Organic Chemistry

Asymmetric Michael reaction of diethyl malonate with crotonaldehyde catalyzed by chiral aminocarboxylates, amino alcoholates, and amino phenolates

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Alkali metal salts of substituted (*S*)-prolines, alkali metal alkoxides of (*S*)-prolinol, and Na salts of chiral substituted 2-amino-2′-hydroxy-1,1′-binaphthyls can catalyze the asymmetric Michael reaction of diethyl malonate with crotonaldehyde to give adducts in >90% yields with *ee* up to 40%. The influences of the catalyst structure, the nature of the alkali metal cation, temperature, the solvent, and salt additives on the reaction outcome were studied.

Key words: diethyl malonate, crotonaldehyde, asymmetric Michael reaction, chiral catalysts, alkali metal salts of substituted prolines, sodium salts of chiral 2-amino-2′-hydroxy-1,1′-binaphthyls.

The possibility of catalyzing the asymmetric Michael reaction has been discovered only in recent years.[1—13] According to the published data,[1] the most promising control of asymmetry in the reactions of conjugated addition involves the use of chiral catalysis, though most of the known catalysts are still difficultly available or are unstable. Effective heterobimetallic complexes of lanthanides[2] are strongly basic, often causing the formation of by-products. With neutral Ni^{II} complexes,[3] low chemical yields of the reaction products are attained, while novel chiral cationic Pd^{II} complexes[4] do not ensure high stereoselectivity (<34% *ee*). With phase-transfer catalysts based on quaternary ammonium salts derived from cinchonidine[5,6] or proline,[7] high *ee* values are reached only for a narrow range of compounds involved in the Michael reaction. In the presence of bases, these ammonium salts decompose to give achiral products which also promote the reaction, thus decreas-

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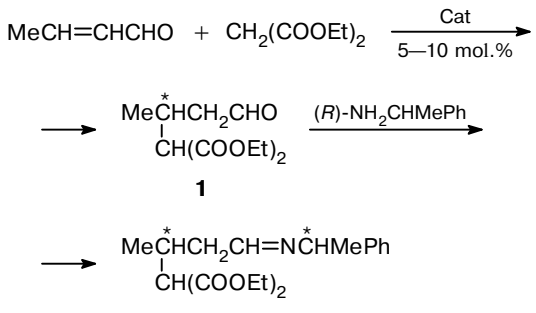
ing its enantioselectivity.[8] This limits the area of application of phase-transfer methods in catalytic asymmetric synthesis. Of topical interest is the search for new chiral phase-transfer catalysts of the formation of a C—C bond without the aforesaid disadvantages.

Earlier, we showed that the Michael reaction can be catalyzed by chiral amino alcohols,[9] chiral diol alcoholates, and amino alcoholates under phase-transfer conditions,[10] where the ability of a catalyst to chelate the alkali metal ion which forms an ion pair with the substrate carbanion is important.[11] (*S*)-Proline salts were also found to catalyze the Michael reaction.[12,13] In the present work, the influence of the structure of amino group-containing catalysts on the yield and enantioselectivity of the asymmetric Michael reaction of diethyl malonate with crotonaldehyde, as well as the influence of the nature of the alkali metal cation, temperature, solvent, and salt additives on the reaction outcome, are discussed.

Results and Discussion

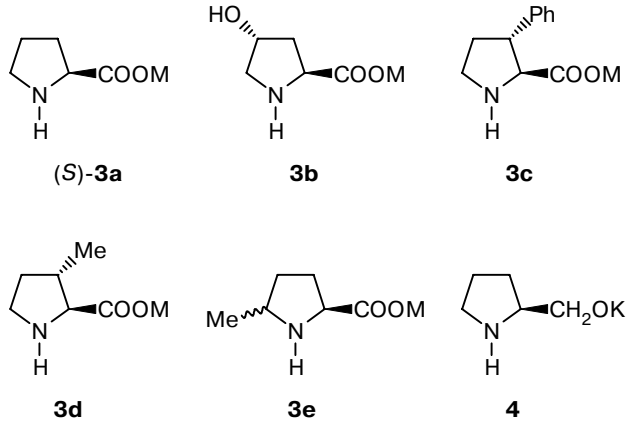
The Michael addition of diethyl malonate to crotonaldehyde shown in Scheme 1 yields ethyl 2-ethoxycarbonyl-3-methyl-5-oxopentanoate (**1**). Ester **1** was converted into diastereomeric Schiff bases (**2**) by the reaction with (*R*)-methylbenzylamine to determine its enantiomeric composition using ^{1}H NMR spectroscopy. The ratio obtained satisfactorily correlates with the optical rotation value of product **1**. The diastereomers were assigned according to the known procedure.[12]

