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Chiral Tertiary Amine/L-Proline Cocatalyzed Enantioselective Morita–Baylis–Hillman (MBH) Reaction

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Keywords: Chirality / Amines / Organocatalysis / Asymmetric catalysis / Morita–Baylis–Hillman reactions / Enantioselectivity

Four types of chiral amines have been synthesized starting from readily available chiral sources. These chiral amines in combination with L-proline have been found to be efficient cocatalysts for the asymmetric Morita–Baylis–Hillman (MBH) reaction between methyl vinyl ketone (MVK) and aromatic aldehydes. The corresponding adducts were formed in reasonable chemical yields and with good enantioselectivities (up to 83% *ee*). Moreover, parallel cocatalytic reactions with the two enantiomers of chiral amine **4** and L-proline revealed that it is the proline stereochemistry that determines the configuration of the newly formed chiral center. In addition, the existence of the free hydroxy group in amine **4a** enhanced the enantioselectivity of the reaction. Based on these findings, a plausible mechanism for this cocatalytic MBH reaction has been proposed.

Introduction

Recently, the tertiary-amine-catalyzed asymmetric Morita–Baylis–Hillman (MBH) reaction has attracted much attention and significant progress has been witnessed in this area.[1] The tertiary amines that have been employed as the catalyst in this reaction can be classified into the following four categories. (1) Chiral tertiary amines without a free hydroxy group that functions as a nucleophile to promote the Michael addition onto activated alkenes.[2] (2) Chiral tertiary amines containing a free hydroxy group. The existence of a suitably positioned hydroxy group can stabilize the enolate intermediate through a hydrogen-bonding interaction between the hydroxy group and the enolate formed in the reaction.[3] (3) Chiral tertiary amines in combination with a Lewis acid or Brønsted acid which acts as cocatalyst in the MBH reaction.[4] (4) Achiral tertiary amines with a chiral Lewis acid or Brønsted acid as a cocatalyst.[5] Only a few examples of tertiary amines without free hydroxy groups have been documented because of their poor enantioselectivities. The best result (75% *ee*) in the coupling of methyl vinyl ketone (MVK) with an aromatic aldehyde was obtained by Hayashi et al.[2d] The second type of tertiary amine catalysts seems more important and efficient. Among them, the alkaloids quinine or quinidine and their derivatives demonstrated good catalytic activity. Hatakeyama and coworkers, employing a quinidine derivative as the catalyst, attained an enantioselectivity of up to 91% *ee*. However, the activated alkene was limited to 1,1,1,3,3,3-hexafluoro-2-propyl acrylate.[3f–3j] By employing the same catalyst Hatakeyama and coworkers also developed a highly diastereoselective racemization-free MBH reaction of chiral *N*-Boc-α-amino aldehydes for the preparation of highly enantiomerically pure α-methylene-β-hydroxy-γ-amino acid derivatives.[3k] Shi and Jiang reinvestigated Hatakeyama's catalyst. Enantioselectivities of 92 and 49% *ee* were obtained when α-naphthyl acrylate and MVK were used as the substrate, respectively.[3l] Krishna et al. reported L-prolinol-catalyzed MBH reaction of MVK with aryl aldehydes in which up to 78% *ee* was obtained.[3m] Recently, some examples of the third type of catalysts were reported. Barrett et al. reported the chiral pyrrolizidine-catalyzed reaction of ethyl vinyl ketone and aromatic aldehydes. The best enantioselectivity of 72% *ee* was observed in the presence of $NaBF_4$.[4a] Miller and coworkers developed an efficient cocatalytic system of L-proline and peptides for the asymmetric MBH reaction of MVK and aromatic aldehydes. The corresponding adducts were formed with up to 81% *ee*.[4b,4c] Only a few catalytic systems of the fourth category have been reported. The achiral weak base imidazole and L-proline cocatalyzed MBH reaction between MVK and aryl aldehydes was examined by Shi et al. Although a rate acceleration of the reaction was clearly observed, the enantioselectivities of the reaction were quite low (5–10% *ee*).[5a] The combination of 1,4-diazabicyclo-[2.2.2]octane (DABCO) and a chiral Lewis acid, formed by treatment of a D-camphor-derived diimino ligand and La-

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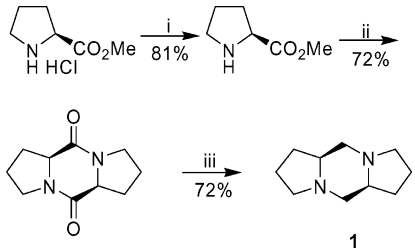
$(OTf)_3$, provided high enantioselectivity (up to 95% *ee*) in an acrylate-based MBH reaction.[5b] Most recently, by using a cocatalyst system involving *N*-methylimidazole and pipecolinic acid, Miller and coworkers realized a catalytic asymmetric intermolecular MBH reaction in which an *ee* of 84% was achieved.[5c] Although only a few examples have been documented for the third type of catalyst, which is supposed to mediate the reaction by dual activation of the electrophile and the nucleophile,[6] it is attracting more and more attention from organic chemists because of its efficacy in rate acceleration and enantioselectivity improvement in asymmetric MBH reactions. Our group has developed some chiral tertiary amine/L-proline cocatalytic systems for the MBH reaction in which enantioselectivities of up to 83% have been observed. This was the best result to be obtained in MVK-based MBH reactions prior to this work. The preliminary results of this work have already been communicated.[7] Herein, the full details of the scope and limitations and the mechanistic insights of this catalytic, asymmetric MBH reaction are described.

Results and Discussion

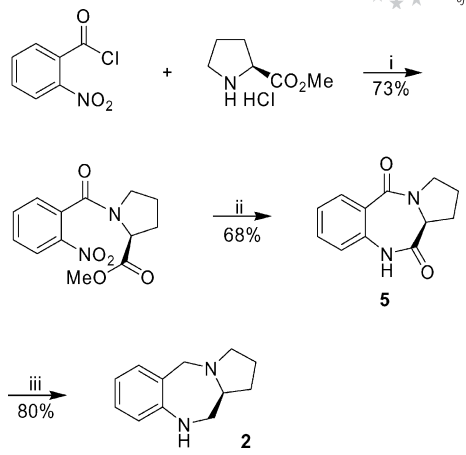
Synthesis of Catalysts

Following Breitmaier and Zadel's procedure,[8] dimerization of L-proline methyl ester and then reduction of the corresponding cyclic dipeptide gave (5a*S*,10a*S*)-(+)-octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine (**1**) (Scheme 1).



