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Four hydroxyls are better than two. The use of a chiral lithium salt of 3,3′-bis-methanol-2,2′-binaphthol as a multifunctional catalyst of enantioselective Michael addition reactions

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ABSTRACT

The catalytic performance of the Li salt of (*S*)- or (*R*)-3,3′-bis[bis-(phenyl)hydroxymethyl]-2,2′-dihydroxy-dinaphthalene-1,1′ (BIMBOL) in asymmetric Michael additions of malonic acid derivatives and toluedine has been studied. Nitrostyrene and cyclohex-2-enone were chosen as Michael acceptors. Efficient asymmetric C–C and C–N bond formations with ee's of up to 95% at room temperature were observed. A transition state model of the malonic ester addition to cyclohex-2-enone has been proposed based on the molecular structure of the acetone solvate of BIMBOL. The impact of the catalyst self-association on its performance is also discussed.

1. Introduction

Asymmetric catalysts, which combine both acidic and basic sites, are attracting ever growing interest in the chemical community because of their greater effectiveness when compared to conventional catalysts that contain only either acidic or basic sites. Such multifunctional catalysts can exhibit both Lewis acidity and Brønsted basicity (heterobimetallic complexes),[1] and contain both Brønsted acidic and Brønsted basic sites (pure organic catalysts).[2] Another emerging simple multifunctional catalytic system is exemplified by chiral lithium binaphtholate salts.[3c] The catalysts contain a Lewis acidic site, and Brønsted basic, and Brønsted acidic sites within the confines of the same chiral molecules. The asymmetric reduction of ketones with trialkoxysilanes[3a] and trimethylsilylcyanation of aldehydes[3b] have successfully been catalyzed by the *mono* lithium salt of (*S*)-BINOL as reported by Kagan et al. The approach was further extended by Nakajima to Mukaiyama-type aldol reactions of trimethoxysilyl enol ethers.[3c,3d] An unexpected beneficial effect of water as an additive on stereoselectivity was observed in the reactions.[3d] The catalytic effects of the lithium binolate were believed to originate from the formation of chiral hypervalent silicon intermediates.[3a–d] Ishihara broadened the use of lithium binolates to direct Mannich-type reaction of keto-esters and aldimines.[3e] He also was the first to recognize the bifunctional (Lewis acidic and Brønsted basic) nature of the catalyst.[3e]

Previously, some of us developed a highly efficient approach for the asymmetric synthesis of aminoacids via phase transfer alkylation[4a,b] and Michael reaction[4b,c] of glycine Ni(II) complexes catalyzed by (*S*)- or (*R*)-2-amino-2′-hydroxy-1,1′-binaphthol (nobin).[4a–c] Alkalie metal nobinates were assumed to be the active catalytic species in the reactions, serving as a base to ionize the CH acid.[4b] The conjugated acids of the nobinates were believed to be responsible for the asymmetric induction with the hydrogen bond solvating the glycine carbanion and simultaneously coordinating the alkalie metal cation in the transition state of alkylation.[4b] We reasoned that further modification of the system by introducing additional hydrogen bond donor groups into the chiral binaphthole scaffold would further improve the performance of the chiral phenolate catalysts. In addition to greater stabilization of the charged intermediates, the longer hydrogen bond arrays would be expected to facilitate the mutual rigid fixation of the reagents in the transition state of the bimolecular reactions of the electrophiles and the conjugated bases of the CH-acids. Finally, the classical condensation reactions of the CH-acids, such as Michael, aldol, Mannich and so forth, are all formally C–C bond forming reactions, accompanied by hydrogen (proton) migration from the CH acid to the electrophile. The creation of a chain of intramolecular hydrogen bonded hydroxyl groups could be expected to facilitate the proton transfer, accompanying the C–C bond formation, as Figure 1 illustrated. Some analogy can be found in the fast proton transport along one-dimensional water chains confined in carbon nanotubes.[5]

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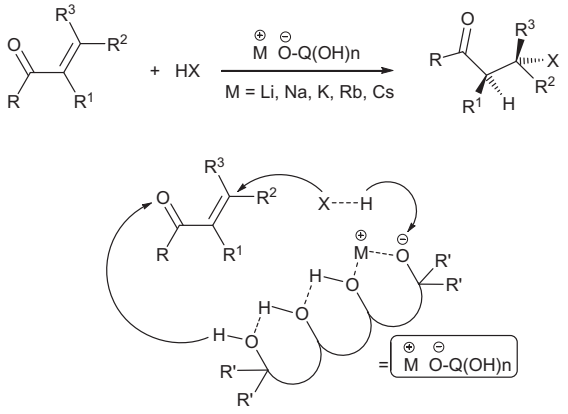


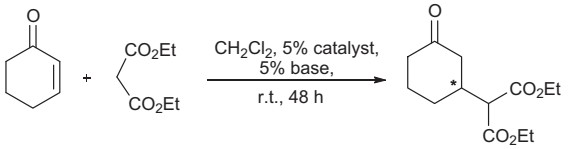
Figure 1. Schematic presentation of a Michael reaction of a CH-acid (XH) catalyzed by a polyalcoholate (polyphenolate) species with the nucleophile/electrophile proton migration facilitated by the multifunctional catalyst.

