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Chiral thiourea derivatives as organocatalyts in the enantioselective Morita-Baylis-Hillman reactions

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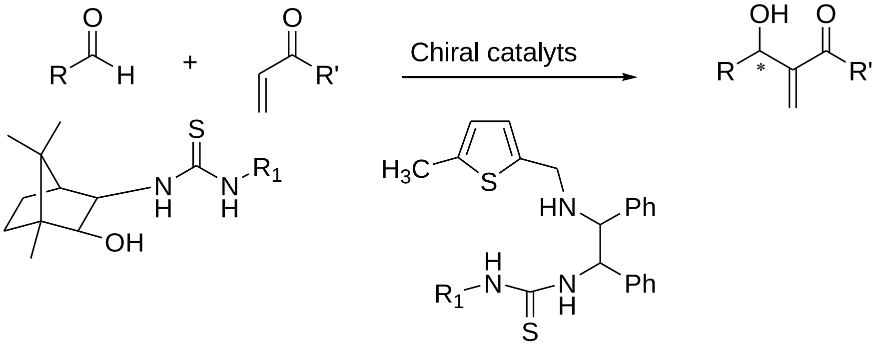
Abstract

Novel chiral bifunctional thiourea derivatives have been synthesised and successfully applied to the intermolecular Morita-Baylis-Hillman (MBH) reaction of an aromatic aldehyde with methyl vinyl ketone (MVK) and to the intramolecular MBH reaction of *ω*-formyl-enone. The corresponding products were obtained with high enantioselectivities (up to 98 % ee). The thiourea organocatalyst derived from a *β*-amino alcohol gave high enantioselectivities (92 % ee) in the intermolecular MBH reaction, whereas the same chiral ligand afforded the corresponding product in high yield (85 %) with moderate enantioselectivity (75 % ee) in the intramolecular MBH reaction. The use of a thiophene ring-containing thiourea derivative gave high enantioselectivities in the intermolecular and intramolecular MBH reactions (85 % and 95 % ee, respectively).



Keyword: Intermolecular Morita-Baylis-Hillman reaction, intramolecular Morita-Baylis-Hillman reaction reaction; *β*-amino alcohol; chiral thiourea derivatives

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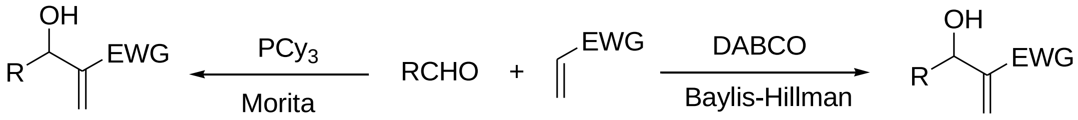
Introduction

The Morita-Baylis-Hillman (MBH) reaction is one of the most important methods for forming C-C bonds[1-3]. It involves the coupling of electron-deficient alkenes with sp^2 hybridised carbon electrophiles, such as aldehydes, ketones and aldimines and is catalysed by nucleophilic amines or phosphines.[4] Various activated alkenes such as enals,[5,6] enones,[7-9] acrylates[10,11] and acrylamides[12,13] have been successfully used in the MBH reaction.

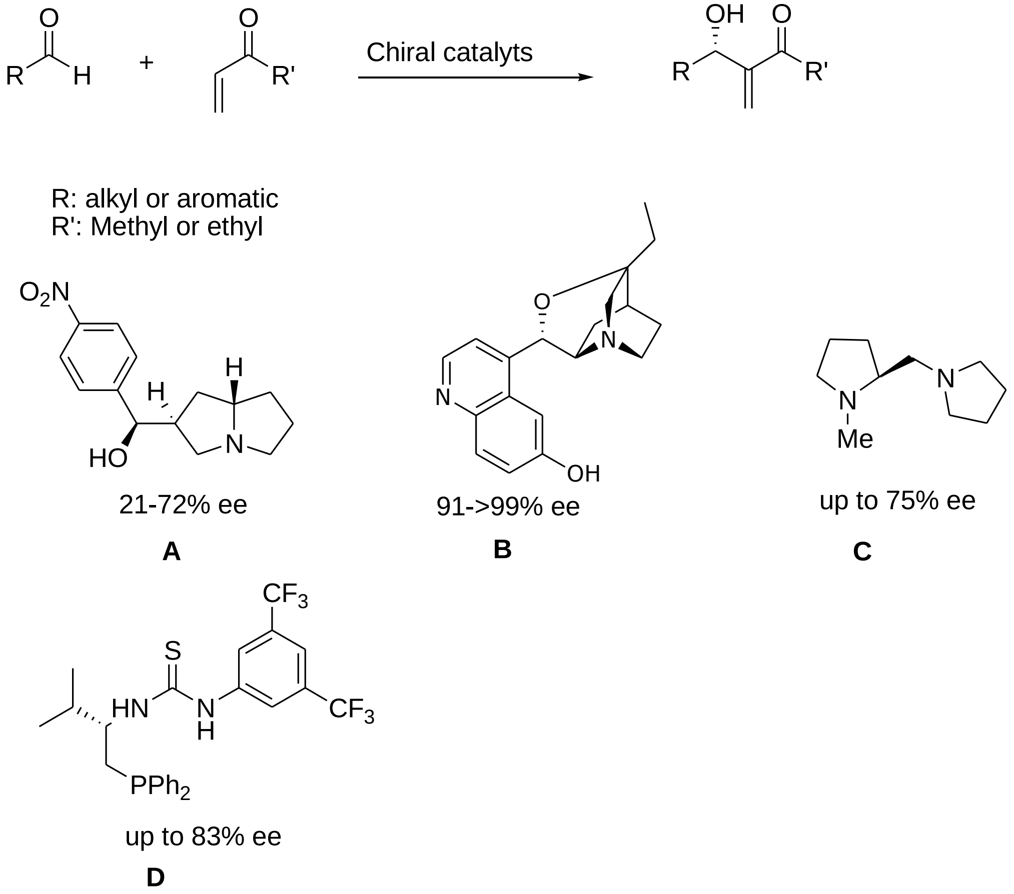
Morita[14] described a novel reaction between various aldehydes and acrylic compounds catalysed by a tertiary phosphine (tricyclohexylphosphine) and yielding vinylic compounds. Subsequently, in 1972, Baylis and Hillman[15] reported a similar reaction between acetaldehyde and ethyl acrylate or acrylonitrile. Instead of phosphines, they used 1,4- diazabicyclo[2.2.2]octane (DABCO) as a Lewis base to obtain products similar to those of Morita's study (Scheme 1).



Scheme 1. The Morita-Baylis-Hillman reaction.

Since then, various chiral catalysts such as chiral Lewis acid or Brønsted-Lowry acid catalysts,[16-18] chiral amino- or phosphino-type catalysts,[19-21] chiral amino acid derivatives,[22,23] a chiral thiourea-type catalyst[24] and chiral ionic liquids[25] have been reported for this asymmetric catalytic process. These chiral catalysts have been developed for intermolecular MBH reactions.[26] Optically active β-hydroxy-α-methylene carbonyl compounds are useful intermediates in natural product synthesis.

To synthesise these compounds, several enantioselective versions of the MBH reaction involving a chiral catalyst have been reported.[27] Barrett et al.[28] used chiral bicyclic pyrrolizidine derivatives (**A**) as asymmetric catalysts for the MBH reaction of ethyl vinyl ketone and an aromatic aldehyde. Hatakeyama et al.[29] used *β*-isocupreidine (**B**) to catalyse the asymmetric MBH reaction between aldehydes and the strongly activated Michael acceptor 1,1,1,3,3,3-hexa-fluoroisopropyl acrylate (HFIP). Hayashi et al.[30] developed chiral diamines (**C**) as catalysts for the MBH reaction of MVK and electron-deficient benzaldehyde, affording adducts with enantioselectivities up to 75 % (Scheme 2).