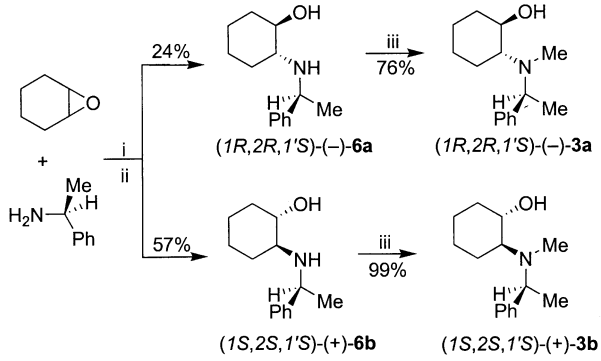
Scheme 1. Reagents and conditions: i. 50% K_2CO_3, 0 °C; ii. 105 °C; iii. $LiAlH_4$/THF, room temp.→reflux temp., N_2.

Chiral tricyclic benzodiazepine **5** was synthesized starting from *o*-nitrobenzoic acid and L-proline methyl ester hydrochloride (Scheme 2). Many procedures for the synthesis of **5** have been reported in which the common starting material is 2-azidobenzoic acid[9] or anthranilic acid (2-aminobenzoic acid).[10] The use of *o*-nitrobenzoic acid as the starting material shortens the access to **5**. Most importantly, **5** was obtained in good chemical yield in the key reduction ring-closing step by utilizing cheap and readily available iron filings as the reductant. Further reduction of **5** provided **2**. This convenient and practical method may be useful for the synthesis of chiral benzodiazepine pharmaceuticals.



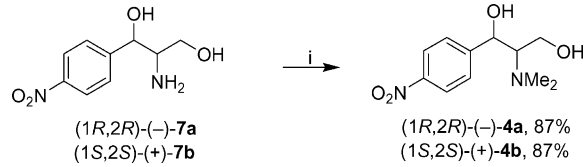
Scheme 2. Reagents and conditions: i. Et_3N/CH_2Cl_2, 0 °C; ii. Fe/AcOH, 110 °C; iii. $LiAlH_4$/THF, –10 °C→reflux temp., N_2.

In accord with Juaristic and coworkers' procedure,[11] the ring-opening of cyclohexene oxide readily took place in the presence of anhydrous lithium perchlorate. The corresponding diastereomeric 2-aminocyclohexanols **6a** (minor, 24%) and **6b** (major, 57%) were separated by column chromatography on silica gel. Further, *N*-methylation of **6a** and **6b** with formaldehyde and formic acid afforded **3a** and **3b**, respectively (Scheme 3).



Scheme 3. Reagents and conditions: i. $LiClO_4$/MeCN, reflux, 18 h; ii. separation of diastereomers by column chromatography; iii. HCO_2H/HCHO, reflux, 4 h.

As the precursor of the antibiotic chloramphenicol, (1*R*,2*R*)-(–)- and (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**7**) are readily available from industrial products. Chiral tertiary amine **4** was most conveniently obtained by *N*,*N*-dimethylation of **7** (Scheme 4).[12]



Scheme 4. Reagents and conditions: HCO_2H/HCHO, reflux, 4 h.

Catalyst Evaluation

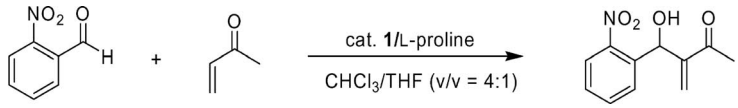
With these chiral tertiary amines in hand, we then carried out the asymmetric MBH reaction, employing the amines as the catalysts. The reaction of *o*-nitrobenzaldehyde and MVK was selected as a model reaction. Almost no reaction was observed after stirring for several days at 20 °C when each of the prepared tertiary amines was employed alone as the catalyst. However, the reactions readily took place with good results on addition of L-proline as an additive (Tables 1, 2, 3, and 4).

Evaluation of results revealed that the solvent has a significant influence on the enantioselectivity of the reaction; for all the reactions, the best enantioselectivities were obtained in a mixture of $CHCl_3$/THF (4:1, v/v) no matter what combination of cocatalyst was employed (Table 1, entry 1, 66% *ee*; Table 2, entry 6, 83% *ee*; Table 3, entry 3, 81% *ee*; Table 4, entry 7, 82% *ee*). In our previous work, polar solvents such as water were found to stabilize the widely accepted charged transition states and intermediates through intermolecular charge–dipole interactions as well as by hydrogen-bonding interactions.[13] These stabilizing interactions, in part, contributed to the observed effect of water dramatically promoting the MBH reaction. However, the addition of water had a detrimental effect on the reaction with the cocatalytic system. For example, the adduct from the **2**/L-proline-catalyzed MBH reaction was obtained in 50% yield with 35% *ee* (Table 2, entry 4). With the addition of water, a clear decrease both in yield and selectivity was observed (19% yield, 3% *ee*).

Comparison of the reactions carried out at different temperatures (0, 20 and 40 °C, respectively, see Table 2, entries 6, 11 and 12, Table 3, entries 3, 8 and 9, Table 4, entries 7, 14 and 15) shows that 20 °C (room temperature) is the optimum reaction temperature for the reaction. Lowering of the temperature results in a decrease both in chemical yield and stereoselectivity. Raising the temperature accelerates the reaction and leads to an increase in yield but a dramatic decrease in the enantiomeric excesses.

It was proved that the catalyst loading and molar ratio of the tertiary amine to L-proline was also an important factor in the reaction. The optimum catalyst loading and molar ratio of catalyst to L-Pro varied depending on the catalyst employed. For example, the best result was obtained with 5 mol-% of **1** and 1:1 of **1** to L-Pro (Table 1,

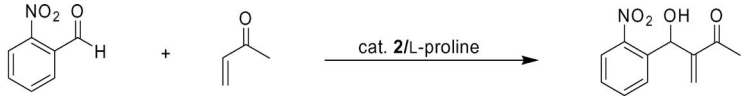
Table 1. Chiral amine **1**/L-proline cocatalyzed MBH reaction between MVK and *o*-nitrobenzaldehyde.[a]



Entry	**1** [mol-%]	**1**/L-Pro	Time [d]	% Yield[b]	% *ee*[c]	Configuration[d,e]
1	5	1:1	5	79	66	*R*
2	10	1:1	2	97	17	*R*
3	3	1:1	7	60	35	*R*
4	5	2:1	6	61	47	*R*
5	5	1:2	4	80	51	*R*

[a] All the reactions were conducted at 20 °C. [b] Isolated yield. [c] Determined by HPLC analysis on a chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.7 mL/min, R_t = 32.8 and 36.6 min. [d] Assigned based on the literature optical rotation value.[4b] [e] The previously reported absolute configuration of the MBH adduct in ref.[7a] is wrong.

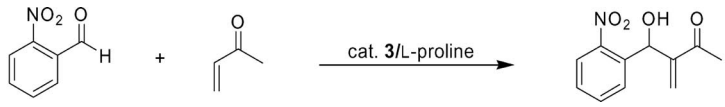
Table 2. Chiral amine **2**/L-proline cocatalyzed MBH reaction between MVK and *o*-nitrobenzaldehyde.