We have chosen Li, Na, and K salts of (*S*)- or (*R*)-3,3′-bis[bis-(phenyl)hydroxymethyl]-2,2′-dihydroxy-dinaphthalene-1,1′ (BIMBOL)[6] as a logical next generation catalyst of the Li-binolate family to study their performance in a model reaction of asymmetric Michael addition of malonic ester and other nucleophiles to cyclohex-2-enone (Scheme 1) and nitrostyrene. The choice of cyclohex-2-enone was based upon the prevalence of substituted cyclohexane motifs in pharmaceutical compounds.[7] Michael addition of malonates to nitrostyrene was recently documented as an efficient approach to antidepressants (*R*)-rolipram and (3*S*,4*R*)-paroxetine.[8]

The comparison of BIMBOL, BINOL, and TADDOL derived catalysts indicated that the proof of principle experiments was successful and that the multifunctional catalyst derived from BIMBOL was much more efficient than the analogs, containing shorter hydrogen bond arrays.

2. Results and discussion

At first, (*R*)- or (*S*)-BIMBOL (Chart 1) was prepared in a three step sequence from (*R*)-BINOL, **1**, via an intermediate **2**.[16] The model reaction (Scheme 1) was conducted in CH_2Cl_2 at ambient temperature. The catalytic Li-salt was prepared from **1**, **2**, (*R*)-TADDOL, (*R*)- or (*S*)-BIMBOL by mixing them with 1 equiv of dry Li-phenolate. The procedure allowed the comparison of TADDOL, **2** and the chiral phenols at the same basicity level.



Scheme 1. The model Michael addition reaction.

First, we examined the model reaction in the presence of 5 mol % of **1** and 1 equiv of LiOPh. The reaction was sluggish with only 16% chemical yield and 30% ee of the Michael adduct after 48 h (Table 1, entry 1). No significant improvement in the catalytic performance was achieved with **2** and (*R*)-TADDOL (Table 1, entries 2 and 3).

Both enantiomers of BIMBOL provided much higher reactivity (Table 1, entries 4 and 5), compared with **1**, **2**, and TADDOL. The reaction was complete within 48 hours with a good stereocontrol (85% ee).

Practically no change in the enantioselectivity of the addition with the progress of the reaction (Table 1, entries 4 and 5) was

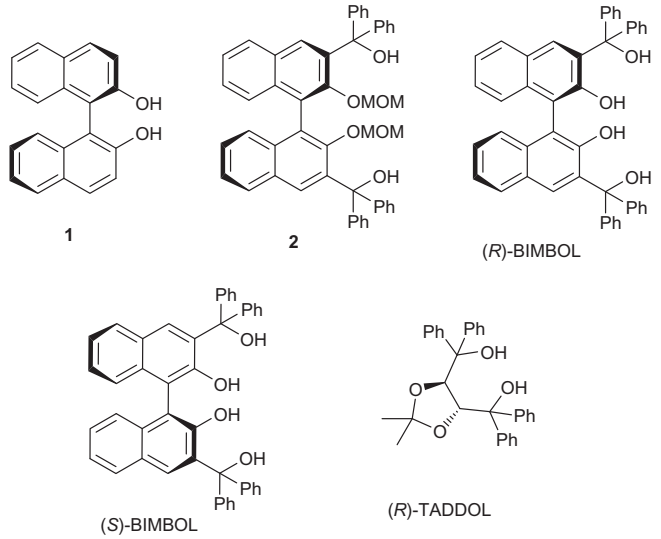


Chart 1.