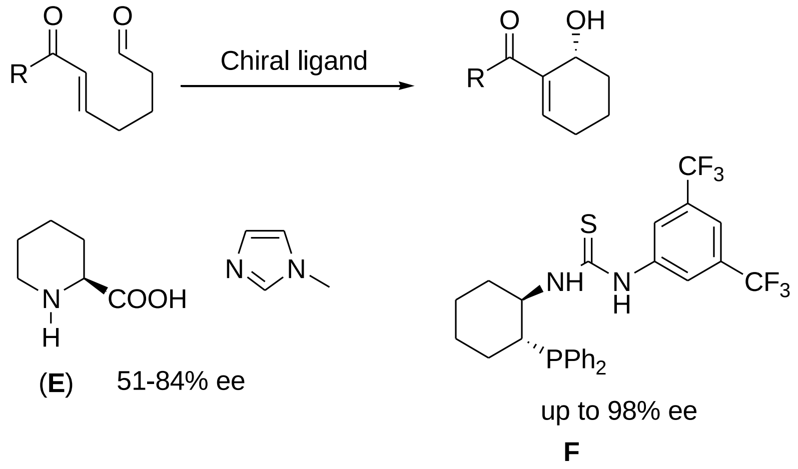


Scheme 2. Enantioselective intermolecular MBH reaction.

Chiral thiourea derivatives such as amino alcohol-derived thiourea and bifunctional phosphinothiourea have been used successfully for the intermolecular MBH reaction.[31-33] In the presence of *L*-valine-derived phosphinothiourea (**D**), the MBH products were obtained in good enantioselectivities (up to 83 % ee) (Scheme 2).[34] The intramolecular MBH reaction can be performed when suitably oriented electrophilic and activated alkene moieties are present in the same molecule, but few examples of intramolecular MBH reactions are found in the literature.

In 1992, Franter and co-workers reported the first asymmetric intramolecular MBH reaction using *p*-chiral phosphine (-)-CAMP to catalyse cyclisation of an enoate onto a ketone to afford cyclopenten-ol ester in 14 % ee.[35-37]

Pipecolinic acid (**E**) and *N*-methylimidazole were used by Miller as a cocatalytic system to catalyse an intermolecular MBH reaction (84 % ee).[38] (Scheme 3).



Scheme 3. Enantioselective intramolecular MBH reaction.

Wu et al.[39] developed chiral cyclohexane-based (**F**) and amino acid-derived phosphinothioureas as catalysts for the enantioselective intramolecular MBH reaction of ω-formyl-α,β-unsaturated carbonyl compounds with up to 98 % and 84 % ee, respectively (Scheme 3). Honh et al.[40] reported the proline-catalysed intermolecular MBH reactions of hept-2-enedial and the corresponding products were obtained in high enantiomeric excess (98 % ee) and good yield (74 %). Gladysz et al.[41] reported an intramolecular MBH reaction in the presence of rhenium-containing phosphine (η^5-C_5H_5)Re(NO)(PPh_3)(CH_2PAr_2), affording the product in 74 % ee.

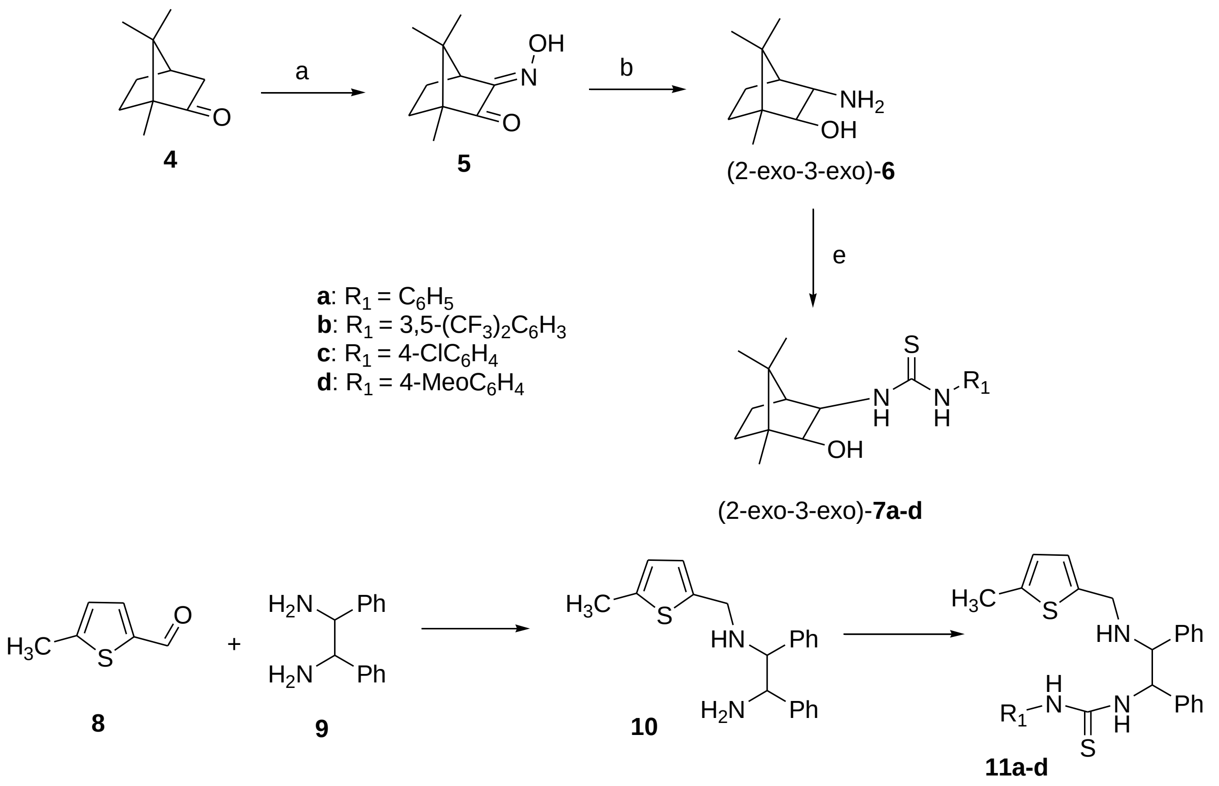
In this study, the intermolecular MBH reaction of an aromatic aldehyde with methyl vinyl ketone (MVK) and the intramolecular MBH reaction of ω-formyl-enone catalysed by the thioureas 7**a-d** and **11a-d** are presented.

Results and Discussion

The synthesis of chiral thiourea derivatives 7a-d. The synthesis of β-amino alcohol **6** from (1*S*)-(-)-camphor was performed according to the literature procedure.[42,43] Chiral amino alcohol-based thioureas **7a-d** were easily obtained by condensation of β-amino alcohol **6** with 1.1 equiv. of the corresponding isothiocyanate in CH_2Cl_2 at room temperature (Scheme 4).

Chiral diamine **10** was prepared in a two-step reaction involving condensation of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **9** with 1 equiv. of 5-methyl thiophene-2-carbaldehyde **8**, followed by reduction with $LiAlH_4$.

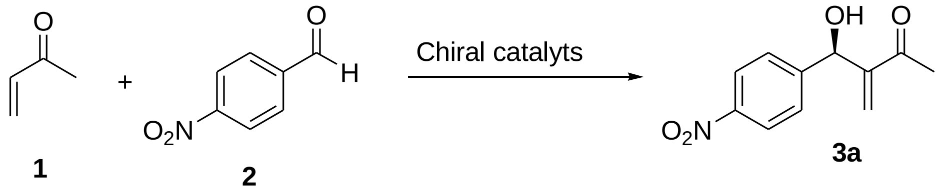
For the synthesis of **7a-d** and **11a-d**, chiral compounds **6** and **10** were stirred with 1.1 equiv. of the corresponding isothiocyanates at room temperature (Scheme 4).



