue, intensive efforts have been devoted to develop practical asymmetric carbon–carbon bond formations[1,7] and only a few manufacturing scale syntheses have been achieved.[5] In recent years, the catalytic asymmetric Michael reaction has been recognized as an efficient method for enantioselective carbon–carbon bond formations because of the usefulness of the corresponding enantiomerically enriched Michael adducts as an attractive chiral source.[8,9d,e] Therefore, development of a highly practical method to synthesize Michael adducts is very desirable. We report our successful efforts toward the development of an improved procedure for the large-scale (greater than kilo scale) synthesis of optically and chemically pure 3-[bis(methoxycarbonyl)methyl]cyclohexanone (**3**) via catalytic asymmetric Michael reaction in high yield without chromatographic separation.

In 1996, we reported that the multifunctional asymmetric catalyst, AlLibis(binaphthoxide) complex (ALB), which was prepared from $LiAlH_4$ and BINOL in a ratio of 1:2, was highly effective for the catalytic asymmetric Michael reaction of cyclic enones with malonates.[9b] Later, this catalyst system was improved by using additional base (KO-*t*-Bu) and MS 4 Å, accelerating the reaction with a slight improvement in both chemical yield and enantioselectivity (Table 1, entry 2).[9d] Although several efficient asymmetric catalysts for the asymmetric Michael reaction have been reported,[9–11] including the $LaNa_3$tris(binaphthoxide) complex,[9a] GaNabis(binaphthoxide) complex,[9f] and La-linked-BINOL complex,[9e] ALB is the most effective catalyst for the present Michael reaction in terms of catalyst efficiency. In addition, all materials in the reaction, including each enantiomer of BINOL, are inexpensive and commercially available. Even using the improved procedure, however, 1 mol% of the catalyst was still required to obtain the product in excellent yield and high enantiomeric excess (entry 2) and 0.3 mol% of the catalyst required 120 h at room temperature to complete the reaction (entry 3).[9d] To apply this chemistry to a manufacturing scale synthesis, we attempted to further improve not only catalyst

Keywords: catalytic asymmetric Michael reaction; practical large-scale synthesis; multifunctional asymmetric catalyst.

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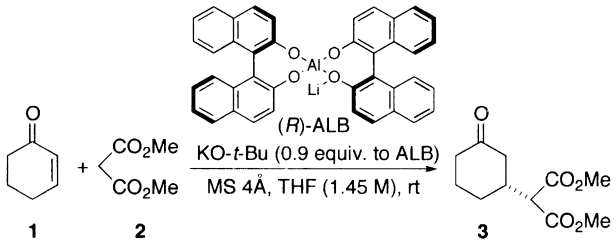
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00141-2

Table 1. Previous results of catalytic asymmetric Michael reaction promoted by ALB



Entry	Scale (mol)	ALB (mol%)	KO-*t*-Bu	MS 4 A	Time (h)	Yield (%)	ee (%)
1	0.001	10.0	−	−	72	90	93
2	0.5	1.0	+	+	72	96	99
3	0.002	0.3	+	+	120	94	99

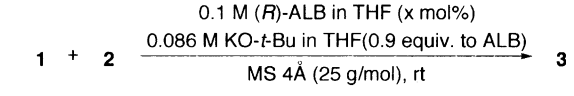
efficiency, such as reducing catalyst loading and reaction time, but also the work-up procedure, such as eliminating the need for chromatographic separation.

2. Results and discussion

We first focused on acceleration of the reaction at ambient temperature. We examined the additive effect, solvent effect, and ligand tuning, and eventually discovered that under highly concentrated conditions (20 M) even 0.25 mol% of the catalyst induced the reaction to proceed very quickly (15 h) without lowering chemical yield (95% combined yield for two successive crystallizations, vide infra) or the high enantiomeric excess (>99% ee) (Table 2, entry 1). The catalyst loading was further reduced and the results are summarized in Table 2. As shown, the use of only 0.05 mol% of the catalyst forced the reaction to completion with analogous chemical yield (94%) and enantioselectivity (98% ee) although it took 48 h (entry 5). In addition, a relatively large-scale reaction (0.5 mol scale) proceeded smoothly without any difficulty (entry 6).

We also examined the work-up procedure of the reaction. In our previous procedure, chromatographic separation was necessary to obtain a high yield (total 96% yield) after two successive crystallizations from toluene/hexane (82% combined yield). Moreover, recovery of the BINOL from the crude mixture using chromatographic separation is not very easy on a large-scale because of the small difference in polarity between BINOL and the product **3**. The improved procedure (Fig. 1) has been streamlined by eliminating the need for chromatographic separation to obtain the product **3** in reasonable yield (>90%) in an optically and chemically pure manner. After an ordinary quenching procedure, the organic layer was half concentrated and treated with hexane with maintenance of the solvent ratio (EtOAc/hexane, 1:4) to afford a pure Michael adduct **3** as a white crystal in more than 90% yield. After concentration of the mother liquor followed by one successive crystallization from

Table 2. Catalytic asymmetric Michael reaction promoted by ALB in highly concentrated conditions



Entry	Scale (mol)	ALB (mol%)	Conc. (M)	Time (h)	ee[a] (%)	Yield[b] (%)	ee[c] (%)
1	0.05	0.25	20	15	>99	95	>99
2	0.05	0.20	24	24	>99	95	>99
3	0.05	0.10	49	10	98	74	>99
4	0.05	0.10	49	24	98	92	>99
5	0.05	0.05	98	48	98	94	>99
6	0.5	0.10	49	24	98	92	>99

[a] Enantiomeric excess of the crude product.
[b] Combined yield of **3** after two successive crystallizations.
[c] Enantiomeric excess of the crystal.