Table 1
Asymmetric Michael additions catalyzed by compounds **1**, **2**, (*R*)-TADDOL, (*R*)-BIMBOL, (*S*)-BIMBOL with lithium phenolate as a cocatalyst[a]

Entry	Catalyst	Yield (%)	ee[b] (%)
1	**1**	16	30 (*R*)
2	**2**	14	60 (*R*)
3	(*R*)-TADDOL	30	40 (*R*)
4	(*R*)-BIMBOL	99	85 (*R*)
5	(*S*)-BIMBOL	99	85 (*S*)

[a] Reaction conditions: cyclohex-2-enone (0.258 mmol), diethyl malonate (0.335 mmol), catalyst (5 mol %), LiOPh (5 mol %), CH_2Cl_2 (1 mL), under Ar, 48 h, rt.
[b] Enantiomeric excess was determined by chiral HPLC analysis using Chiralpak AS-H columns.

detected, as Figure 2 illustrated. Evidently, the nature of the catalytic species remains the same during the condensation with no catalyst deterioration taking place in the process.

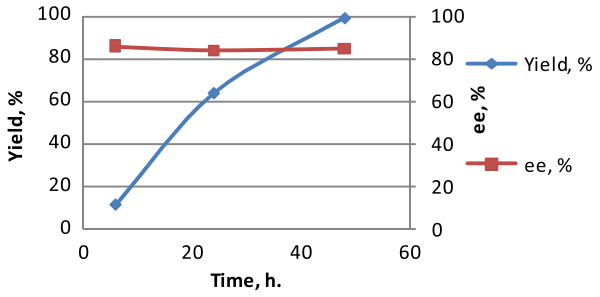


Figure 2. The variation of the enantiomeric purity of the Michael adduct with the progress of the reaction catalyzed by the catalytic system (*S*)-BIMBOL and LiOPh in CH_2Cl_2.

Table 2 summarizes the effects of changing the alkalie metal cations on the performance of the BIMBOL-phenolate catalytic system. Both LiOPh, NaOPh, and KOPh catalyzed the condensation to some extent without any BIMBOL added (Table 2, entries 1, 5, and 8) but the addition of BIMBOL completely inhibited the reaction in the cases of NaOPh and KOPh (entries 6 and 9) and greatly improved the performance in the case of LiOPh (entry 2). Other strongly basic Li salts, such as BuLi and LiOH, were even better catalytic additives, affording greater enantioselectivity in the reaction (Table 2, entries 3 and 4). The data show the important role of the metal Lewis acidity, as its expected increase follows the order

Table 2
Asymmetric Michael addition catalyzed by (*S*)-BIMBOL and different bases[a]

Entry	Base	Yield (ee) (%)
1[b]	LiOPh	47
2	LiOPh	99 (85 (*S*))
3	LiOH	65 (85 (*S*))
4	BuLi	99 (88 (*S*))
5[b]	NaOPh	35
6	NaOPh	0
7	NaH	0
8[b]	KOPh	43
9	KOPh	0
10	KO^{t}Bu	0
11	KOH	0

[a] Reaction conditions: cyclohex-2-enone (0.258 mmol), diethyl malonate (0.335 mmol), catalyst (5 mol %), base (5 mol %), CH_2Cl_2 (1 mL), under Ar, 48 h, rt.
[b] No (*S*)-BIMBOL was added.

Li > Na > K. In addition, BuLi, LiOH and LiOPh are all stronger bases than the conjugated base of BIMBOL (intramolecular hydrogen bonds making phenol groups of BIMBOL more strongly acidic compared to PhOH, vide infra). The observation hinted at the lithium salt of BIMBOL being the real catalytic particle in the addition.

In order to determine the optimal catalytic ratio of BIMBOL/LiOPh, a serious of experiments were conducted with the total concentration of the catalyst kept constant but the ratio of the two catalytic components varied. The Job plot[9] of the chemical yields and ee of the product versus the ratio is shown in Figure 3. Evidently, the most efficient catalytic system contained a 1/1 ratio of BIMBOL/LiOPh, which supports the notion of the monolithium salt of BIMBOL as the best catalytically active species. Another active catalytic species seems to have a 1/2 ratio of the components. There is a significant minimum in chemical yield (the rate of the addition) at 1/1.5 ratio. Greater than 1/1 relative amounts of BIMBOL to LiOPh inhibited the catalytic activity of the system. The observation can be rationalized by assuming the formation of coordinatively saturated bis-BIMBOL/LiOPh species with no or low catalytic activity. The collected data indicated a complex structure of the real catalytic species, presumably consisting of different Li-phenolate associates, each having its own catalytic properties.