Entry	**2** [mol-%]	**2**/L-Pro	Solvent[a]	Temp. [°C]	Time [d]	% Yield[b]	% *ee*[c]	Configuration[d]
1	5	2:1	DMF	20	3	34	52	*S*
2	5	2:1	CH_3CN	20	3	53	75	*R*
3	5	2:1	THF	20	5	80	63	*R*
4	5	2:1	CH_3OH	20	8	50	35	*R*
5	5	2:1	THF/$CHCl_3$		5	82	58	*R*
6	5	2:1	$CHCl_3$/THF	20	5	68	83	*R*
7	5	3:1	$CHCl_3$/THF	20	45	45	27	*R*
8	5	1:1	$CHCl_3$/THF	20	7	55	26	*R*
9	10	2:1	$CHCl_3$/THF	20	3	78	63	*R*
10	3	2:1	$CHCl_3$/THF	20	7	71	45	*R*
11	5	2:1	$CHCl_3$/THF	0	8	50	76	*R*
12	5	2:1	$CHCl_3$/THF	40	3	77	27	*R*

[a] All the mixed solvents were used in a ratio of 4:1 (v/v). [b] Isolated yield. [c] Determined by HPLC analysis on a chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.7 mL/min, R_t = 32.8 and 36.6 min. [d] Assigned based on the literature optical rotation value.[4b]

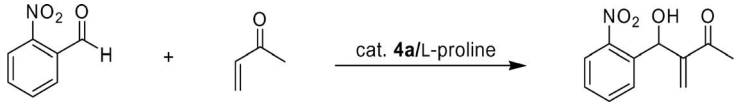
Table 3. Chiral amine **3**/L-proline cocatalyzed MBH reaction between MVK and *o*-nitrobenzaldehyde.



Entry	**3** [mol-%]	**2**/L-Pro	Solvent[a]	Temp. [°C]	Time [d]	% Yield[b]	% *ee*[c]	Configuration[d]
1	**3a**, 30	1:1	CH_3CN	20	5	88	17	*R*
2	**3a**, 30	1:1	THF	20	5	83	12	*R*
3	**3a**, 30	1:1	$CHCl_3$/THF	20	6	66	81	*R*
4	**3a**, 30	1:2	$CHCl_3$/THF	20	3	77	35	*R*
5	**3a**, 30	2:1	$CHCl_3$/THF	20	7	35	54	*R*
6	**3a**, 40	1:1	$CHCl_3$/THF	20	4	84	74	*R*
7	**3a**, 20	1:1	$CHCl_3$/THF	20	7	56	61	*R*
8	**3a**, 30	1:1	$CHCl_3$/THF	0	6	56	29	*R*
9	**3a**, 30	1:1	$CHCl_3$/THF	40	3	70	26	*R*
10	**3b**, 30	1:1	$CHCl_3$/THF	20	7	61	51	*R*

[a] All the mixed solvents were used in a ratio of 4:1 (v/v). [b] Isolated yield. [c] Determined by HPLC analysis on a chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.7 mL/min, R_t = 32.8 and 36.6 min. [d] Assigned based on the literature optical rotation value.[4b]

Table 4. Chiral amine **4a**/L-proline cocatalyzed MBH reaction between MVK and *o*-nitrobenzaldehyde.



Entry	**4a** [mol-%]	L-Proline [mol-%]	Solvent [a]	Temp. [°C]	Time [d]	% Yield[b]	% *ee*[c]	Configuration[d]
1	10	30	MeCN	20	5	73	45	*R*
2	10	30	THF	20	5	76	77	*R*
3	10	30	$F_2CHCF_2CH_2OH$	20	5	37	52	*R*
4	10	30	$CHCl_3$/MeCN	20	5	60	68	*R*
5	10	30	THF/MeCN	20	5	27	63	*R*
6	10	30	CH_3CN/THF	20	5	54	67	*R*
7	10	30	$CHCl_3$/THF	20	5	64	82	*R*
8	5	15	$CHCl_3$/THF	20	7	52	44	*R*
9	20	60	$CHCl_3$/THF	20	3.5	52	45	*R*
10	10	10	$CHCl_3$/THF	20	5	49	66	*R*
11	10	5	$CHCl_3$/THF	20	6	53	82	*R*
12	10	40	$CHCl_3$/THF	20	14	45	59	*R*
13	10	20	$CHCl_3$/THF	20	5.5	74	74	*R*
14	10	30	$CHCl_3$/THF	0	6	44	72	*R*
15	10	30	$CHCl_3$/THF	40	2	76	19	*R*

[a] All the mixed solvents were used in a ratio of 4:1 (v/v). [b] Isolated yield. [c] Determined by HPLC analysis on a chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.7 mL/min, R_t = 32.8 and 36.6 min. [d] Assigned based on the literature optical rotation value.[4b]

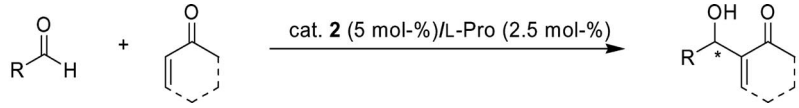
entry 1, 66% *ee*). For the catalyst **2**, the highest *ee* value (83%) was also observed with a catalyst loading of 5 mol-%, but with a 2:1 molar ratio of **2** to L-Pro (Table 2, entry 6). The optimum catalyst system involving **3** consists of 30 mol-% of chiral amine **3a** and 30 mol-% of L-proline, affording an enantioselectivity of 81% *ee* (Table 3, entry 3). For the catalytic system of amine **4a** and L-proline, 10 mol-% of **4a** and a 1:3 molar ratio of **4a** to L-Pro was the optimum choice (Table 4, entry 7, 82% *ee*).

Substrate Scope

Based on these results, a set of aromatic aldehydes was employed in reactions with different activated alkenes under the optimized reaction conditions for chiral amines **2**, **3a**, and **4a**, respectively. The experimental results are listed in Tables 5, 6, and 7.

As shown in Tables 5, 6, and 7, these cocatalytic systems demonstrate a moderate substrate generality. The electron-deficient aromatic aldehydes were converted into the corresponding MBH adducts in fair-to-good yields with acceptable reaction times. Moreover, good enantioselectivities were observed for those aldehydes bearing a nitro group on the benzene ring. Moderate enantiomeric excesses were obtained for other aromatic aldehydes substituted with electron-withdrawing groups. As for the activated alkenes, MVK proved to be the most suitable. Others, such as 2-cyclohexenone and acetonitrile, exhibit poor reactivity in this reaction. Although almost the same highest *ee* value was observed for the catalysts **2**, **3a** and **4a** (83, 81 and

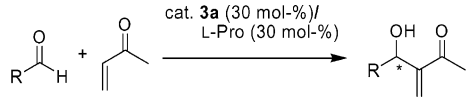
Table 5. Chiral amine **2**/L-proline cocatalyzed MBH reaction.