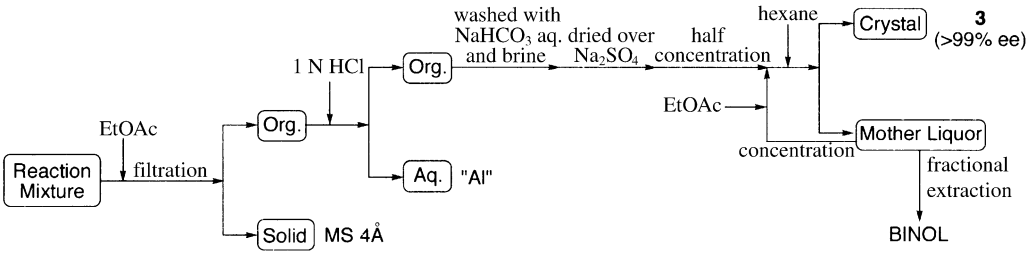
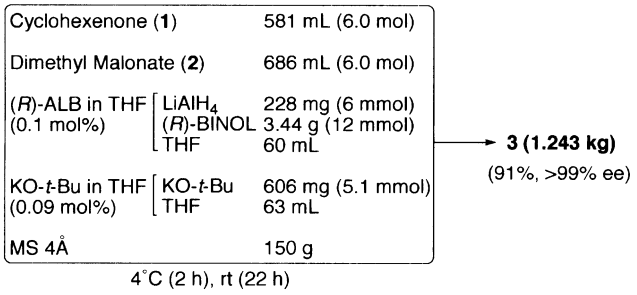


Figure 1. The improved work-up procedure of catalytic asymmetric Michael reaction promoted by ALB.



Scheme 1. Catalytic asymmetric Michael reaction promoted by ALB on greater than kilo scale.

EtOAc/hexane (1:4), the combined yield reached up to 95% (Table 2, entry 2, first: 93%, second: 2%). In addition, BINOL was recovered from the mother liquor by subsequent fractional extraction in about 80% yield (see Section 4).

Having achieved a highly practical catalytic asymmetric synthesis of the Michael adduct **3**, we next performed pre-manufacturing scale (greater than kilo scale) synthesis (Scheme 1). From an industrial point of view, we decided to use 0.1 mol% of the catalyst to complete the reaction in 24 h at ambient temperature. To a suspension of dried MS 4 Å (150 g), dimethyl malonate (**2**) (686 mL, 6.0 mol), 0.1 mol% of (*R*)-ALB in THF (containing only 3.4 g of BINOL), and 0.09 mol% of KO-*t*-Bu in THF was slowly added 2-cyclohexenone (**1**) (581 mL, 6.0 mol) at 4°C. Because significant elevation of the reaction temperature (>30°C) was observed without an ice-water bath, the reaction temperature was maintained at ca. 4°C using an ice-water bath for 2 h. After additional stirring at ambient temperature (20–25°C) for 22 h, 1.24 kg of the desired product **3** was obtained as a white crystal in 91% combined yield following three successive crystallizations (first: 76%, second, 11%, third: 4%). The enantiomeric excess of the crude product and the crystal was determined to be 98% ee and greater than 99% ee, respectively, by HPLC analysis. The purity of the crystal was estimated to be greater than 99% on the basis of elemental analysis and ^{1}H and ^{13}C NMR spectra. To the best of our knowledge, the described method is one of the most practical and efficient catalytic asymmetric carbon–carbon bond formations with great enantioselectivity.

3. Conclusions

In conclusion, we successfully developed a highly practical and efficient procedure for large-scale (up to 6 mol) synthesis of enantiomerically pure (*R*)-3-[bis(methoxycarbonyl)methyl]cyclohexanone (**3**). In a highly concentrated condition, the Michael reaction was catalyzed efficiently by 0.1 mol% of ALB complex with 0.09 mol% of KO-*t*-Bu and MS 4 Å to completion in 24 h. Further studies of catalyst loading demonstrated that even 0.05 mol% of the catalyst forced the reaction to completion. In addition, the improved work-up procedure made it possible to isolate the pure product **3** in up to 95% yield without chromatographic separation. The described method renders enantiomerically pure Michael adducts readily available on greater than kilo scale.