Scheme 1

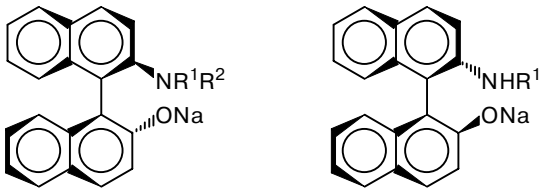


The results of the addition (see Scheme 1) catalyzed by proline salts, its substituted analogs (**3a**—**e**), sodium or potassium derivatives of (*S*)-prolinol (**4**), and chiral *N*-substituted 2-amino-2′-hydroxy-1,1′-binaphthyls (**5a**—**e**, NOBINs) are presented in Table 1. Compound **1** is not formed without catalysts. The best results were obtained for catalysts **3a**—**e**. The reaction was carried out both under the conditions of phase-transfer catalysis with addition of solid alkali[5—8,11] and with preformed salts **3a**—**e** (see Refs. 12, 13). Both versions provide similar results (see Table 1, entries *1* and *8*). With (*S*)-proline, product (*S*)-**1** is formed (see Table 1, entries *1*—*7*), while the use of (*R*)-proline affords, naturally, the enantiomer (*R*)-**1** (see entry *8*). The reaction outcome is influenced by the nature of the alkali metal in salts **3a**. On passing from lithium to sodium and potassium, the reaction enantioselectivity is insignificantly enhanced (from 16 to 21%) (see entries *2*, *3*, *6*—*8*), while the use of cesium decreases it by half (see entry *4*). In contrast to the previous data,[12] the presence of rubidium reduces *ee* even more strongly (see entry *5*). With an equimolar amount of 18-crown-6 together with potassium salt of (*S*)-**3a** (see entry *9*), the asymmetric induction is reversed to give (*R*)-**1**.

It is known that the addition of copper salts to chelating systems sometimes enhances the enantioselectivity of the Michael reaction.[14] In our case, the addition of equimolar amount of copper salts to the catalyst increases *ee* in CH_2Cl_2 (*cf.* entries *8* and *13*) and decreases it in THF (*cf.* entries *10* and *12*).



3: M = Li, Na, K, Rb, Cs



R^1R^2 = H (NOBIN) (**a**), Me (**e**); R^1 = H, R^2 = Me (**b**); R^1 = *cyclo*-C_6H_{11} (**c**), 1-adamantyl (**d**)

While studying the conditions for the use of aminocarboxylates **3**, we found that *ee* increases to 25% both with an increase in the amount of catalyst **3a** to 15 mol.% and with a decrease in temperature to −10 °C (see entries *7* and *6*, respectively). A similar effect (an increase in *ee* to 32—38%) is observed in solvating solvents such as Et_2O, Bu_2O, and THF (see entries *10*

Table 1. The Michael reaction of diethyl malonate with crotonaldehyde in the presence of catalysts **3a—e**, **4**, and **5a—e** at 18 °C