Entry	R	Activated alkene	Time [d]	% Yield[a]	% *ee*[b]
1	2-nitrophenyl	MVK	5	68	83
2	3-nitrophenyl	MVK	4	76	59
3	3-methoxy-2-nitrophenyl	MVK	10	66	52
4	4-chloro-2-fluorophenyl	MVK	5	66	31
5	5-chloro-2-nitrophenyl	MVK	5	54	32
6	1-nitro-2-naphthyl	MVK	5	70	46
7	2-nitrophenyl	2-cyclohexenone	8	44	37

[a] Isolated yield. [b] Determined by HPLC analysis with a chiral column.

Table 6. Chiral amine **3a**/L-proline cocatalyzed MBH reaction.



Entry	R	Time [d]	% Yield[a]	% *ee*[b]
1	2-nitrophenyl	6	66	81
2	3-nitrophenyl	5	56	63
3	3-methoxy-2-nitrophenyl	8	60	59
4	4-chloro-2-fluorophenyl	7	71	49
5	3-fluorophenyl	10	66	46
6	1-nitro-2-naphthyl	5	73	61

[a] Isolated yield. [b] Determined by HPLC analysis with a chiral column.

82%, respectively), we recommend **4a**/L-proline as the most suitable reaction system in terms of both the availability of the catalyst and substrate generality.

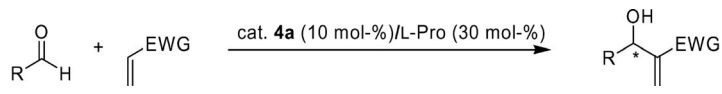
Match/Mismatch Effect Between the Chiralities of Chiral Amines and L-Proline

The performance of parallel cocatalytic reactions with chiral amine **4a** (or **4b**) and L-proline revealed this cocatalyst system displayed a clear match/mismatch effect between the chiralities of the chiral amine **4** and L-proline. The combination of L-proline and (1*R*,2*R*)-(–)-**4a** afforded the best results (82% *ee*). Replacement of the *R*,*R* amine by the *S*,*S* amine resulted in a decrease in the enantioselectivity (69% *ee*). However, both cocatalysts (–)-**4a**/L-proline and (+)-**4b**/L-proline produced the *R* adduct, indicating that the configuration of the newly formed chiral center was determined by the chirality of the proline. The same phenomenon was also observed for the chiral amine **3**. Under the same conditions, diastereomeric **3b** gave much lower selectivity (Table 3, entries 3 and 10, 81 vs. 51% *ee*). This result implies that **3b** and L-proline constitute a mismatched cocatalyst.

Preliminary Mechanistic Survey

We have chosen (1*R*,2*R*)-2-dimethylamino-1-(4-nitrophenyl)-1,3-propanediol (**4a**) as the example to investigate whether the free hydroxy group in the chiral amine plays a major role in chirality induction in the MBH reaction. Thus, the following compounds were synthesized

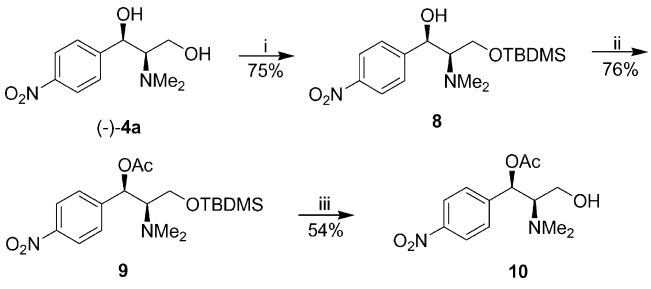
Table 7. Chiral amine **4a**/L-proline cocatalyzed MBH reaction.



Entry	R	Activated alkene	Time [d]	% Yield[a]	% *ee*[b]
1	2-nitrophenyl	MVK	5	64	82
2	3-nitrophenyl	MVK	5	92	72
3	3-methoxy-2-nitrophenyl	MVK	8	70	52
4	4-chloro-2-fluorophenyl	MVK	6	79	37
5	1-naphthyl	MVK	10	46	39
6	1-nitro-2-naphthyl	MVK	5	91	54
7	2-pyridinyl	MVK	6	71	30
8	2-nitrophenyl	methyl acrylate	7	46	55
9	2-nitrophenyl	2-cyclohexenone	7	50	41
10	2-nitrophenyl	acetonitrile	10	36	13

[a] Isolated yield. [b] Determined by HPLC analysis with a chiral column.

(Scheme 5) and employed as the catalyst in combination with L-proline in the coupling of *o*-nitrobenzaldehyde and MVK: Compound **4a** with the terminal hydroxy group masked as a silyl ether (**8**), with both hydroxy groups protected (**9**), and with the secondary alcohol selectively acetylated **10**. The results are listed in Table 8.



Scheme 5. Reagents and conditions: i. *t*BuMe$_2$SiCl, Et$_3$N, DMAP/CH$_2$Cl$_2$, 25 °C, 18 h; ii. AcCl, Et$_3$N, DMAP/CH$_2$Cl$_2$, 0–25 °C, 5 h; iii. *n*Bu$_4$NF/THF, 25 °C, 40 min.

Table 8. Catalytic activities of **4a** and its hydroxy-protected derivatives.[a]

Entry	Cocatalyst system	% Yield[b]	% *ee*[c]	Config.[d]
1	**4a**/L-proline	64	82	*R*
2	**8**/L-proline	49	25	*R*
3	**9**/L-proline	57	13	*R*
4	**10**/L-proline	57	15	*R*

[a] The coupling of *o*-nitrobenzaldehyde and MVK was carried out in CHCl$_3$/THF (4:1, v/v) at 20 °C for 5 days with 10 mol-% of catalyst in a 1:3 molar ratio of chiral amine **4a** to proline. [b] Isolated yield. [c] Determined by HPLC analysis on a chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.7 mL/min, R_t = 32.8 and 36.6 min. [d] Assigned based on the literature optical rotation value.[4b]

As shown in Table 8, a dramatic decrease in enantioselectivity as well as a small decrease in yield was observed with partial or total masking of the hydroxy group (Table 8, entries 2–4). Moreover, it is worth noting that the *ee* value obtained for catalyst **8** with a protected hydroxy group at the 1-position was higher than that of compound **10** with a terminal hydroxy group, which implies that the hydroxy group at the 1-position has a more important influence on the reaction and may participate in the formation of the transition state.

Currently the exact mechanism is still unclear for the chiral tertiary amine/L-proline cocatalyzed asymmetric MBH reaction. List and coworkers have thoroughly investigated L-proline-catalyzed direct asymmetric aldol reactions and assumed this reaction occurred via an enamine intermediate derived from L-proline.[14] This type of enamine intermediate also fits the chiral tertiary amine/L-proline cocatalyzed asymmetric MBH reaction.[4b,5a] Based on the enamine concept and the accepted traditional MBH reaction mechanism combined with the aforementioned findings, we have proposed a transition state for this reaction which is presented as a Newman projection along with the forming C–C bond in Figure 1.