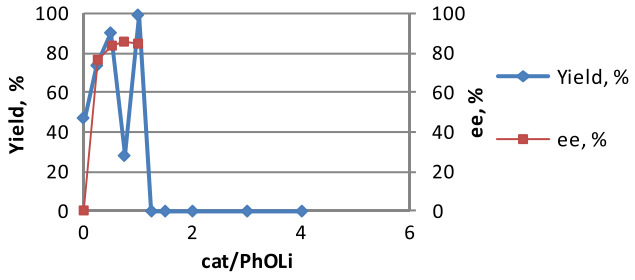


Figure 3. Job's plot of the effect of the BIMBOL/LiOPh ratio on the catalytic activity of the mixture. Reaction conditions: cyclohex-2-enone (0.26 mmol), diethyl malonate (0.34 mmol), CH_2Cl_2 (1 mL), under Ar, 48 h, rt. The total concentration of BIMBOL [either (*R*)- or (*S*)-enantiomer] plus LiOPh was kept constant and equal to 10 mol % (2.6×10^{-5} mol). Each point was an average of 5 experiments.

As expected, the solvent affected the catalytic performance (Table 3) with CH_2Cl_2, toluene, and ether being the best in the series in terms of both chemical yield and enantioselectivity (Table 3, entries 1–3). On the other hand, donor dipolar solvents such as MeCN and dioxane inhibited the reaction (Table 3, entries 5 and 7), presumably competing with the substrates for hydrogen bonds with Brønsted acidic sites and coordinating to the Lewis acidic site. Hexane and CCl_4 were also poor solvents (Table 3, entries 4 and 6), most likely, because of their low polarity, facilitating the formation of catalyst aggregates with inferior catalytic activities.

Table 3
Asymmetric Michael addition catalyzed by compound (*S*)-BIMBOL with LiOPh as cocatalyst in different solvents[a]

Entry	Solvent	Yield (%)	ee (%)
1	CH_2Cl_2	99	85(*S*)
2	Toluene	99	87(*S*)
3	Ether	99	85(*S*)
4	Hexane	80	27(*S*)
5[b]	Dioxane	58	4(*R*)
6	CCl_4	63	64(*S*)
7	CH_3CN	15	14(*S*)

[a] Reaction conditions: cyclohex-2-enone (0.258 mmol), diethyl malonate (0.335 mmol), catalyst (5 mol %), LiOPh (5 mol %), solvent (1 mL), under Ar, 48 h, rt.
[b] Reaction was carried out with catalyst (*R*)-BIMBOL.

The formation of catalyst aggregates was also supported by the observation of nonlinear effects[10] in the reaction. The plot of the enantiomeric purity of the product versus the enantiomeric purity of the catalyst is shown in Figure 4. The chemical yields within a 48 h period were also plotted. The values of the product ee have deviated from the theoretical linear correlation for the classical monomeric catalyst case.

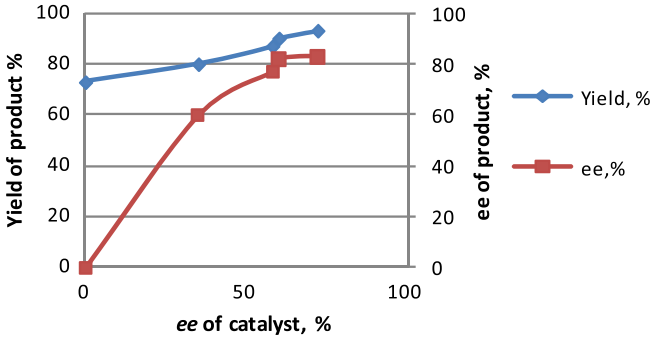


Figure 4. The plot of the enantiomeric purity and the chemical yield of the product versus the enantiomeric purity of BIMBOL: Reaction conditions: cyclohex-2-enone (0.258 mmol), diethyl malonate (0.335 mmol), catalyst (*R*)-BIMBOL or (*S*)-BIMBOL (5 mol %), LiOPh (5 mol %), CH_2Cl_2 (1 mL), 72 h, under Ar, rt.

The positive deviations from linearity were not the result of experimental error points, as each point was the average of 3–5 experimental data. The conversion also strongly depended on the catalyst ee, indicating increased catalytic activity of enantiomerically enriched species.