Scheme 4. Synthetic route of the chiral thiourea derivatives.

The enantioselective MBH reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone (MVK).

To determine the best catalyst, the model reaction of *p*-nitrobenzaldehyde and MVK was initially performed in the presence of 10 mol% of catalysts **7** and **11a-d**, and the results are summarised in Table 1, (Scheme 5) .

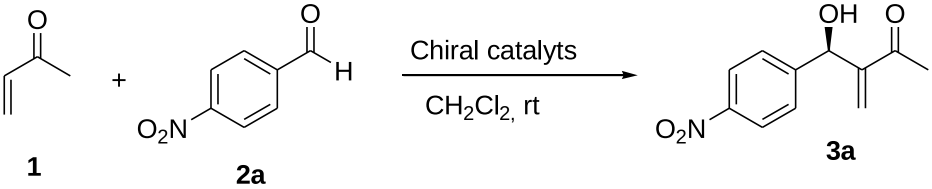


Scheme 5. Enantioselective intermolecular MBH reaction.

Chiral ligand screening showed that β-amino alcohol-based thiourea **7a** provided the corresponding product in high chemical yield (80 %) with 60 % ee. The use of **7b** as a chiral ligand-bearing strong electron-withdrawing substituent on the phenyl group afforded MBH adduct **3a** in 78 % yield with 80 % ee. In the presence of **7c** or **7d** as the chiral ligand, the corresponding MBH product **3a** was obtained in 75 % chemical yield with 70 % ee and 78 % chemical yield with 65 % ee, respectively (Table 1, entries 3, 4). In the presence **11a**-**d**, good enantioselectivities and chemical yields were obtained (Table 1, entries 5–8). Performing the MBH reaction with **11a** gave the corresponding product in 78 % yield with 72 % ee. The use of **11b** as the chiral ligand afforded the corresponding product in 77 % yield with 74 % ee.

The enantioselectivity decreased with an increase in the reaction time from 30 to 60 min. In the presence of **7a**, a higher conversion (85 % yield) was obtained after 60 min, but the enantioselectivity decreased (72 % ee) (entry 11). The MBH product after 45 min was obtained in 78 % chemical yield with 92 % ee. The absolute configuration of the intermolecular MBH products, *R*, was assigned by comparing the retention time (chiral HPLC) with its literature values.[23,30,31,33,48]

Table 1. Screening of the chiral ligands for the MBH reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone (MVK)[a]



Entry	Catalyst (yield %)	Time (min)	Yield[b] (%)	ee[c]%
1	**7a** (60)	30	80	60
2	**7b** (78)	30	78	80
3	**7c** (64)	30	75	70
4	**7d** (60)	30	78	65
5	**11a** (65)	30	78	72
6	**11b** (79)	30	72	85
7	**11c** (63)	30	83	75
8	**11d** (60)	30	80	62
9	**7a**	15	72	75
10	**7a**	45	78	92
11	**7a**	60	85	72

[a] The reaction were performed using 10 mol% of chiral ligand, 5 equiv of MVK in 1 mL solvent at room temperature.

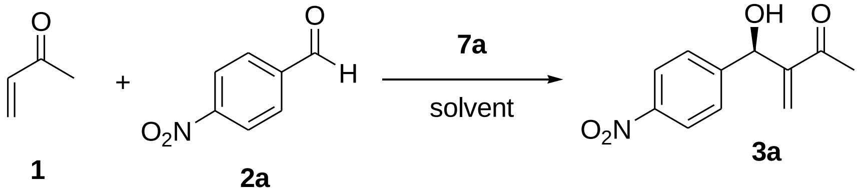
[b] Isolated yields.

[c] Determined by HPLC using Chiral OD-H column

Because **7a** gave the highest enantioselectivity in the MBH reaction of *p*-nitrobenzaldehyde with MVK, it was identified as most effective among the chiral ligand series (Table 1, entry 10) and was selected for optimising further the reaction conditions.

Then, the solvent effect on the MBH reaction of *p*-nitrobenzaldehyde with MVK was investigated using **7a** as the chiral ligand. The results, outlined in Table 2, show that the highest enantiomeric excess (92 %) was observed in CH_2Cl_2. In polar solvents such as EtOH, DMF and MeCN, the MBH adduct **3a** was obtained in low yield and ee (Table 2, entries 5-7). The lowest enantioselectivity was obtained in DMSO. Increasing the reaction temperature from room temperature to 40 °C decreased the ee value to 77 % (Table 2, entries 4, 9), whereas decreasing the reaction temperature to −15 °C obtained the corresponding product in 45 % yield with 65 % ee(Table 2, entry 10).

Table 2. Effects of the solvents and reaction temperature on the MBH reaction of *p*-nitrobenzaldehyde with MVK[a]



Entry	Solvent	Temp. (°C)	Yield[b] (%)	ee[c]%
1	CH_2Cl_2	rt	78	92
2	$CHCl_3$	rt	76	85
3	Toluen	rt	75	85
4	THF	rt	70	90
5	EtOH	rt	75	68
6	DMF	rt	80	65
7	CH_3CN	rt	60	60
8	DMSO	rt	82	55
9	THF	40	90	77
10	THF	-15	45	65

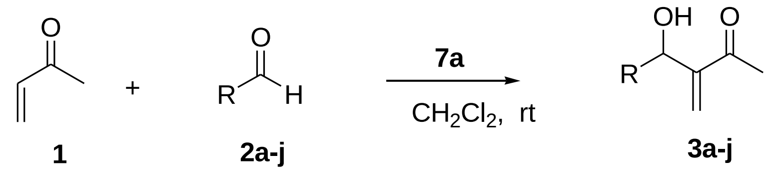
[a] The reaction were performed using 10 mol% of chiral ligand, 5 equiv of MVK
in 1 mL solvent at room temperature.

[b] Isolated yields.

[c] Determined by HPLC using Chiral OD-H column.

To investigate the effect of electron-withdrawing and electron-donating substituents, the asymmetric MBH reaction was performed with different aromatic aldehydes using conditions optimised for ligand **7a** (10 mol% of **7a** catalyst, 5 equiv. of MVK, CH_2Cl_2 as a solvent, room temperature). The results are summarised in Table 3. The electronic effects on the aromatic ring of the aldehyde affected the reactivity and selectivity. Electron-withdrawing substituents gave higher enantioselectivities than did electron-donating substituents. It is known that the electrophilicity of the carbonyl carbon atom in aryl aldehydes is increased by electron-withdrawing groups and decreased by electron-donating groups; therefore, the substrates with an electron-withdrawing substituent are expected to afford a faster reaction, leading to higher enantioselectivity. In fact, a lower enantioselectivity was observed for the *meta*-substituted benzaldehyde compared to that of its relevant *para*-substituted analogue (entry 3 and 4). With ligand **7a**, the lowest enantiomeric excesses were observed for aromatic aldehydes bearing *ortho* substituents, probably due to the *ortho* effects (entry 2 and 7). In the presence of ligand **7a,** the non-substituted benzaldehyde afforded the product with 85 % ee but in low yield (62 %). The yields and ee values decreased (62 % yield, 55 % ee) when the methoxy group on the phenyl ring was at the *para* position(entries 10).