First, nucleophilic attack of the amino group of proline and subsequent dehydration of the carbinol amine intermediate lead to the formation an iminium species. Michael addition of amine **4a** to the iminium then provides an enamine ion-pair. There may exist a favorable hydrogen-bonding interaction between the hydroxy group at the 1-position and the carboxylate. Then the enamine attacks the *re* face of the aromatic aldehyde carbonyl sp^2 carbon center leading to the desired (*R*)-hydroxy configuration.

Conclusion

In conclusion, some chiral tertiary amines have been synthesized starting from readily available chiral sources such as L-proline, (*S*)-α-phenylethylamine, and the precursor of the antibiotic chloramphenicol. These chiral amines have been successfully applied in combination with L-proline as efficient cocatalysts for the asymmetric MBH reaction be-

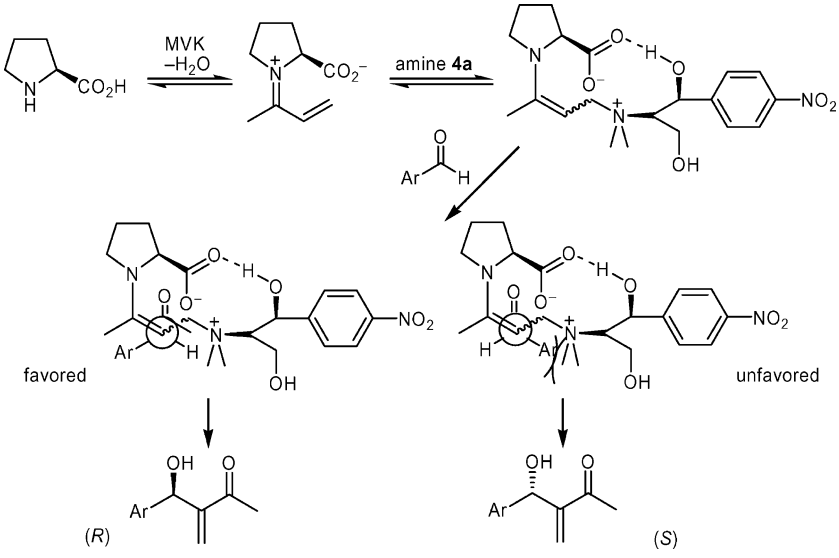


Figure 1. Transition state for the (–)-**4a**/L-proline-catalyzed MBH reaction between aromatic aldehyde and MVK.

tween aromatic aldehydes and MVK. The corresponding adducts were obtained in fair-to-good yields and with good enantioselectivity (up to 83% *ee*). Moreover, it was found that it is the proline stereochemistry that determines the configuration of the newly formed chiral center. In addition, the hydroxy groups at the 1,3-positions of amine **4a** play an important role in determining the enantioselectivity of the reaction. Based on the enamine concept and the traditional MBH reaction mechanism combined with the experimental results, a transition state for this reaction has been proposed.

Experimental Section

General: ^{1}H NMR spectra were recorded in $CDCl_3$ with a Bruker AMX-300 or Varian 400 MHz instrument using TMS as an internal standard. Specific rotations were measured with a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined with an HP-1100 instrument (chiral column; mobile phase: hexane/*i*PrOH). Elemental analyses were conducted with a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined with a T-4 melting point apparatus and are uncorrected.

(5a*S*,10a*S*)-(+)-Octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine (1): Compound **1** was prepared according to the literature procedure.[8] Pale yellow solid, 72% yield, m.p. 44–48 °C, $[\alpha]_D^{20}$ = +7.2 (*c* = 2.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.56–1.84 (m, 8 H), 2.37–2.48 (m, 4 H), 2.55–2.57 (m, 4 H), 2.76–2.83 (m, 2 H) ppm. $C_{10}H_{18}N_2$ (166.26): calcd. C 72.24, H 10.91, N 16.85; found C 72.17, H 10.77, N 16.71.

(*S*)-(+)-Benzodiazepinedione (5): Triethylamine (14.40 g, 141 mmol) was added to a stirred solution of L-proline methyl ester hydrochloride (10.60 g, 64 mmol) in dichloromethane (200 mL). Then a solution of *o*-nitrobenzoyl chloride (14.30 g, 77 mmol) in dichloromethane (50 mL) was added dropwise at 0 °C to the resulting mixture. After the addition was complete the reaction mixture was warmed gradually to room temperature and stirred for 18 h. The reaction mixture was diluted with dichloromethane, washed with water, and dried with anhydrous sodium sulfate. After removal of the solvent, the crude product was purified by column chromatography on silica gel (200–300 mesh, eluted with 2:1 petroleum ether/ethyl acetate) to afford *N*-(2-nitrobenzoyl)-L-proline methyl ester (12.89 g, 73.0%). ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 1.89–2.10 (m, 3 H), 2.21–2.39 (m, 1 H), 3.17–3.25 (m, 1 H), 3.30–3.38 (m, 1 H), 3.81 (s, 3 H, CH_3), 4.74 (dd, *J* = 8.1, 4.2 Hz, 1 H, NCH), 7.31–7.74 (m, 3 H_{ar}), 8.20 (d, *J* = 8.4 Hz, 1 H_{ar}) ppm.

Iron filings (25.20 g, 450 mmol) were added to a solution of *N*-(2-nitrobenzoyl)-L-proline methyl ester (12.51 g, 45 mmol) in glacial acetic acid (200 mL) at room temperature. The reaction mixture was heated at 110 °C until total consumption of the starting material (monitored by TLC, 4–6 h). After filtration the filtrate was extracted with chloroform (3 × 75 mL). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate until free of acid and dried with anhydrous sodium sulfate. After removal of solvent, the residue was recrystallized from water to afford the title compound as a pale yellow solid (6.51 g, 68.0%). M.p. 219–221 °C. ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 2.00–2.04 (m, 3 H), 2.74–2.80 (m, 1 H), 3.56–3.65 (m, 1 H), 3.77–3.84 (m, 1 H), 4.10 (d, *J* = 6.0 Hz, 1 H), 7.01 (d, *J* = 5.1 Hz, 1 H_{ar}), 7.25 (dt, *J* = 5.1, 1.2 Hz, 1 H_{ar}), 7.47 (dt, *J* = 7.8, 1.8 Hz, 1 H_{ar}), 8.00 (dt, *J* = 7.8, 1.5 Hz, 1 H_{ar}), 8.47 (s, 1 H, NH) ppm. $C_{12}H_{12}N_2O_2$ (216.23): calcd. C 66.65, H 5.59, N 12.96; found C 66.67, H 5.61, N 12.94.