If the monomeric Li salts were the predominant and catalytic species in the reaction mixture, the rate of the reaction would not depend on the catalyst ee and the conversion would remain the same within the ee interval. Formation of some insoluble material was observed in the case of racemic and partially enriched catalyst, indicating the possible operation of a 'reservoir effect' removing the racemic aggregates from the reaction media.[10] The catalyst aggregation phenomena are well established in some cases of bifunctional asymmetric catalysis.[11a] Some literature precedents for different catalytic activities of several polynuclear aggregates of Li phenolates exist, as exemplified by ROP of lactides catalyzed with phenolates.[11b]

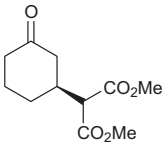
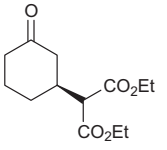
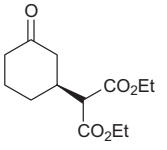
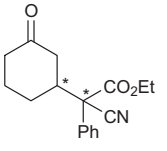
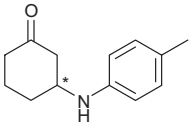
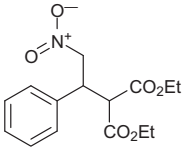
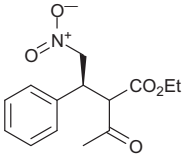
The product chemical yield and ee varied with dilution of the reaction media. Four times the dilution resulted in an increase of the chemical yield from 66% to 99% and ee from 68% to 85% (Table 4, entries 1 and 5, 6). The best enantioselectivity of the reaction was observed at 0.5 mL of the solution with the ee of the product equal to 95%, albeit with only 60% chemical yield (Table 4, entry 2). A further six-fold dilution resulted in a significant loss of catalytic activity of the catalyst (Table 4, entries 7 and 8). The data supports the notion of different catalytic aggregate formation at different concentrations of the catalyst.

Table 4
The influence of dilution on the performance of (*S*)-BIMBOL[a]

Run	Solvent (mL)	C_{cat} (10^{-3} mol/L)	Yield (%)	ee (%)
1	0.25	51.5	66	68(*S*)
2	0.5	25.8	60	95(*S*)
3	0.75	17.2	26	83(*S*)
4[b]	0.75	17.2	27	86(*R*)
5	1	12.9	99	85(*S*)
6[b]	1	12.9	99	85(*R*)
7	1.5	8.6	41	83(*S*)
8	2	5.85	2	n.d.

[a] Reaction conditions: cyclohex-2-enone (0.258 mmol), diethyl malonate (0.335 mmol), catalyst (*S*)-BIMBOL (5 mol %), LiOPh (5 mol %), CH_2Cl_2 (varied from 0.25 mL to 2 mL), 48 h under Ar, rt.
[b] The experiment was conducted with (*R*)-BIMBOL.

Table 5
Asymmetric Michael addition catalyzed by compounds (*S*)-BIMBOL and lithium phenolates in CH_2Cl_2[a]

Entry	Product	Yield (%)	dr	ee (%) (Conf)
1		33	—	80 (*S*)
2		99	—	85 (*S*)
3[b]		60	—	95 (*S*)
4		90	1/1.2	43/36 (n.d.)
5[c]		70	—	16–45 (n.d.)
6		99	—	0
7		99	1/1	99/10 (n.d.)

[a] Reaction conditions: cyclohex-2-enone (0.258 mmol), catalyst (5 mol %), LiOPh (5 mol %), solvent (1 mL), under Ar, 48 h, rt.
[b] Solvent 0.5 mL
[c] Catalyst (5 mol %)/BuLi (5 mol %).

We explored the scope of the reaction with a different set of CH acids and Michael acceptors (Table 5).

Ethyl and methyl esters of malonic acid added to cyclohex-2-enone with ee in the range of 80–95% (Table 5, entries 1–3). Cyanophenylacetic ester also added to cyclohex-2-enone under the conditions although ee dropped to 43% (Table 5, entry 4). The addition of toluidine to cyclohex-2-enone was also catalyzed by (*S*)-BIMBOL with moderate ee of 40% (Table 5, entry 5). To the best of our knowledge it was the first case of the asymmetric catalytic reaction of such a weak nucleophile catalyzed by a purely organic chiral catalyst. But the addition of ethyl malonate to nitrostyrene led to the racemic product under the same conditions (Table 5, entry 6). Ethyl acetoacetate added to nitrostyrene with 1:1 ratio of the resulting diastereoisomers but with very high enantioselectivity of one diastereoisomer (Table 5, entry 7).

The crystal structure of the acetone solvate of (*R*)-BIMBOL is shown in Figure 5. The salient feature of the structure is the system of intramolecular phenolic OH to alcoholic OH (and vice versa) hydrogen bonds. Simultaneously, both phenolic hydroxyl and alcoholic groups of BIMBOL participated in hydrogen bonding of two acetone molecules. The acetone molecules link neighboring BIMBOL molecules forming uninterrupted chains in the crystal.