Entry	Catalyst	Salt cation or base	Solvent	Time /h	Yield of **1** (%)	*ee* of **1** (%)[a]
1	5% (*S*)-**3a**	K[b]	CH_2Cl_2	12	70	19(*S*)
2	5% (*S*)-**3a**	Na	CH_2Cl_2	72	90	20(*S*)
3	5% (*S*)-**3a**	Li	CH_2Cl_2	72	90	16(*S*)
4	10% (*S*)-**3a**	Cs	CH_2Cl_2	90	60	10(*S*)[c]
5	10% (*S*)-**3a**	Rb	CH_2Cl_2	24	50	7(*S*)
6[d]	5% (*S*)-**3a**	K	CH_2Cl_2	72	60	25(*S*)
7	15% (*S*)-**3a**	K	CH_2Cl_2	72	60	24.5(*S*)
8	5% (*R*)-**3a**	K	CH_2Cl_2	72	90	21(*R*)
9	10% (*S*)-**3a**, 10% 18-краун-6	K	THF	70	15	25(*R*)
10	10% (*S*)-**3a**	K	THF	24	65	38(*S*)
11	10% (*S*)-**3a**	K	Et_2O[e]	24	80	32(*S*)
12	10% (*S*)-**3a**, CuI	K	THF	70	70	30(*S*)
13	5% (*S*)-**3a**, CuI[f]	K	CH_2Cl_2	24	90	32(*S*)
14	5% (*S*)-**3b**	K	CH_2Cl_2	72	58	6(*S*)
15	5% (*S*)-**3c**	K	CH_2Cl_2	18	78	27(*S*)
16	5% (*S*)-**3d**	K	CH_2Cl_2	24	70	25(*S*)
17	5% (*S*)-**3e**	K	CH_2Cl_2	18	90	12(*R*)[c]
18	10% (*S*)-**3c**	K[g]	Et_2O	24	80	8(*S*)
19[d]	5% (*S*)-**3c**	Rb	CH_2Cl_2	70	80	1.5(*S*)[c]
20	10% (*S*)-**3c**	K	THF	70	80	28(*S*)
21	10% (*S*)-**3c**, CuI	K	Et_2O	24	60	40(*S*)
22	10% **4**	—	CH_2Cl_2	168	40	8(*S*)
23	10% **4**[h]	10% Bu^tOK	CH_2Cl_2	80	15	22(*S*)
24	5% **5a**	5% NaH	CH_2Cl_2[j]	48	95	5.5(*R*)
25	5% **5b**	5% NaH	CH_2Cl_2[j]	48	85	1.5(*R*)
26	5% **5c**	5% NaH	CH_2Cl_2[j]	48	95	8.5(*S*)
27	5% **5d**	5% NaH	CH_2Cl_2[j]	48	95	3(*S*)
28	5% **5e**	5% NaH	CH_2Cl_2[j]	48	98	0

[a] Determined by ^{1}H NMR spectroscopy.
[b] Phase-transfer conditions: the catalyst (5%), KOH (solid), and CH_2Cl_2.
[c] Determined from the optical rotation value.
[d] At −10 °C.
[e] The use of Bu_2^nO does not change *ee*.
[f] The use of CuCN or CuBr does not change *ee*.
[g] Special conditions of drying the catalyst and the reagents; the reaction was carried out in the presence of 4 Å molecular sieves.
[h] The use of an additional equimolar amount of CuI increased the yield to 50%, *ee* remaining unchanged.
[j] The use of THF and ether does not change *ee*, while the yield decreases.

and *11*). The influence of the substituents in the pyrrolidine ring on the stereoselectivity of the process was studied for potassium salts of substituted prolines **3b—e**. The stereoselectivity was found to decrease for (2*S*,4*R*)-4-hydroxyproline (**3b**) (see entry *14*) and to increase from 21 to 27% (compared to **3a**) for (2*S*,3*R*)-3-phenylproline (**3c**) (see entry *15*) and for (2*S*,3*S*)-3-methylproline (**3d**) (see entry *16*). (2*S*)-5-Methylproline **3e** was used as a mixture of *cis* and *trans* isomers (see entry *17*) to give an (*R*)-product, *i.e.*, the stereoselectivity is reversed.

Virtually complete removal of traces of water from the reaction medium, variations of the reaction time and temperature, change of a solvent, and the use of other bases for salt formation do not increase the degree of asymmetric induction (see entries *18—20*). The best *ee* value (40%) was obtained with potassium salt of (2*S*,3*R*)-phenylproline **3c** with addition of CuI in ether (see entry *21*).