Table 3. The enantioselective MBH reaction involving various substituted aldehydes[a]



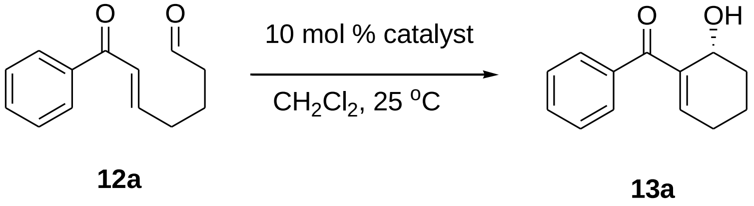
Entry	R	Yield[b] (%)	ee[c]%
1	4-$NO_2C_6H_4$, **2a**	78	92
2	2-$NO_2C_6H_4$, **2b**	78	81
3	3-$NO_2C_6H_4$, **2c**	68	89
4	4-CNC_6H_4, **2d**	65	87
5	4-CF_3" C_6H_4, **2e**	67	90
6	4-ClC_6H_4, **2f**	55	90
7	2-ClC_6H_4, **2g**	65	85
8	4-BrC_6H_4, **2h**	58	89
9	C_6H_5, **2i**	62	85
10	4-$MeOC_6H_4$, **2j**	62	55

[a] The reaction were performed using 10 mol% of chiral ligand, 5 equiv of MVK in 1 mL solvent at room temperature.

[b] Isolated yields.

[c] Determined by HPLC using Chiral OD-H column

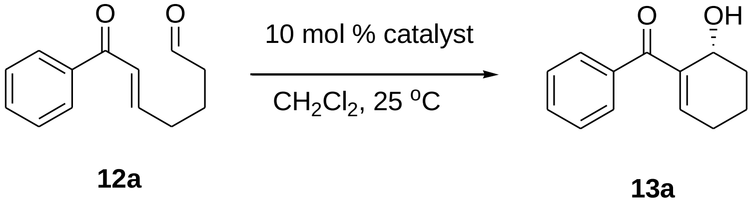
The enantioselective intramolecular MBH reaction of *ω*-formyl-enone catalyzed by *β*-amino alcohol-based thiourea 7 and 11a-d.



Scheme 6. Enantioselective intramolecular MBH reaction.

Chiral thiourea derivatives **7** and **11a**-**d** were examined in the enantioselective intramolecular MBH reaction of *ω*-formyl-enone as the model substrate (Scheme 6). *β*-Amino alcohol-based thioureas **7a** were used as catalysts in the intramolecular reaction of substrate **12a** in CH_2Cl_2 at room temperature, and the MBH product **13a** was obtained in 65 % chemical yield with good enantioselectivity (72 % ee). As shown in Table 4, the structure of the chiral ligands significantly affected the enantioselectivity and the chemical yield. The thiourea moiety of the chiral ligands played an important role in obtaining a high yield and enantioselectivity. Chiral thiourea derivatives **7b** and **11b**, bearing strong electron-withdrawing substituents at the phenyl ring, afforded the corresponding product in 63 % chemical yield with 95 % ee and in 65 % chemical yield with 94 % ee, respectively. Chiral ligand **7b** provided the corresponding product in higher enantioselectivity and chemical yield than ligands **7a**,**c**,**d** did (Table 4, entries 1-4). These observations were agreement with the observations of Wu et *al.*[39] The absolute configuration of the intramolecular MBH products is *R*-configuration, which was assigned by comparing the retention time (chiral HPLC) with those reported in the literatures.[30,39,41,48,46]

Table 4. Catalysts screening for the intramolecular MBH reaction of **12a**[a]



Entry	Catalyst (yield%)	Yield[b](%)	ee[c](%)
1	**7a**	65	72
2	**7b**	63	95
3	**7c**	74	65
4	**7d**	73	60
5	**11a**	67	68
6	**11b**	65	94
7	**11c**	76	75
8	**11d**	73	65

[a] The reaction were performed using 10 mol% of chiral ligand, 5 equiv of *ω*-formyl-enone in 1 mL solvent at room temperature, 45 min.

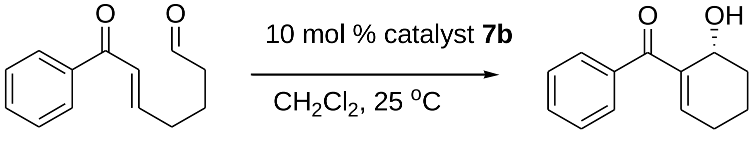
[b] Isolated yields.

[c] Determined by HPLC using Chiral OD-H column.

Because **7b** gave the highest enantioselectivity in the intramolecular MBH reaction, it was identified as most effective among the chiral ligand series (Table 4, entry 2) and was selected for optimising further the reaction conditions.

To further improve the enantioselectivity of **12a**, the effect of solvent on the enantioselective intramolecular MBH reaction of ω-formyl-enone was investigated (Table 5, entries 1–8). The enantioselective intramolecular MBH reaction was performed in solvents such as *n*-hexane, toluene, $CHCl_3$, CH_2Cl_2, THF, acetone, CH_3CN, DMF, MeOH and EtOH. Table 5 shows that CH_2Cl_2 was the most appropriate solvent (entry 4). In DMF, the corresponding product was obtained in 10 % chemical yield with 25 % ee (entry8). In MeOH, the MBH product **13a** was obtained in moderate chemical yield (72 %) but with poor enantioselectivity (12 % ee) (entry 9).

Table 5. The effect of the solvents on the intramolecular MBH reaction[a]



12a **13a**

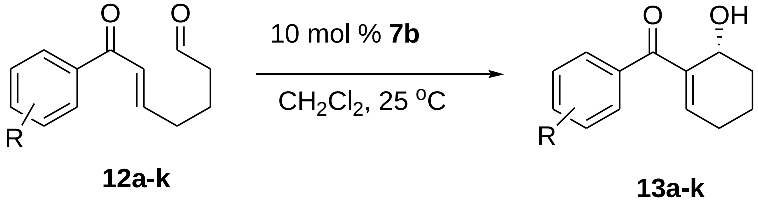
Entry	Solvent	Yield[b] (%)	ee[c](%)
1	*n*-Hexane	45	75
2	Toluene	43	55
3	$CHCl_3$	85	65
4	CH_2Cl_2	63	95
5	THF	36	70
6	Acetone	66	72
7	CH_3CN	70	65
8	DMF	10	25
9	MeOH	72	12
10	EtOH	75	59

[a] The reaction were performed using 10 mol% of chiral ligand, 5 equiv of
ω-formyl-enone in 1 mL solvent at room temperature.
[b] Isolated yields.
[c] Determined by HPLC using Chiral OD-H column.

The enantioselective intramolecular MBH reaction involving various *ω*-formyl-enone substrates was investigated, and the results are summarised in Table 6. All the substituted aromatic enones were converted to the MBH reaction product in 62–95 % ee. As shown in Table 6, the substrates with an electron-withdrawing substituent at the *para* position of the phenyl ring afforded higher enantioselectivity than those with an electron-donating substituent or without a phenyl substituent.

With a substrate-bearing substituent at the *ortho* position of the phenyl group, the corresponding product was obtained in excellent yield with poor enantioselectivity, due to the *ortho* effect (entries 2 and 8).

Table 6. The enantioselective intramolecular MBH reaction involving various *ω*-formyl-enone substrates[a]



Entry	Ar	Yield[b] (%)	ee[c](%)
1	C_6H_5, **12a**	87	83
2	4-NO_2-C_6H_4, **12b**	63	95
3	2-Br-C_6H_4, **12c**	90	75
4	3-Br-C_6H_4, **12d**	90	78
5	4-Br-C_6H_4, **12e**	85	80
6	4-Cl-C_6H_4, **12f**	83	81
7	4-F-C_6H_4, **12g**	78	80
8	2-Me-C_6H_4, **12h**	95	62
9	4-Me-C_6H_4, **12i**	80	65
10	4-MeO-C_6H_4, **12j**	78	60
11	Thiophen-2-yl, **12k**	65	72

[a] The reaction were performed using 10 mol% of chiral ligand, 5 equiv of *ω*-formyl-enone
in 1 mL CH_2Cl_2 at room temperature.

[b] Isolated yields.

[c] Determined by HPLC using Chiral OD-H column.