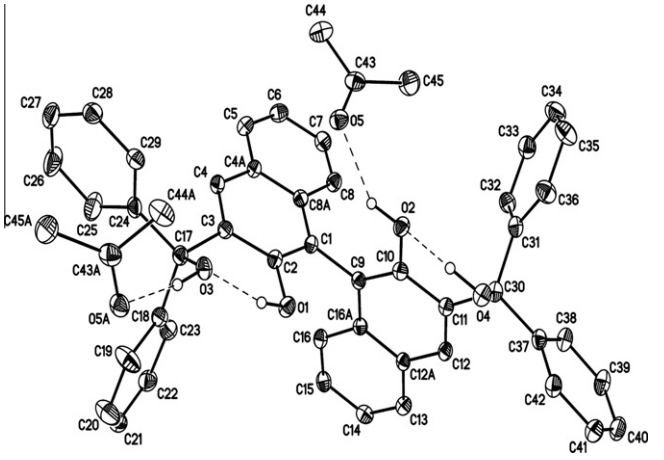


Figure 5. Molecular structure of (*R*)-BIMBOL. The solvate acetone molecules, one of which is crystallographically dependent, are depicted. The disordered acetone solvate molecule is not shown for the sake of clarity. Only the hydrogen atoms of hydroxy-groups are presented. Dashed lines indicate intermolecular hydrogen bonds.

The following mechanism of the Michael addition can be considered (Fig. 6). The pK_a of phenolic hydroxyls in DMSO equals 17–18[12a] and that of malonic ester is 16.4.[12a] Thus, the Li salt of BIMBOL can easily activate the malonic ester by converting it into the conjugated carbanion, with BIMBOL itself transformed into a neutral species. The Li cation is coordinated by both the anion and the OH groups of BIMBOL (Fig. 6). This coordination should result in a Lewis acid promoted increase of the Brønsted acidity[13] of the OH groups and, thus, facilitate the hydrogen bond transfer along the intramolecular chain of the four OH groups, the last of the chain activating the Michael acceptor.

As a result, the two reagents are rigidly positioned relative to each other. The formation of the C–C bond is accompanied by the proton transfers along the BIMBOL intramolecular chain of hydrogen bonds (Fig. 1). The forming cyclohexenol was expected to have a pK_a value in the range of 29–31[12a] and can be assumed to be much less acidic than the hydrogen bond activated diphenylcarbinol group of BIMBOL. A great increase in the acidity of hydroxyl groups connected by a chain of intramolecular hydrogen bonds is a well established phenomenon.[12b] Thus, there seems to be no acidity obstacle to the proton transfers.

The data summarized in Table 5 hint that the orientation of Michael acceptor within the transition state of the addition does

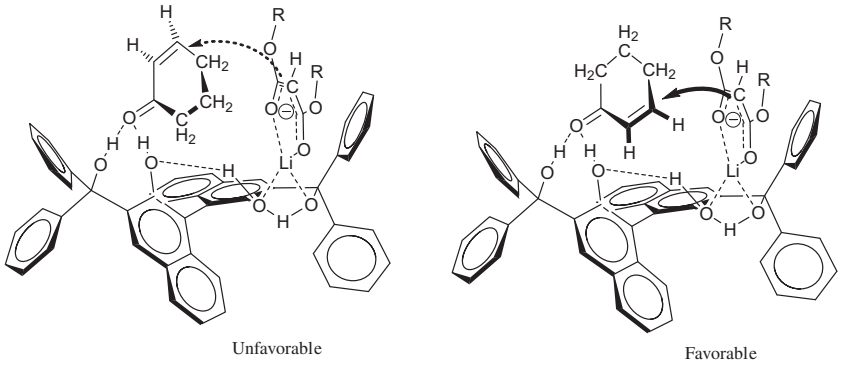


Figure 6. Proposed transition state of (*S*)-BIMBOL catalyzed addition of malonic ester to cyclohex-2-enone.

depend on the structure of the nucleophile. Otherwise all the substrates would have produced the corresponding adducts with the same high enantioselectivity.

The proposed mechanism of the reaction may have some bearing on the positive effect of water and alcohol addition to some Li-binolate catalyzed reactions. Possibly, the additives create some additional proton transfer chains to improve performance of the catalyst.

3. Conclusion

Evidently, the experiments support the notion of the multifunctional nature of the BIMBOLate Li catalytic system with Lewis acidic, Brønsted basic and Brønsted acidic sites, acting in concert in the transition state of the Michael addition. The catalytic system represents a perspective alternative to the enamine-type catalysis of the Michael addition reactions.[14] The system can be easily modified with the acidity of its hydroxyl groups increased. The catalyst aggregate formation could also be controlled by varying the steric properties of the diphenylcarbinol moieties. Further work to explore the scope of the catalytic system and its future generations is ongoing in our laboratory and will be reported in due course.