As was determined by us earlier,[9] amino alcohol **4** catalyzes the Michael reaction of crotonaldehyde with methyl nitroacetate, but its enantioselectivity is low in the case of diethyl malonate (see entry *22*). The use of potassium alcoholate **4** increases *ee* to 22% (see entry *23*). Na-phenolate of (*S*)-(+)-NOBIN[11b] **5a** also provides high chemical yields, but with low *ee* values (see entry *24*). With NOBINs **5b—e**, the degree of asymmetric induction changes only slightly; (*R*)-catalyst favors the formation of (*S*)-**1** and *vice versa* (see entries *25—27*). (*S*)-*N*,*N*-Dimethyl-NOBIN **5e** gives race-

mate **1** in almost quantitative yield (see entry *28*). It should be noted that the previously used catalysts, including phase-transfer ones, afforded racemate **1** only in 12—36% yields.[15—17]

Asymmetric aldol condensation catalyzed by (*S*)-proline is traditionally believed to follow the mechanism involving intermediate immonium salts.[18] The formation of such salts involving the carbonyl group of the acceptor, which enable the asymmetric induction in the addition of a donor, also occurs in the reactions of *Z*-enones with aliphatic nitro compounds and derivatives of diethyl malonate catalyzed by (*S*)-proline salts.[12] Apparently, the catalysis by amino compounds **3—5** can follow the same mechanism. However, in contrast to data from Ref. 12, the optical yield of product **1** was found to increase in solvating solvents and depend in a more complex way on the apparent cation size. In addition, *N*,*N*-dimethyl-NOBIN **5e**, which cannot form immonium salts, under conditions used by us catalyzes the nonstereoselective formation of the product in high yield. This indicates that the true mechanism is more complicated than that described earlier.[12,13] The chiral catalyst may function as a base, as was assumed for the Michael reaction with methyl methacrylate[10] catalyzed by amino alcoholates. The chelation of the alkali metal ion[10,11] or copper ion[14,19] by bidentate catalysts **3—5** can give the known type of intermediate,[14] which not only forms an ion pair with the substrate carbanion[11] and activates enal,[14] but also can be a stereodiscriminator of the addition.

Thus, among the catalysts studied, amino carboxylates **3a—e** are the most efficient catalysts of the Michael reaction of diethyl malonate with crotonaldehyde to give the target product in high chemical yields (up to 90%) and asymmetric induction up to 40%. These results correlate with average *ee* values, which do not exceed 20—50% in the Michael reaction with acyclic substrates.[7,10,12,13] The reactions of crotonaldehyde with diethyl malonate, like the previously studied reaction with methyl nitroacetate,[9] is of interest because of the possibility of using the product obtained[20] for the synthesis of difficultly accessible 3-methylproline and its derivatives with high *ee*.[21,22]

Experimental

^{1}H NMR spectra were recorded on Bruker 200 and Bruker 400 instruments. Optical rotation was measured on a Perkin—Elmer 241 polarimeter. $CHCl_3$ and CH_2Cl_2 were distilled over P_2O_5 (water content ≤0.01% according to the Fischer method); THF and ethers were distilled over $LiAlH_4$. Granulated NaOH and KOH (Reakhim), $CsOH \cdot 2H_2O$, and 50% aqueous RbOH (Aldrich) were used.

(*S*)-Proline **3a** and (2*S*,4*R*)-4-hydroxyproline **3b** (Aldrich) were used. (2*S*,3*R*)-3-Phenylproline **3c**, (2*S*,3*S*)-3-methylproline **3d**, and (2*S*)-5-methylproline **3e** (*cis*/*trans* = 1/1) were prepared as described in Ref. 24. Amino carboxylates **3a—e** were synthesized by adding an equivalent of the corresponding metal hydroxide in aqueous ethanol with subsequent removal of the solvent according to the known procedure.[12] (*S*)-Prolinol **4** was obtained by the reduction of (*S*)-proline.[9] (*S*)-(+)-2-Amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, **5a**) and its *N*-derivatives were prepared according to the published procedure.[23] Sodium and potassium derivatives were obtained *in situ* by the reactions of amino alcohol **4** and amino phenols **5a—e** (M = H) with an equimolar amount of a base (NaH or Bu^tOK) in CH_2Cl_2 immediately before use according to the known procedure.[11]