Conclusions

In summary, we have developed the MBH reaction of an aromatic aldehyde with MVK and the intramolecular MBH reaction of *ω*-formyl-enone catalysed by thioureas 7**a-d** and **11a-d**. The reaction proceeds under very mild conditions to quickly afford the desired product in good to excellent yields with generally excellent enantiomeric excesses. The use of (1*R*,2*S*)-**7b** as a chiral ligand bearing a strong electron-withdrawing substituent at the phenyl group afforded the hydroxyl enone with low enantioselectivity (40 % ee) in the intermolecular MBH reaction, whereas the same ligand gave the highest enantioselectivity (97 % ee) in the intramolecular MBH reaction. Thiophene ring-containing thiourea derivatives bearing a strong electron-withdrawing substituent on the phenyl group **11b** gave a high enantioselectivity in the intermolecular MBH reaction (85 % ee), whereas the same ligand afforded the cyclic hydroxyl enones with excellent enantioselectivity (94 % ee). The application of these ligands to the other asymmetric reactions is now under investigation.

Experimental Section

General. Reagents and solvents were purchased from Aldrich, Merck and Fluka. All solvents were dried before use according to the standard procedures. All reactions were carried out under Ar atmosphere and monitored by thin-layer chromatography (TLC) on Merck silica gel plates (60 F-254) using UV light or phosphomolybdic acid in methanol. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. All NMR spectra were recorded on a Bruker DPX-400 MHz spectrometer at room temperature. Chemical shifts (parts per million) are reported relative to TMS. Coupling constant are expressed as J values in Hertz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Elemental analyses (C, H, N, S) were carried out on a Carlo Erba Model Thermo Scıentıfıc Flash 2000 elemental analyzer. Optical rotations were recorded on a Autopol IV polarimeter. All melting points were measured with an Electrothermal melting point instrument. Elemental analyses were carried out on a LECO CHNS-932 series analyzer. Enantiomeric excesses were determined by HPLC analysis using a Shimadzu and Thermo Finnigan analyzer.

Synthesis of chiral catalysts 7a-d. Camphor was converted to 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane **5** using *ter*-butyl nitrite dry THF in the presence of *ter*-sodium butylate[42,43]. 3-Amino-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane **6** was obtained from the reduction of **5** with $LiAlH_4$ by refluxing in dry ether with 79 % yield, according to literature procedure.[42-45]

β-Amino alcohol **6** (1.0 mmol) was dissolved in CH_2Cl_2 (2.0 mL) was added the corresponding solution of isothiocyanate (1.1 mmol) in CH_2Cl_2 (2.0 mL) at the room temperature. The reaction mixture was allowed to stir at same temperature until reaction completed (monitoring by TLC). The solvent removed under reduced pressure and the the residue was purified by column chromatography (petroleum ether/ethyl acetate).

1-1(3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2yl)-3-phenylthiourea (7a). White solid; 69 % yield; mp 172-174 °C, $[\alpha]_D^{25}$ = -1.28 (c=0.32, $CHCl_3$); ^{1}HNMR: (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.98 (s, 3H), 1.09 (s, 3H), 1.24-1.31 (m, 2H), 1.42-1.47 (m, 1H), 1.64 (d, *J* 4.23 Hz, 1H), 1.67-1.69 (m, 1H), 1.83-1.88 (m, 1H), 2.65 (d, *J* 7.2 Hz, 1H), 3.47 (d, *J* 7.3 Hz, 1H), 6.45-7.12 (m, 5H); ^{13}C-NMR: (100 MHz, $CDCl_3$) 11.23, 21.36, 21.99, 27.29, 32.48, 46.91, 48.79, 52.28, 65.49, 78.48, 126.12-130.23, 138.32, 182.25. Anal. Calcd. for $C_{17}H_{24}N_2OS$ C, 67.07; H, 7.95; N, 9.20; S, 10.53; found: C, 67.12; H, 7.91; N, 9.22; S, 10.52.

(1-(3,5-Bis(trifluormethyl)phenyl)-3-(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2yl)urea (7b). White solid; 78 % yield; mp 180-182- °C, $[\alpha]_D^{25}$ = -1.19 (c=0.482, $CHCl_3$);^{1}HNMR: (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 1.45-1.49 (m, 2H,), 1.65 (d, *J* 4.1 Hz, 1H), 1.69-1.72 (m, 1H), 1.84-1.91 (m, 1H), 2.91 (d, *J* 7.3 Hz, 1H), 3.59 (d, *J* 7.3 Hz, 1H), 7.12 (broad s, 2H), 7.27 (s, Ar-H, 1H),; ^{13}C-NMR: (100 MHz, $CDCl_3$) 11.26, 21.48, 22.09, 27.35, 32.56, 47.28, 48.92, 52.67, 65.78, 78.89, 125.67, 126.8, 127.12, 132.14, 138.19, 182.23 Anal. Calcd. for $C_{19}H_{22}F_6N_2OS$ C, 51.81; H, 5.03; N, 6.36; S, 7.28; found: C, 51.86; H, 5.09; N, 6.34; S, 7.29.

1-(4-chlorophenyl)-3-(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2yl)thiourea (7c). White solid; 64 % yield; mp 174-146 °C, $[\alpha]_D^{25}$ = -1.22 (c=0.34, $CHCl_3$); ^{1}HNMR: (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.13 (s, 3H), 1.15 (s, 3H), 1.47-1.51 (m, 2H), 1.66 (d, *J* 4.2 Hz, 1H), 1.71-1.73 (m, 1H), 1.83-1.90 (m, 1H), 2.79 (d, *J* 7.3 Hz, 1H), 3.45 (d, *J* 7.3 Hz, 1H), 6.89 (d, *J* 6.7 Hz, 1H), 7.15 (d, *J* 6.7 Hz, 1H), ^{13}C-NMR: (100 MHz, $CDCl_3$) 11.25, 21.43, 22.04, 27.31, 32.42, 47.20, 48.83, 52.62, 65.72, 78.81, 127.65, 129.18, 132.18, 138.21, 183.25; Anal. Calcd. for $C_{17}H_{23}ClN_2OS$ C, 60.25; H, 6.84; N, 8.27; S, 9.49; found: C, 60.20; H, 6.81; N, 8.29; S, 9.52.

1-(3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2yl)-3-(4-methoxyphenyl)thiourea (7d). White solid; 60 % yield; mp 169-171 °C; $[\alpha]_D^{25}$ = -1.18 (c=0.51, $CHCl_3$); ^{1}HNMR: (400 MHz, $CDCl_3$) δ 0.79 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.127-1.49 (m, 2H,), 1.59 (d, *J* 4.2 Hz, 1H), 1.69-1.71 (m, 1H), 1.80-1.89 (m, 1H), 2.75 (d, *J* 7.3 Hz, 1H), 3.41 (d, *J* 7.3 Hz, 1H), 3.58 (s, 3H), 6.38 (d, *J* 6.7 Hz, 1H), 6.55 (d, *J* 6.7 Hz, 1H), ^{13}C-NMR: (100 MHz, $CDCl_3$) 13.7, 21.41, 21.78, 22.82, 32.23, 47.11, 48.78, 52.58, 55.9, 60.2, 78.74, 127.60, 128.12, 129.8, 138.19, 183.13; Anal. Calcd. for $C_{18}H_{26}N_2O_2S$ C, 64.64; H, 7.84; N, 8.38; S, 9.59; found: C, 64.60; H, 7.80; N, 8.42; S, 9.69.