(*S*)-(–)-Benzodiazepine (2): A suspension of lithium aluminium hydride (1.60 g, 142 mmol) in dry THF (42 mL) was added to a solution of compound **5** (3.02 g, 14 mmol) in dry THF (105 mL) at –10 °C under nitrogen. After the addition, the resulting mixture was warmed gradually to room temperature and then heated at reflux until total consumption of the starting material (monitored by TLC, 4–6 h). The reaction was cooled to 0 °C, quenched with careful addition of chilling water, and extracted with ethyl acetate (3 × 75 mL). The combined organic phase was washed with saturated brine and dried with anhydrous sodium sulfate. Removal of the solvent afforded the target compound with satisfactory purity (2.10 g, 80.0%). M.p. 102–104 °C, $[\alpha]_D^{20}$ = –177.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 1.41–1.54 (m, 1 H), 1.75–1.99 (m, 3 H), 2.44–2.63 (m, 2 H), 2.75 (dd, *J* = 12.6, 9.6 Hz, 1 H, one proton of NCH_2), 3.16 (dt, *J* = 8.4, 2.7 Hz, 1 H, CH), 3.33 (dd, *J* = 12.6, 1.5 Hz, 1 H, one proton of NCH_2), 3.52 (d, *J* = 13.5 Hz, 1 H, one proton of $PhCH_2$), 3.83 (d, *J* = 13.5 Hz, 1 H, one proton of $PhCH_2$), 3.86 (br., 1 H, NH), 6.72 (dd, *J* = 7.8, 0.6 Hz, 1 H_{ar}), 6.83 (dt, *J* = 7.5, 1.2 Hz, 1 H_{ar}), 7.04–7.13 (m, 2 H_{ar}) ppm. $C_{12}H_{16}N_2$ (188.26): calcd. C 76.55, H 8.57, N 14.88; found C 76.57, H 8.50, N 14.71.

2-(α-Phenylethylamino)cyclohexanol (6): Anhydrous lithium perchlorate (5.32 g, 50 mmol) was added to a solution of cyclohexene oxide (4.91 g, 50 mmol) in acetonitrile (10 mL). The resulting mixture was then stirred until complete solution of the salt. (*S*)-α-Phenylethylamine (6.06 g, 50 mmol) was added dropwise to the stirred clear solution at room temperature. Then the reaction mixture was refluxed for 18 h, diluted with water (20 mL), and extracted with diethyl ether (3 × 40 mL). The combined ethereal solution was dried with anhydrous sodium sulfate and evaporated under reduced pressure. The oily residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate/triethylamine = 10:1:0.1) to afford 2-aminocyclohexanol **6** as a pair of diastereoisomers.

6b: Pale yellow oil (first fractions, 6.21 g, 56.9%), $[\alpha]_{546}^{20}$ +0.82 (*c* = 1.1, MeOH). ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 0.98–1.16 (m, 4 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 1.57–1.68 (m, 3 H), 2.00–2.05 (m, 1 H), 2.25 (s, 3 H), 2.20–2.29 (m, 1 H), 3.34 (dt, *J* = 5.2, 9.9 Hz, 1 H), 3.72 (q, *J* = 6.9 Hz, 1 H), 3.89 (br., 1 H), 7.21–7.34 (m, 5 H_{ar}) ppm.

6a: Colorless crystal (later fractions, 2.65 g, 24.3%), m.p. 45–47 °C, $[\alpha]_{546}^{20}$ –109.6 (*c* = 1.2, MeOH). ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 1.17–1.27 (m, 4 H), 1.36 (d, *J* = 6.9 Hz, 3 H), 1.57–1.72 (m, 3 H), 2.05 (s, 3 H), 2.13–2.16 (m, 1 H), 2.62–2.70 (m, 1 H), 3.41 (dt, *J* = 5.2, 9.9 Hz, 1 H), 3.69 (q, *J* = 6.9 Hz, 1 H), 3.95 (br., 1 H), 7.24–7.34 (m, 5 H_{ar}) ppm.

(–)-(1*R*,2*R*,1′*S*)- (3a) and (+)-(1*S*,2*S*,1′*S*)-2-[Methyl(α-phenylethyl)-amino]cyclohexanol (3b): 2-Aminocyclohexanol **6** (2.19 g, 10 mmol), 37% aqueous formaldehyde solution (1.14 g, 14 mmol), and 85% formic acid (1.29 g, 28 mmol) were placed in a 25 mL round-bottomed flask. The resulting mixture was refluxed until the release of carbon dioxide had ceased (ca. 4 h). The excess formaldehyde and formic acid were removed under reduced pressure, then an aqueous ammonia solution (25%, 1.36 g) was added, and the resulting mixture was stirred at 80 °C for 20 min. After cooling to room temperature the reaction mixture was extracted with dichloromethane (3 × 30 mL). Evaporation of the dried (anhydrous sodium sulfate) solution gave the crude product **3** which was further purified by column chromatography on silica gel (200–300 mesh, gradient elution with petroleum ether and ethyl acetate).

3b: Colorless crystal (1.77 g, 76%), m.p. 72–74 °C, $[\alpha]_D^{20}$ = +45.2 (*c* = 1.0, MeOH). ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 0.98–1.16 (m, 4 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 1.57–1.68 (m, 3 H), 2.00–2.05 (m, 1 H), 2.25 (s, 3 H), 2.20–2.29 (m, 1 H), 3.34 (dt, *J* = 5.2, 9.9 Hz, 1

H), 3.72 (q, J = 6.9 Hz, 1 H), 3.89 (br., 1 H), 7.21–7.34 (m, 5 H_{ar}) ppm. $C_{15}H_{23}NO$ (233.34): calcd. C 77.20, H 9.94, N 6.00; found C 77.45, H 9.84, N 6.07.

3a: Pale yellow oil (2.31, 99%), $[\alpha]_D^{20}$ = –68.2 (c = 1.0, MeOH). ^1H NMR ($CHCl_3$, 300 MHz): δ = 1.17–1.27 (m, 4 H), 1.36 (d, J = 6.9 Hz, 3 H), 1.57–1.72 (m, 3 H), 2.05 (s, 3 H), 2.13–2.16 (m, 1 H), 2.62–2.70 (m, 1 H), 3.41 (dt, J = 5.2, 9.9 Hz, 1 H), 3.69 (q, J = 6.9 Hz, 1 H), 3.95 (br., 1 H), 7.24–7.34 (m, 5 H_{ar}) ppm. $C_{15}H_{23}NO$ (233.34): calcd. C 77.20, H 9.94, N 6.00; found C 77.20, H 9.90, N 6.16.

(1*R*,2*R*)- (4a) and (1*S*,2*S*)-2-(Dimethylamino)-1-(4-nitrophenyl)-1,3-propanediol (4b): Chiral tertiary amine **4** was prepared according to the literature procedure.[12]

4a: M.p. 97.5–99 °C, $[\alpha]_D^{20}$ –26.2 (c = 1, EtOH).