The Michael addition of diethyl malonate to crotonaldehyde (general procedure). A mixture of diethyl malonate (2.72 g, 17 mmol) and crotonaldehyde (1.19 g, 17 mmol) in 10 mL of CH_2Cl_2 was stirred with a salt of (*S*)-proline **3a** (1.7 mmol) at 18 °C for 18 h. After 2*M* HCl was added, the products were extracted twice with CH_2Cl_2. The combined extracts were washed with water, dried with $MgSO_4$, filtered, concentrated, passed through a layer of silica gel (3—5 cm), and concentrated. The resulting mixture was analyzed by ^{1}H NMR spectroscopy in the presence of a certain amount of AcOH to determine the yield of compound (*S*)-**1**. The product was additionally purified by preparative TLC on silica gel in hexane—ethyl acetate (3 : 1).[15—17] Found (%): C, 56.94; H, 7.83. $C_{11}H_{18}O_5$. Calculated (%): C, 57.39; H, 7.88. For (*S*)-**1** $[\alpha]_D^{20}$ +5.5 (*c* 0.66, $CHCl_3$), *ee* 25% (*S*) was determined by ^{1}H NMR spectroscopy for diastereomeric derivatives (see below). ^{1}H NMR ($CDCl_3$), δ: 1.05 (d, 3 H, MeCH, *J* = 6.8 Hz); 1.25 (t, 6 H, 2 Me, *J* = 7.0 Hz); 2.60 (m, 3 H, $CHCH_2$); 3.34 (d, 1 H, $CH(COOR)_2$, *J* = 6.8 Hz); 4.18 (q, 4 H, 2 CH_2, *J* = 7.0 Hz); 9.75 (dd, 1 H, CH, *J* = 1.7 and 0.9 Hz). The literature data[15—17] for ethyl 2-ethoxycarbonyl-3-methyl-5-oxopentanoate **1**: b.p. 105 °C (0.5 Torr). ^{1}H NMR ($CDCl_3$), δ: 1.08 (d, 3 H, Me, *J* = 6.8 Hz); 1.29 (t, 6 H, *J* = 7.0 Hz); 2.77 (m, 3 H); 3.42 (d, 1 H, *J* = 6.8 Hz); 4.23 (q, 4 H, *J* = 7.0 Hz); 9.8 (dd, 1 H, *J* = 1.7 and 0.9 Hz).

Diastereomeric Schiff bases (**2**) were synthesized from equimolar amounts of compound **1** and (*R*)-methylbenzylamine by mixing them in CH_2Cl_2 with addition of an excess of $MgSO_4$. After one day, filtration followed by concentration gave compound **2** in >90% yield as a mixture of (*S*,*R*)- and (*R*,*R*)-diastereomers. ^{1}H NMR ($CDCl_3$), δ: 0.95, 1.00 (both d, 3 H, MeCH, *J* = 6.8 Hz); 1.18, 1.23 (both t, 6 H, 2 Me, *J* = 7.0 Hz); 1.42 (d, 3 H, MeCH(Ph), *J* = 6.4 Hz); 2.12—2.63 (m, 3 H, $CHCH_2$); 3.28 (d, 1 H, $CH(COOR)_2$, *J* = 7.6 Hz); 4.08—4.15 (m, 5 H, 2 (CH_2)+MeCH(Ph)); 7.1—7.3 (m, 5 H, Ph); 7.6 (s, 1 H, CH=). The diastereomeric excess for compounds **2** was determined as a difference between the intensities of signals for the $MeCH(CHR)CH_2$ fragment in the ^{1}H NMR spectra at δ 0.95 and 1.00, corresponding to (*S*,*R*)- and (*R*,*R*)-diastereomers. The *ee* values of **3a** for a series of repeated experiments was reproduced with an accuracy of 1% (relative).

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