4. Experimental

^{1}H NMR spectra were recorded on Bruker Avance 300 (300.13 MHz) spectrometers; chemical shifts were measured relative to the residual protons of the deuterated solvent ($CDCl_3$). Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 5-cm cell temperature-stabilized at 25 °C. Column chromatography was performed with the use of Silica Gel Kieselgel 60 (Merck). Elemental analyses were carried out in the Laboratory of Microanalysis of the A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences. All solvents were purified according to standard procedures.

The enantiomeric purity of the synthesized Michael adducts was determined by chiral HPLC analysis (Chiralpak AS-H chiral stationary phase, *i*PrOH/hexane 1–9, 210 nm). The absolute configuration of the major product of the cyclohex-2-enone/malonic ester condensation was determined by comparison with the reported value of the specific rotation.[15]

4.1. Preparation (*R*)-BIMBOL and (*S*)-BIMBOL

Catalyst (*R*)-BIMBOL and (*S*)-BIMBOL was synthesized according to a reported procedure.[16]

The product was recrystallized from acetone. The enantiomeric purity of (*R*)-BIMBOL was 98% ee, (*S*)-BIMBOL was 100% ee as determined by using HPLC-Kromasil KR100-5CHI-DMB column (solvent: hexane/*i*PrOH = 98/2, flow rate: 0.8 mL/min). The specific rotation of (*R*)-BIMBOL $[\alpha]_D^{25} = +112.3$ (*c* 1.00, $CHCl_3$), and that of (*S*)-BIMBIL $[\alpha]_D^{25} = -100.5$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 2H), 7.34–7.23 (m, 24H), 7.13 (s, 2H), 7.10 (d, *J* = 6 Hz, 2H), 6.57 (s, 2H), 4.67 (s,2H). ^{13}C (70 MHz, $CDCl_3$): δ 151.2, 145.4, 145.2, 133.8, 133.2, 130.8, 128.9, 128.4, 128.1, 128.0, 127.8, 127.5, 124.2, 124.1, 114.2, 82.9. Anal. Calcd for $C_{46}H_{34}O_4$ (*R*)-BIMBOL: C, 84.90; H, 5.27. Found: C, 84.98; H, 5.35.

4.2. Asymmetric Michael reaction (general procedure)

A Schlenk flask was evacuated and filled with argon, whilst being heated with a heatgun. Then the flask was cooled to room temperature under a flow of argon. A catalyst (0.013 mmol) and a base (0.013 mmol) were added to the flask and a cyclohex-2-enone (0.025 mL, 0.258 mmol) solution in CH_2Cl_2 was added. Then the solution was stirred for 5 min and diethyl malonate (0.05 mL, 0.0536 g, 0.335 mmol) was added. The reaction mixture was stirred for 48 h under Ar. The catalyst was removed from the reaction mixture by column chromatography on silica gel, using hexane/EtOAc 5:1 as an eluent. The enantiomeric purity of the product was determined by chiral HPLC.

4.2.1. Diethyl 2-(3-oxocyclohexyl)malonate

Prepared according to general procedure. The product was obtained in 98% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.19–1.24 (m, 6H), 1.40–1.52 (m, 1H), 1.55–1.70 (m, 1H), 1.88–1.92 (m, 1H), 1.98–2.06 (m, 1H), 2.15–2.26 (m, 2H), 2.31–2.50 (m, 3H), 3.23 (d, *J* = 7.8 Hz, 1H), 4.11–4.19 (m, 4H). The enantiomeric excess was determined by HPLC analysis with a Chiralpak AS-H column (9:1 hexanes/isopropanol, 1 mL/min, 210 nm): 17.51 min, 20.67 min.

4.2.2. (3*S*)-Ethyl-2-acetyl-4-nitro-3-phenylbutyrate

To a stirred solution of catalyst (0.011 g, 0.0167 mmol) and LiOPh (0.0169 mmol) in dry CH_2Cl_2 was added *trans*-β-nirostyrene (0.05 g, 0.335 mmol) and then acetoacetate (0.043 g, 0.335 mmol) After being stirred for 48 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel, using hexane/EtOAc 5:1 as an eluent. R_f = 0.3. The diastereomers could not be separated. Colorless oil; $[\alpha]_D^{25} = -28.1$ (*c* 0.57 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.99 (t, *J* = 6.9 Hz, 1.8 H), 1.27 (t, *J* = 7.2 Hz, 1.5 H), 2.05 (s, 1.3H), 2.27 (s, 1.6H), 3.89–4.02 (m. 1.6H), 4.07–4.23 (m, 2.5H), 4.71 (d, *J* = 6 Hz, 1H), 4.80–4.82 (m, 0.8H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.23–7.28 (m, 3H). The enantiomeric excess was determined by HPLC analysis with a Chiralcel AD column (9:1 hexanes/isopropanol, 1 mL/min, 210 nm). Reaction times: (major enantiomer) 8.68; 14.65 min, (minor enantiomer) 9.86; 23.92 min.