4b: M.p. 97–97.5 °C, $[\alpha]_D^{20}$ = +26.5 (c = 1, EtOH).

(1*R*,2*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(dimethylamino)-1-(4-nitrophenyl)-1-propanol (8):[15] Compound **4a** (1.20 g, 5 mmol), *tert*-butylchlorodimethylsilane (0.83 g, 5.5 mmol), triethylamine (0.56 g, 5.5 mmol), DMAP (0.05 g, 0.2 mmol), and dichloromethane (25 mL) were placed in a 50 mL flask. The resulting mixture was stirred at room temperature for 18 h (monitored by TLC), then washed with water, and the aqueous layer was extracted with dichloromethane. The combined organic phase was washed with brine and dried with anhydrous sodium sulfate. After removal of the solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient elution with petroleum ether and ethyl acetate) to afford compound **8** as a colorless oil (1.16 g, 73%). $[\alpha]_D^{20}$ = +16.2 (c = 1, $CHCl_3$). ^1H NMR ($CHCl_3$, 400 MHz): δ = –0.04 (s, 3 H), –0.03 (s, 3 H), 0.87 (s, 9 H), 2.46–2.50 (m, 8 H), 3.46 (dd, J = 6.0, 11.2 Hz, 1 H), 3.64 (dd, J = 2.8, 11.2 Hz, 1 H), 4.62 (d, J = 9.6 Hz, 1 H), 7.60 (d, J = 8.8 Hz, 2 H_{ar}), 8.20 (d, J = 8.8 Hz, 2 H_{ar}) ppm.

(1*R*,2*R*)-1-Acetoxy-3-(*tert*-butyldimethylsiloxy)-2-(dimethylamino)-1-(4-nitrophenyl)propane (9): A solution of acetyl chloride (1 mL) in dichloromethane (5 mL) was added dropwise to a stirred solution of **8** (0.71 g, 2 mmol), DMAP (0.05 g, 0.2 mmol), and triethylamine (1 mL) in dichloromethane (5 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 5 h (monitored by TLC). The reaction mixture was successively washed with water and brine and then dried with anhydrous sodium sulfate. After removal of the solvent the residue was purified by column chromatography on silica gel (200–300 mesh, gradient elution with petroleum ether and ethyl acetate) to provide compound **9** as a colorless oil (0.60 g, 76%). $[\alpha]_D^{20}$ –56.5 (c = 1, $CHCl_3$). ^1H NMR ($CHCl_3$, 400 MHz): δ = –0.05 (s, 3 H), –0.02 (s, 3 H), 0.88 (s, 9 H), 2.11 (s, 3 H), 2.45 (s, 6 H), 2.87–2.91 (m, 1 H), 3.40 (dd, J = 4.8, 10.8 Hz, 1 H), 3.72 (dd, J = 4.4, 10.4 Hz, 1 H), 6.08 (d, J = 7.6 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 2 H_{ar}), 8.19 (d, J = 8.4 Hz, 2 H_{ar}) ppm. $C_{19}H_{32}N_2O_5Si$ (396.55): calcd. C 57.54, H 8.13, N 7.06; found C 57.45, H 8.64, N 6.91.

(1*R*,2*R*)-3-Acetoxy-2-(dimethylamino)-3-(4-nitrophenyl)-1-propanol (10): A mixture of **9** (0.77 g, 2 mmol) and tetrabutylammonium fluoride (1.57 g, 6 mmol) in THF (10 mL) was stirred at room temperature for 40 min. The reaction mixture was diluted with water (10 mL) and then extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried with anhydrous sodium sulfate. After removal of the solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient elution with petroleum ether and ethyl acetate) to give compound **10** as a colorless oil (0.31 g, 54% yield). $[\alpha]_D^{20}$ = +27.8 (c = 1, $CHCl_3$). ^1H NMR ($CHCl_3$, 400 MHz): δ = 1.92 (s, 3 H), 2.49 (s, 6 H), 2.75–2.80 (m, 1 H), 4.02–4.05 (m, 3 H) 4.48 (d, J = 9.6 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 2 H_{ar}), 8.20 (d, J = 8.4 Hz, 2 H_{ar}) ppm. $C_{13}H_{18}N_2O_5$ (282.29): calcd. C 55.31, H 6.43, N 9.92; found C 55.42, H 6.54, N 10.01.

General Procedure for the Chiral Tertiary Amine/L-Proline Cocatalyzed MBH Reaction: Activated alkene (6 mmol) was added to a solution of aldehyde (2 mmol), chiral amine (as depicted in the text), and L-proline (as depicted in the text) in solvent (2.5 mL). The resulting mixture was stirred at 20 °C until completion of the reaction (monitored by TLC). After removal of the solvent, the residue was purified by column chromatography on silica gel (200–300 mesh, gradient elution with petroleum ether/ethyl acetate) to afford the product.

3-[Hydroxy(2-nitrophenyl)methyl]but-3-en-2-one:[4c] Yellow-brown solid, m.p. 80–82 °C. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.38 (s, 3 H, CH_3), 3.47 (br., 1 H, OH), 5.80 (s, 1 H, CH), 6.18 (s, 1 H, =CH), 6.22 (s, 1 H, =CH), 7.47 (t, J = 8.0 Hz, 1 H_{ar}), 7.66 (t, J = 8.0 Hz, 1 H_{ar}), 7.78 (d, J = 8.0 Hz, 1 H_{ar}), 7.98 (d, J = 8.0 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 90:10, flow rate 0.7 mL/min, R_t = 32.8 (minor) and 36.6 min (major).

3-[Hydroxy(3-nitrophenyl)methyl]but-3-en-2-one:[5a] Viscous oil. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.33 (s, 3 H, CH_3), 3.55 (s, 1 H, OH), 5.64 (s, 1 H, CH), 6.09 (s, 1 H, =CH), 6.27 (s, 1 H, =CH), 7.47 (t, J = 8.0 Hz, 1 H_{ar}), 7.69 (d, J = 8.0 Hz, 1 H_{ar}), 8.08 (d, J = 8.0 Hz, 1 H_{ar}), 8.18 (s, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 0.8 mL/min, R_t = 63.9 (minor) and 73.4 min (major).

3-[Hydroxy(3-methoxy-2-nitrophenyl)methyl]but-3-en-2-one:[4c] Viscous oil. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.34 (s, 3 H, CH_3), 3.47 (br., 1 H, OH), 3.89 (s, 3 H, OCH_3), 5.65 (s, 1 H, CH), 5.96 (s, 1 H, =CH), 6.23 (s, 1 H, =CH), 6.99 (d, J = 8.4 Hz, 1 H_{ar}), 7.13 (d, J = 8.4 Hz, 1 H_{ar}), 7.43 (t, J = 8.4 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 90:10, flow rate 1.0 mL/min, R_t = 36.8 (minor) and 42.4 min (major).