Synthesis of chiral diamine 10. According to our previously procedure,[46,47] the formylation of 2-methyl thiophene was performed according to Vismeier Haack method.
5-Methyl thiophene-2-carbaldehyde **8** (5mmol) were dissolved in 10 mL benzene to which was added (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (5 mmol) under nitrogen atmosphere. The mixture was refluxed for 4 h and water was removed in a Dean–Stark trap. Reaction was controlled by TLC. Imine was concentrated to dryness without purification. The synthesized imine was dissolved in 15 mL Et_2O and added to a suspension of 1.40 mmol $LiAlH_4$ in 10 mL Et_2O. The mixture was refluxed for 8 h and controlled by TLC. When the reaction was completed, the mixture was cooled to room temperature and quenched with 15 mL water. It was extracted with ether (3x10 mL) and dried over $MgSO_4$. The mixture was filtered and the solvent was evaporated. Crude product **10** were purified by flash column chromatography(EtOAc–hexane, 1:1)

***(*1*S*,2*S*)-*N*-((5-Methylthiophen-2-yl)methyl)-1,2-diphenylethane-1,2-diamine (10).** Brown oil, 80 % yield; R_f:0.15 (EtOAc:hexane, 1:1); $[\alpha]_D^{25}$ = -1.41 (c=0.38, $CHCl_3$); ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 3.86 (d, 1H, *J* 14.4 Hz, 1H), 3.91 (d, 1H, *J* 14.4 Hz, 1H), 4.53 (d, *J* 4.5, 1H), 4.55 (d, J 4.5 1H,), 6.59 (d, *J* 3.6 Hz, 1H), 6.74 (d, *J* 3.60 Hz, 1H), 7.156-7.33 (m, 10H, Ar*H*), 7.86 (s, 2H);^{13}C NMR ($CDCl_3$,100 MHz) δ 15.72, 48.23, 60.74, 67.08, 105.97, 108.06, 126.9, 127.02, 128.1, 128.5, 128.8, 138.52, 143.76. Anal. Calcd. for $C_{20}H_{22}N_2S$ C, 74.49; H, 6.88; N, 8.69; S, 9.94; found: C, 74.52; H, 6.85; N, 8.70; S, 9.93.

Synthesis of thiourea derivatives (11a-d). To solution of chiral compound **10** (1.0 mmol) in CH_2Cl_2 (2.0 mL) was added the corresponding solution of isothiocyanate (1.1 mmol) in CH_2Cl_2 (2.0 mL) at room temperature and reaction mixture was allowed to stir at same temperature until reaction completed (monitoring by TLC). The solvent removed under reduced pressure and the the residue was purified by column chromatography (petroleum ether/ethyl acetate).

1-((1*S*,2*S*)-2-((5-Methylthiophen-2-yl)methylamino)-1,2-diphenylethyl)-3-phenylthiourea (11a). White solid; 65 % yield; mp 182-184 °C; $[\alpha]_D^{25}$ = -1.76 (c=0.25, $CHCl_3$); ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 3.88 (d, 1H, *J* 14.4 Hz, 1H), 3.93 (d, 1H, *J* 14.4 Hz, 1H) 4.55 (d, *J* 2.8, 1H), 4.57 (d, *J* 2.8, 1H), 6.52 (d, *J* 3.6 Hz, 1H), 6.64 (d, *J* 3.6 Hz, 1H), 6.95-7.33 (m, 15H, Ar*H*), ^{13}C NMR ($CDCl_3$,100 MHz) δ 15.72, 48.23, 62.74, 67.08, 125.46, 126.03, 126.92, 127.02, 127.28, 128.0, 128.6, 138.45, 143.52, 181.42; Anal. Calcd. for $C_{27}H_{27}N_3S$ C, 70.86; H, 5.95; N, 9.18; S, 14.01; found: C, 70.82; H, 5.97; N, 9.21; S, 14.00.

1-((1*S*,2*S*)-2-((5-Methylthiophen-2-yl)methylamino)-1,2-diphenylethyl)-3-(3,5-bis(trifluoromethyl)phenyl) thiourea (11b). White solid; 79 % yield; mp 183-184 °C; $[\alpha]_D^{25}$ = -1.26 (c=0.62, $CHCl_3$); ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 3.93 (d, 1H, *J* 14.4 Hz, 1H), 3.96 (d, 1H, *J* 14.4 Hz, 1H) 4.61 (d, *J* 2.8, 1H), 4.65 (d, *J* 2.8, 1H), 6.59 (d, *J* 3.6 Hz, 1H), 6.72 (d, *J* 3.6 Hz, 1H), 7.10 (broad s, 2H), 7.25 (s, Ar-H, 1H), 7.32-7.42 (m, 10H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 15.92, 48.29, 61.54, 67.73, 120.14, 125.53, 126.23, 127.45-128.56, 132.61, 137.23, 138.23, 138.55, 138.79, 144.57, 181.57; Anal. Calcd. For $C_{29}H_{25}F_6N_3S_2$ C, 58.67; H, 4.24; F, 19.20; N, 7.08; S, 10.80; found: C, 58.64; H, 4.27; N, 7.05; S, 10.80.

1-((1*S*,2*S*)-2-((5-Methylthiophen-2-yl)methylamino)-1,2-diphenylethyl)-3-(4-chlorophenyl)thiourea (11c). White solid; 63 % yield; mp 179-181 °C; $[\alpha]_D^{25}$ = -1.87 (c=0.35, CHCl$_3$); ^{1}H NMR: (CDCl$_3$, 400 MHz) δ 2.36 (s, 3H), 3.94 (d, 1H, *J* 14.4 Hz, 1H), 3.98 (d, 1H, *J* 14.4 Hz, 1H) 4.63 (d, *J* 2.9, 1H), 4.67 (d, *J* 2.9, 1H), 6.57 (d, *J* 3.6 Hz, 1H), 6.68 (d, *J* 3.6 Hz, 1H), 6.82 (d, *J* 8.7 Hz, 2H), 7.17 (d, *J* 8.7 Hz, 2H), 7.35-7.59 (m, 10H). ^{13}C NMR (CDCl$_3$,100 MHz) δ 15.82 48.45, 61.68, 67.89, 125.89, 126.12, 126.89, 127.12, 127.25, 127.98, 128.03, 128.65, 129.12, 131.12, 135.27, 136.45, 138.35, 138.57, 143.59, 181.49; Anal. Calcd. for $C_{27}H_{269}ClN_3S_2$ C, 65.90; H, 5.33; N, 8.54; S, 13.03; found: C, 65.92; H, 5.36; N, 8.55; S, 12.95.

1-((1*S*,2*S*)-2-((5-Methylthiophen-2-yl)methylamino)-1,2-diphenylethyl)-3-(4-methoxyphenyl)thiourea (11d). White solid; 60 % yield; mp 173-175°C; $[\alpha]_D^{25}$ = -1.27 (c=0.53, CHCl$_3$); ^{1}H NMR: (CDCl$_3$, 400 MHz) 2.30 (s, 3H), 3.90 (d, 1H, *J* 14.4 Hz, 1H), 3.95 (d, 1H, *J* 14.4 Hz, 1H) 4.50 (d, *J* 6.0, 1H), 4.62 (d, *J* 6.0, 1H), 6.42 (d, *J* 3.6 Hz, 1H), 6.58 (d, *J* 3.6 Hz, 1H), 6.67 (d, *J* 6.8 Hz, 1H), 6.99 (d, *J* 6.8 Hz, 1H), 7.10-7.23 (m, Ar-H, 10H); ^{13}C NMR (CDCl$_3$,100 MHz) δ 15.95, 48.45, 55.82, 61.68, 67.89, 125.28, 125.92, 126.02, 126.82, 127.15, 127.32, 127.82, 128.02, 128.72, 129.46, 136.27, 138.36, 138.57, 143.45, 156.72, 182.27; Anal. Calcd. for $C_{28}H_{29}N_3OS_2$ C, 68.96; H, 5.99; N, 8.62; S, 13.15; found: C, 68.92; H, 5.97; N, 8.64; S, 13.22.