4.2.3. 3-(*p*-Tolylamino)cyclohexanone

The catalyst (0.0169 g, 0.026 mmol) and BuLi (0.016 mL, 1.6 M) in dry Et_2O was stirred for 30 min. The solution was evaporated than cyclohex-2-enone (0.05 g, 0.52 mmol) and *p*-toluidine (0.056 g, 0.52 mmol) in dry CH_2Cl_2 were added. After being stirred for 48 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel, using hexane/EtOAc 5:1 as an eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.70–1.81 (m, 2 H), 2.05–2.11 (m, 2 H), 2.28 (s, 3H), 2.35–2.50 (m, 4H), 2.84–2.89 (dd, J = 3.6 Hz, J = 10 Hz, 1H), 3.80 (m, 1H), 6.58 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H). The enantiomeric excess was determined by HPLC analysis with a Chiralpak AS-H column (9:1 hexanes/isopropanol, 1 mL/min, 254 nm). Reaction times: (major enantiomer) 27.58 min, (minor enantiomer) 23.66 min.

4.2.4. Ethyl (2-cyano-2-(3-oxocyclohexyl)-2-phenylacetate

Prepared according to the general procedure. A catalyst (0.0169 g, 0.026 mmol) and LiOPh (0.026 mmol) were added to the flask and cyclohex-2-enone (0.05 g, 0.252 mmol) solution in CH_2Cl_2 was added. Then the solution was stirred for 5 min and ethyl 2-cyano-2 phenylacetate (0.098 g, 0.52 mmol) was added. The reaction mixture was stirred for 48 h under an argon atmosphere. The catalyst was removed from the reaction mixture by column chromatography on silica gel, using hexane/EtOAc 5:1 as an eluent. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.26–1.31 (m, 3H), 1.48–1.61 (m, 1H), 1.74–1.96 (m, 2H), 2.03–2.26 (m, 2H), 2.34–2.48 (m, 2H), 2.65–2.61 (m, 1H), 2.86–2.95 (m, 1H), 4.17–4.38 (m, 2H), 7.42–7.49 (m, 3H), 7.58–7.67 (m, 2H). The enantiomeric excess was determined by HPLC analysis with a Chiralcel OD column (95/5 hexanes/isopropanol, 1 mL/min, 210 nm). Reaction times: (major enantiomer) 8.68; 14.65 min, (minor enantiomer) 9.86; 23.92 min.

4.3. Syntheses of lithium phenolates were conducted according to the literature procedure[17]

The crystal of (*R*)-BIMBOL ($C_{46}H_{34}O_4 \times 1.75C_3H_6O$, M = 752.37) is monoclinic, space group $P2_1$, at T = 120 K: a = 15.9754(13) Å, b = 9.2420(7) Å, c = 16.0119(13) Å, β = 116.745(2)°, V = 2111.2(3) Å^3, Z = 2, d_{calcd} = 1.184 g/cm^3, F(0 0 0) = 796, μ = 0.076 mm^{-1}. Data were collected on a Bruker SMART 1 K CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, φ and ω scan mode, θ_{max} = 27°). The structure was solved by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The independent part of the unit cell of (*R*)-BIMBOL contains two acetone solvate molecules, one of which is disordered over two sites with the occupancies of 0.50:0.25. The hydrogen atoms of the hydroxy-groups in (*R*)-BIMBOL were localized in the difference-Fourier map and included in the refinement with fixed positional and isotropic displacement parameters (U_{iso}(H) = 1.5U_{eq}(O)). The other hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters (U_{iso}(H) = 1.5U_{eq}(C) for the CH_3-groups and U_{iso}(H) = 1.2U_{eq}(C) for the other groups). The absolute structure of (*S*)-BIMBOL cannot be objectively determined, because it includes no heavy atoms with Z > Si. The final divergence factors were R_1 = 0.060 for 3912 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.159 for all 4889 independent reflections, S = 1.006. All calculations were carried out using the SHELXTL program.[18] Crystallographic data for (*R*)-BIMBOL have been deposited with the Cambridge Crystallographic Data Center. CCDC 794881 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

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