3-[(4-Chloro-2-fluorophenyl)hydroxymethyl]but-3-en-2-one: Viscous oil. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.34 (s, 3 H, CH_3), 3.64 (br., 1 H, OH), 5.78 (s, 1 H, CH), 5.88 (s, 1 H, =CH), 6.18 (s, 1 H, =CH), 7.18 (dd, J = 9.6, 1.6 Hz, 1 H_{ar}), 7.28 (dd, J = 8.0, 1.6 Hz, 1 H_{ar}), 7.34 (t, J = 8.0 Hz, 1 H_{ar}) ppm. $C_{11}H_{10}ClFO_2$ (228.64): calcd. C 57.78, H 4.41; found C 57.64, H 4.25. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 1.0 mL/min, R_t = 32.7 (minor) and 34.6 min (major).

3-[(5-Chloro-2-nitrophenyl)hydroxymethyl]but-3-en-2-one:[16] Colorless crystal, m.p. 85–85.5 °C. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.39 (s, 3 H, CH_3), 3.54 (br., 1 H, OH), 5.75 (s, 1 H, CH), 6.17 (s, 1 H, =CH), 6.24 (s, 1 H, =CH), 7.42 (dd, J = 8.8, 2.0 Hz, 1 H_{ar}), 7.78 (d, J = 2.0 Hz, 1 H_{ar}), 7.96 (d, J = 8.8 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 0.8 mL/min, R_t = 20.3 (major) and 26.6 min (minor).

3-[Hydroxy(1-nitro-2-naphthyl)methyl]but-3-en-2-one:[4c] Viscous oil. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.36 (s, 3 H, CH_3), 3.57 (br., 1 H, OH), 5.89 (s, 1 H, CH), 6.01 (s, 1 H, =CH), 6.29 (s, 1 H, =CH), 7.58–7.78 (m, 4 H_{ar}), 7.90 (d, J = 8.0 Hz, 1 H_{ar}), 7.99 (d, J = 8.0 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 93:7, flow rate 0.75 mL/min, R_t = 52.5 (minor) and 59.5 min (major).

3-[(3-Fluorophenyl)methyl]hydroxybut-3-en-2-one:[17] Viscous oil. ^1H NMR ($CHCl_3$, 400 MHz): δ = 2.35 (s, 3 H, CH_3), 3.27 (br., 1 H, OH), 5.58 (d, J = 3.6 Hz, 1 H, CH), 5.99 (s, 1 H, =CH), 6.22 (s, 1 H, =CH), 6.95 (dt, J = 8.0, 2.4 Hz, 1 H_{ar}), 7.08 (dd, J = 10.0,

2.0 Hz, 1 H_{ar}), 7.12 (d, J = 8.0 Hz, 1 H_{ar}), 7.27–7.32 (m, 1 H_{ar}) ppm. HPLC conditions: OD-H column, hexane/2-propanol = 90:10, flow rate 1.0 mL/min, R_t = 18.1 (minor) and 19.4 min (major).

3-[Hydroxy(1-naphthyl)methyl]but-3-en-2-one:[18] Viscous oil. ^{1}H NMR ($CHCl_3$, 400 MHz): δ = 2.35 (s, 3 H, CH_3), 3.24 (br., 1 H, OH), 5.66 (s, 1 H, CH), 6.19 (s, 1 H, =CH), 6.45 (s, 1 H, =CH), 7.47–7.52 (m, 3 H_{ar}), 7.67 (d, J = 7.2 Hz, 1 H_{ar}), 7.82 (d, J = 8.0 Hz, 1 H_{ar}), 7.86–7.89 (m, 2 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 1.0 mL/min, R_t = 37.7 (minor) and 45.4 min (major).

3-[Hydroxy(2-pyridyl)methyl]but-3-en-2-one:[5a] Viscous oil. ^{1}H NMR ($CHCl_3$, 400 MHz): δ = 2.33 (s, 3 H, CH_3), 4.81 (br., 1 H, OH), 5.69 (s, 1 H, CH), 6.15 (s, 1 H, =CH), 6.21 (s, 1 H, =CH), 7.15–7.18 (m, 1 H_{ar}), 7.41 (d, J = 8.0 Hz, 1 H_{ar}), 7.61–7.66 (m, 1 H_{ar}), 8.49 (d, J = 8.0 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 0.8 mL/min, R_t = 21.8 (minor) and 23.2 min (major).

2-[Hydroxy(2-nitrophenyl)methyl]cyclohex-2-enone:[19] Yellow solid, m.p. 124–125 °C. ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 1.98 (quint, J = 6.4 Hz, 2 H, CH_2), 2.34–2.38 (m, 2 H, CH_2), 2.44–2.48 (m, 2 H, CH_2), 3.70 (br., 1 H, OH), 6.17 (s, 1 H, =CH), 6.62 (t, J = 4.0 Hz, 1 H, =CH), 7.44 (t, J = 8.0 Hz, 1 H_{ar}), 7.64 (t, J = 8.0 Hz, 1 H_{ar}), 7.81 (d, J = 8.0 Hz, 1 H_{ar}), 7.92 (d, J = 8.0 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 0.8 mL/min, R_t = 53.3 (major) and 58.5 min (minor).

Methyl 2-[Hydroxy(2-nitrophenyl)methyl]acrylate: Straw colored oil.[20] ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 2.03 (br., 1 H, OH), 3.73 (s, 3 H, CH_3), 5.73 (s, 1 H, CH), 6.20 (s, 1 H, =CH), 6.37 (s, 1 H, =CH), 7.47 (t, J = 8.1 Hz, 1 H_{ar}), 7.65 (t, J = 8.1 Hz, 1 H_{ar}), 7.75 (d, J = 8.1 Hz, 1 H_{ar}), 7.95 (d, J = 8.1 Hz, 1 H_{ar}) ppm. HPLC conditions: OD-H column, hexane/2-propanol = 90:10, flow rate 1.0 mL/min, R_t = 16.2 (major) and 19.6 min (major).

2-[Hydroxy(2-nitrophenyl)methyl]acrylonitrile:[16] Viscous oil. ^{1}H NMR ($CHCl_3$, 400 MHz): δ = 3.07 (br., 1 H, OH), 6.01 (s, 1 H, CH), 6.15 (s, 1 H, =CH), 6.19 (s, 1 H, =CH), 7.56 (t, J = 8.0 Hz, 1 H_{ar}), 7.75 (t, J = 8.0 Hz, 1 H_{ar}), 7.85 (d, J = 8.0 Hz, 1 H_{ar}), 8.05 (d, J = 8.0 Hz, 1 H_{ar}) ppm. HPLC conditions: AD-H column, hexane/2-propanol = 95:5, flow rate 0.8 mL/min, R_t = 37.0 (major) and 39.9 min (major).

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