4. Experimental

4.1. General method and material

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. The chemical shifts (ppm) were determined relative to Me_4Si. Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. Optical rotation was measured on a JASCO P-1010 polarimeter. EI mass spectra were measured on JEOL JMS-DX303. The enantiomeric excess was determined by HPLC analysis. Melting point was measured on a Yamato melting point apparatus model MP-21. THF was distilled from sodium benzophenone ketyl prior to use. 2-Cyclohexenone (**1**) and dimethyl malonate (**2**) were purified by simple distillation under reduced pressure. Lithium aluminum hydride, potassium *tert*-butoxide, and (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL) were purchased at high commercial quality and were used without further purification. Powdered molecular sieve 4 Å (MS 4 Å), which was purchased from Fluka (catalog No. 69836), was dried at 180°C under reduced pressure (2 mmHg) for 6 h prior to use. The dehydration ability of dried MS 4 Å was estimated by the following experiment. Freshly distilled THF (30 mL) in 100 mL flask was placed under argon for 4 h with or without MS 4 Å (10 g), and then the amount of water in the THF was determined by Karl Fischer titration (without MS 4 Å: 45 ppm, with undried MS 4 Å: 36 ppm, with dried MS 4 Å: 18 ppm).

4.2. Preparation of 0.1 M THF solution of (*R*)-AlLibis-(binaphthoxide) ((*R*)-ALB)

To a suspension of $LiAlH_4$ (powder, 342 mg, 9 mmol), which was *freshly just opened* in a dry box prior to use, in THF (40 mL) was slowly added a solution of (*R*)-BINOL (5.154 g, 18 mmol), which was dried at 50°C for 3 h under reduced pressure (2 mmHg), in THF (40 mL, plus 2×5 mL for rinse) via cannula at 4°C. After stirring at the same temperature for 30 min and remaining at room temperature for an additional 1 h, the resulting mixture was kept standing without stirring for 12 h and the supernatant was used as 0.1 M THF solution of (*R*)-ALB.

4.2.1. Catalytic asymmetric Michael reaction on greater than kilo scale: synthesis of (*R*)-3-[bis(methoxycarbonyl)-methyl]cyclohexanone (3). A dried 2 L round-bottomed flask containing dried powdered MS 4 Å (150 g) was purged with argon and cooled to 4°C in an ice-water bath. Dimethyl malonate (**2**) (686 mL, 6.0 mol), 0.1 M THF solution of (*R*)-ALB (60 mL, 0.1 mol%), and 0.086 M THF solution of KO-*t*-Bu (63 mL, 0.09 mol%) were successively added to the flask. Finally, 2-cyclohexenone (**1**) (581 mL, 6.0 mol) was slowly added to the mixture within 30 min. After stirring for 90 min, the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 22 h. At this point, the desired Michael adduct **3** precipitated out as a white solid. The precipitate was dissolved with EtOAc (1 L) and the resulting suspension was filtered through a Celite pad eluting with EtOAc (3×200 mL) to remove MS 4 Å. The combined organic layers were washed with 1N HCl (2×200 mL), saturated

aqueous $NaHCO_3$ solution (200 mL), and brine (2× 200 mL). The organic extract was dried over Na_2SO_4 and concentrated to ca. 2 L, containing ca. 700 mL of EtOAc, under reduced pressure. The enantiomeric excess of the crude product was determined to be 98% ee after purification of an analytical amount (ca. 20 mg) of the crude product by silica gel column chromatography (acetone/hexane, 1:9). Hexane (3 L) was added to the residue with vigorous stirring to afford **3** (First: 1036 g) as a white crystal. The mother liquor was concentrated and crystallized further from EtOAc/hexane (1:4) to afford **3** (second: 154 g). After one additional crystallization (third: 53 g), the combined yield reached 91%. The enantiomeric excess of each crystal was determined to be greater than 99% ee [DAICEL CHIRALPAK AS, hexane/2-propanol (87.5:12.5, v/v), flow rate: 0.5 mL/min, retention time: 47 min (*R*)-isomer and 67 min (*S*)-isomer, detected at 210 nm]. In addition, (*R*)-BINOL was recovered from the mother liquor as follows. After separation of the product **3** by three successive crystallizations, the mother liquor was concentrated under reduced pressure, and the residue was dissolved with toluene (200 mL) and extracted with 1N NaOH (2×150 mL). The combined aqueous layers were acidified to pH 3 with 1N HCl and extracted with EtOAc (2× 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude BINOL (2.73 g, ca.79%) as a pale yellow solid. The enantiomeric excess of the recovered BINOL was determined to be greater than 99% ee [DAICEL CHIRALPAK AD, hexane/2-propanol (90:10, v/v), flow rate: 0.75 mL/min, retention time: 24 min (*R*)-isomer and 28 min (*S*)-isomer, detected at 254 nm]. The spectral data and analytical data of **3** were in agreement with those previously reported.[9a] Anal. calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; Found: C, 57.90; H, 7.12; $[\alpha]_D^{28}=+3.75$ (*c* 2.28, $CHCl_3$) (>99% ee); mp 54.5–55.5°C.

Acknowledgements

This work was supported by CREST, The Japan Science and Technology Corporation (JST), RFTF of Japan Society for the Promotion of Science, a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan, Grant-in-Aid from the Tokyo Biochemical Research Foundation, and fellowship from Heiwa Nakajima Foundation (to Y. X.).

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