Enantioselective intermolecular Morita–Baylis–Hillman reaction. A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique. To soluition of chiral ligand in 5 mL CH$_2$Cl$_2$ was added 2-nitrobenzaldehyde (0.015 mmol), and methyl vinyl ketone (0.029 mmol). The resulting mixture was stirred until complete loss of starting material was observed by TLC (2:1 hexane/ethyl acetate). The reaction mixture was diluted with chloroform and purification via silica gel chromatography (SiO$_2$, CHCl$_3$) afforded the corresponding products **3**. Compounds **3a–i** are known compounds; they were characterized by comparing their ^{1}H, ^{13}C NMR spectra with those published in the literature.[23,30,48] The ee values were determined by HPLC analysis with a chiral column.

(*R*)-3-[Hydroxy-(4-nitrophenyl)-methyl]-but-3-en-2-one (3a).[23] 72 % yield, 92 % ee, ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.38 (s, 3H), 3.35 (d, *J* = 5.6 Hz, 1H, OH), 5.71 (d, *J* 5.6 Hz, 1H), 6.06 (s, 1H), 6.30 (s, 1H), 7.58 (d, *J* 8.8 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H); ^{13}C-NMR (CDCl$_3$, 100MHz): δ 26.3, 72.4, 123.8, 127.5, 127.9, 147.7, 149.4, 149.7, 199.6, HPLC (OD-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0mL/min): t_R=28.7 min (major), 32.4 min (minor).

(*R*)-3-[Hydroxy-(2-nitrophenyl)-methyl]-but-3-en-2-one (3b).[23] 78 % yield, 84 % ee, $[\alpha]_D^{25}$ = -151.0 (*c* 0.5, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.41 (s, 3H), 3.50 (s, 1H), 5.82 (s, 1H), 6.19 (s, 1H), 6.25 (s, 1H), 7.49 (t, *J* 7.6 Hz, 1H), 7.69 (t, *J* 7.6 Hz, 1H), 7.81 (d, *J* 8.0 Hz, 1H), 7.97 (d, *J* 8.0 Hz, 1H; ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 25.4, 67.9, 124.8, 126.4, 128.9, 129.4, 133.7, 136.94, 148.5, 149.3, 201.2; HPLC (AD-H column, λ = 254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.7 mL/min): t_R=25.7 min (minor), 28.4 min (major).

(*R*)-3-[Hydroxy-(3-nitrophenyl)-methyl]-but-3-en-2-one (3c).[48] 68 % yield, 89 % ee; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.39 (s, 3H), 3.34 (s, 1H), 5.69 (s, 1H), 6.11 (s, 1H), 6.31 (s, 1H), 7.54 (t, *J* 8.0 Hz, 1H), 7.75 (d, *J* 7.6 Hz, 1H), 8.17 (d, *J* 8.4 Hz, 1H), 8.25 (s, 1H); ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 26.7, 72.8, 121.9, 122.8, 127.7, 129.8, 132.9, 143.4, 148.8, 149.3, 200.7; HPLC (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.8 mL/min): t_R=21.4 min (minor), 24.7 min (major).

(*R*)-3-[Hydroxy-(4-cyanophenyl)-methyl]-but-3-en-2-one (3d).[30] 65 % yield, 87 % ee; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.37 (s, 3H), 3.34 (s, 1H), 5.65 (s, 1H), 6.08 (s, 1H), 6.29 (s, 1H), 7.51 (d, *J* 7.6 Hz, 2H), 7.65 (d, *J* 7.6 Hz, 2H); HPLC (AS-H column, λ=220 nm, eluent: hexane/2-propanol = 85/15, flow rate: 1.0 mL/min): t_R=21.4 min (major), 27.6 min (minor).

(*R*)-3-[Hydroxy-(4-trifluoromethyl-phenyl)-methyl]-but-3-en-2-one (3e).[30] 67 % yield, 98 % ee; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 3.38 (d, *J* 5.4 Hz, 1H), 5.69 (d, *J* 5.4 Hz, 1H), 6.04 (d, *J* 1.2 Hz, 1H), 6.28 (s, 1H), 7.51 (d, *J* 8.0 Hz, 2H), 7.62 (d, *J* 8.0 Hz, 2H); HPLC (AS-H column, λ=220 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R = 8,9 min (major), 10,9 min (minor).

(*R*)-3-[Hydroxy-(4-chlorophenyl)-methyl]-but-3-en-2-one (3f).[30] 55 % yield, 90 % ee; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 3.17 (d, *J* 5.2 Hz, 1H), 5.60 (d, *J* = 5.2 Hz, 1H), 601 (d, *J* 1.1 Hz, 1H), 6.25 (s, 1H), 7.33 (s, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 26.9, 72.9, 127.19, 128.3, 128.9, 133.8, 141.2, 150.0, 200.9; HPLC AS-H column, λ=254 nm, eluent: hexane/2-propanol = 85/15, flow rate: 1.0 mL/min): t_R = 9.5 min (major), 11.7 min (minor).

(*R*)-3-[Hydroxy-(2-chlorophenyl)-methyl]-but-3-en-2-one (3g).[30] 65 % yield, 85 % ee; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (s, 3H), 3.47 (d, *J* 4.5 Hz, 1H), 5.69 (s, 1H), 6.03 (d, *J* 4.5 Hz, 1H), 6.22 (s, 1H), 7.21-7.26 (m, 1H), 7.31-7.39 (m, 2H), 7.59-7.63 (m, 1H); HPLC (AD-H column, λ=220 nm, eluent: hexane/2-propanol = 90/10, flow rate: 1.0 mL/min): t_R=21.4 min (minor), 24.7 min (major).

(*R*)-3-[Hydroxy-(4-bromophenyl)-methyl]-but-3-en-2-one (3h).[30] 58 % yield, 89 % ee, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 3.18 (d, *J* 5.2 Hz, 1H), 5.61 (d, *J* 5.2 Hz, 1H), 5.96 (s, 1H), 6.25 (s, 1H), 7.27 (d, *J* 8.4 Hz, 2H), 7.49 (d, *J* 8.4 Hz, 2H); HPLC (AS-H column, λ = 220 nm, eluent: hexane/2-propanol = 95/5, flow rate: 1.0 mL/min): t_R=18.7 min (major), 25.7 min (minor).

(*R*)-3-[Hydroxy-phenylmethyl]-but-3-en-2-one (3j).[30] 62 % yield, 78 % ee; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 3.14 (d, *J* 4.4 Hz, 1H), 5.65 (d, *J* 4.8 Hz, 1H), 6.05 (s, 1H,), 6.25 (s, 1H), 7.32-7.41-(m, 5H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 26.9, 73.4, 126.1, 126.9, 127.7, 128.6, 141.8, 151.4, 200.8; HPLC (AD-H column, λ=220 nm, eluent: hexane/2-propanol=95/5, flow rate: 0.8 mL/min): t_R=21.8 min (minor), 25.7 min (major).

4-hydroxy-4-(4-methoxyphenyl)-3-methylenebutan-2-one (3i).[30] 62 % yield, 55 % ee; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 3.81 (s, 3H), 5.62 (d, *J* 3.9 Hz, 1H), 5.74 (br, 1H), 6.11 (s, 1H,), 6.27 (s, 1H), 6.91 (d, *J* 9.0 Hz, 2H), 7.29 (d, *J* 9.0 Hz, 2H); HPLC (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.8 mL/min): t_R=17.5 min (minor), 18.4 min (major).

Enantioselective intramoleculer Morita–Baylis–Hillman reaction. To a solution of chiral thiourea derivative (0.02 mmol, in CH_2Cl_2 (1.0 mL) was added substrates 8 (0.2 mmol) at room temperature. The reaction mixture was stirred at room temperature until the reaction completed (monitoring by TLC). The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography to afford the intramolecular Baylis–Hillman adducts. Compounds 1**3a–k** are known compounds; they were characterized by comparing their ^{1}H, ^{13}C NMR spectra with those published in the literature[18,19,21,25]. The ee values were determined by HPLC analysis with a chiral column.[30,41,46,48]

(*R*)-(6-Hydroxycyclohex-1-enyl)(phenyl) methanone (13a).[46,48] 87 % yield, 83 % ee; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.67-1.71 (m, 1H), 1.85-1.99 (m, 3H), 2.25-2.41 (m, 2H), 3.53 (d, *J* 1.2 Hz, 1H), 4.79 (d, *J* 1.2 Hz, 1H), 6.79 (t, *J* 4.0 Hz, 1H), 7.45 (t, *J* 7.2 Hz, 2H), 7.57 (t, *J* 7.2 Hz, 1H), 7.68 (d, *J* 7.2 Hz, 2H); HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=95/5, flow rate: 1.0 mL/min): t_R=9.8 min (major), 11.7 min (minor).

(*R*)-(6-hydroxycyclohex-1-enyl)(4-nitrophenyl)methanone (13b).[46,48] 63 % yield, 95 % ee; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.68-1.73 (m, 1H), 1.85-1.99 (m, 3H), 2.25-2.43 (m, 2H), 3.39 (s, 1H), (br s, 1H), 4.80 (s, 1H), 6.75 (s, 1H), 7.81 (d, *J* 8.4 Hz, 2H), 8.12 (d, *J* 8.4 Hz, 2H); HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.9 mL/min): t_R=21.5 min (minor), 43.8 min (major).

(*R*)-(2-Bromophenyl)(6-hydroxycyclohex-1-enyl)methanone (13c).[46,48] 90 % yield, 75 % ee; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.62-1.73 (m, 1H); 1.78-1.99 (m, 3H), 2.17-2.39 (m, 2H), 3.38 (s, 1H), 4.82 (t, *J* 4.4 Hz, 1H), 6.63 (t, *J* 4.0 Hz, 1H), 7.27-7.41 (m, 3H), 7.62 (d, *J* 8.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.9, 26.3, 29.9, 63.5, 120.1, 127.5, 128.9, 130.7, 133.3, 140.9, 141.76, 150.9, 198.9; HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t$_R$=9.5 min (major), 18.42 min (minor).

(*R*)-(3-Bromophenyl)(6-hydroxycyclohex-1-enyl)methanone (13d).[46,48] 90 % yield, 78 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.65-1.71 (m, 1H), 1.82-1.99 (m, 3H), 2.25-2.45 (m, 2H), 3.39 (s, 1H), 4.77 (s, 1H), 6.75 (t, *J* 4.0 Hz, 1H), 7.38 (t, *J* 8.0 Hz, 1H), 7.59 (d, *J* 8.0 Hz, 1H), 7.70 (d, *J* 8.0 Hz, 1H), 7.80 (s, 1H); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 17.8, 26.7, 29.9, 64.3, 123.1, 127.9, 130.2, 132.6, 134.9, 139.6, 140.3, 148.2, 197.9; HPLC analysis(AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flowrate: 1.0 mL/min): t$_R$=12.6 min (minor),14.8 min (major).

(*R*)-(4-Bromophenyl)(6-hydroxycyclohex-1-enyl)methanone (13e).[46,48] 85 % yield, 80 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.65-1.74 (m, 1H), 1.85-12.02 (m, 3H), 2.26-2.42 (m, 2H), 2.59 (br s, 1H), 4.79 (s, 1H), 6.78 (t, *J* =4.0 Hz, 1H), 7.57 (d, *J* 8.4 Hz, 2H), 7.65 (d, *J* 8.4 Hz, 2H); HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t$_R$=20.3 min (minor), 23.7 min (major).

(*R*)-(4-Chlorophenyl)(6-hydroxycyclohex-1-enyl)methanone (13f).[30,48] 83 % yield, 81 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.65-1.73 (m, 1H), 1.89-1.99– (m, 3H), 2.27-2.45 (m, 2H), 2.54 (br s, 1H), 4.78 (s, 1H), 6.73 (t, *J* 4.0 Hz, 1H), 7.47 (d, *J* 8.4 Hz, 2H), 7.68 (d, *J* 8.4 Hz, 2H); HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t$_R$=8,7 min (major), 13.5 min (minor).

(*R*)-(4-Fluorophenyl)(6-hydroxycyclohex-1-enyl)methanone (13g).[30,48] 78 % yield, 80 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.65-1.73– (m, 1H), 1.88-1.99 (m, 3H), 2.21-2.43 (m, 2H), 3.45 (s, 1H), 4.78 (s, 1H), 6.72 (t, *J* 4.0 Hz, 1H), 7.15 (t, *J* 8.4 Hz, 2H), 7.72-7.77 (m, 2H); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 17.84, 26.5, 30.3, 64.3, 115.9, 131.4, 134.4, 141.2, 146.7, 165.6, 197.9; HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.8 mL/ min): t$_R$=12.9 min (minor), 15.0 min (major).

(*R*)-(6-Hydroxycyclohex-1-enyl)(o-tolyl)methanone (13h)[39] 95 % yield, 62 % ee; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 1.59-1.69 (m, 1H), 1.79-1.94 (m, 3H), 2.17-2.35 (m, 2H), 2.32 (s, 3H), 3.55 (br s, 1H), 4.77 (br s, 1H), 6.62 (t, *J* = 4.0 Hz, 1H), 7.231 (m, 3H), 7.34 (m, 1H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 17.9, 19.9, 27.0, 30.2, 642, 125.2, 127.8, 130.2, 131.2, 135.9, 139.3, 141.9, 149.1, 202.1; HPLC analysis (Chiralcel OD column, λ=254 nm, eluent; hexanes: ethanol=98/2, flow rate; 0.75 mL/min; t$_R$=13.4 min (major), 27.1 min (minor).

(*R*)-(6-Hydroxycyclohex-1-enyl)(p-tolyl)methanone (13i)[41] 80 % yield, 65 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.62-1.68 (m, 1H), 1.86-1.98 (m, 3H), 2.21-2.38 (m, 2H), 2.43 (s, 3H), 2.93 (br s, 1H), 4.75 (s, 1H), 6.73 (t, *J* 4.0 Hz, 1H), 7.26 (d, *J* 7.6 Hz, 2H), 7.59 (d, *J* 8.0 Hz, 2H); HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flowrate: 1.0 mL/min): t$_R$=15.8 min (major), 17.8 min (minor).

(*R*)-(6-Hydroxycyclohex-1-enyl)(4-methoxyphenyl) methanone (13j)[41] 78 % yield, 60 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.64-1.70 (m, 1H), 1.86–1.97 (m, 3H), 2.24-2.41 (m, 2H), 3.62 (br s, 1H), 3.91 (s, 3H), 4.73 (s, 1H), 6.68 (t, *J* 4.0 Hz, 1H), 6.97 (d, *J* 8.8 Hz, 2H), 7.73 (d, J *J* 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 17.5, 26.5, 30.0, 55.7, 65.3, 114.1, 130.4, 132.1, 139.9, 145.2, 163.4, 198.8; HPLC analysis (AS-H column, λ=254 nm, eluent: n-hexane/i-propanol= 90/10, flow rate: 1.0 mL/min): t$_R$ = 15.2 min (major), 31.3 min (minor);

(*R*)-(6-Hydroxycyclohex-1-enyl)(thiophen-2-yl)methanone (13k).[30,48] 65 % yield, 72 % ee; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.62-1.71 (m, 1H), 1.79-1.97 (m, 3H), 2.27-2.45 (m, 2H), 2.72 (s, 1H), 4.71 (s, 1H), 6.98 (t, *J* 4.0 Hz, 1H), 7.13-7.19 (m, 1H), 7.65 (d, *J* 2.8 Hz, 1H), 7.71 (d, *J* 4.8 Hz, 1H); HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t$_R$=11.2 min (major), 18.2 min (minor).

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