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PAPER

C_2-symmetric proline-derived tetraamine as highly effective catalyst for direct asymmetric Michael addition of ketones to chalcones†

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A C_2-symmetric tetraamine catalyst was developed for the asymmetric Michael addition of ketones to chalcones. The corresponding adducts 1,5-dicarbonyl compounds were obtained in good chemical yields with high levels of diastereo- and enantioselectivities (up to >99 : 1 dr and 93% ee) under mild conditions. By studying the ESI-MS of the intermediates, a proposed mechanism was disclosed.

Introduction

The Michael addition reaction is widely recognized as a powerful tool for the generation of carbon–carbon bonds in organic synthesis.[1] During the past few years, a tremendous growth in the number of organocatalyzed highly stereoselective Michael addition reactions has been witnessed.[2] However, most of organocatalyzed Michael addition reactions employed either highly active Michael donors (*e.g.*, 1,3-dicarbonyls,[3] nitroalkanes[4] and dicyanomethane[5]) or highly active Michael acceptors (*e.g.*, nitroalkenes[6] and sulfones[7]). Enantioselective catalytic Michael addition of ketones to enones has remained significantly less developed probably due to the low reactivity and high steric hindrance of substrates. As far as we know, only few papers have been published on the asymmetric Michael addition of ketones to chalcones. Wang *et al.* accomplished the addition of ketones to chalcones for the first time with high enantioselectivity using a chiral pyrrolidinylmethylsulfonamide catalyst a (Fig. 1).[8] We reported an amino acid ionic liquid b (Fig. 1)[9] and a pyrrolidine–pyridine base catalyst c (Fig. 1)[10] for this type Michael addition reaction. While these catalysts were effective in this type of Michael addition with moderate to high enantioselectivities, they are not without their shortcomings. Specifically, a long reaction time (more than 4 days), high catalyst loading (200 mol%) and low chemical yield (45–70%). And these will put up the cost and limit their application in the pharmaceutical industry and other fields. Therefore, design and develop more efficiency catalysts aimed at overcoming these limitations in Michael addition reactions remains a great challenge in organic synthesis chemistry.

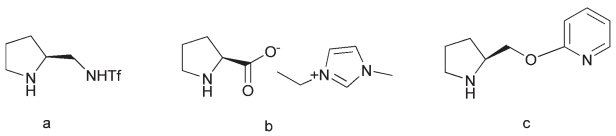

Fig. 1 Some organocatalysts for Michael addition of ketones to chalcones.

Of the developed organocatalysts in asymmetric catalysis, chiral amines derived from nature amino acid or cinchona alkaloids, which contain primary amine,[11] diamines[12] and triamines,[13] have proven to be powerful and been applied for the asymmetric catalytic Michael addition successfully. To the best of our knowledge, there have no tetraamines as organocatalysts for the Michael reaction. Therefore, in an effort to search for new and high effective catalysts, in this paper, we first disclosed such a set of tetraamines organocatalysts, which were tested in asymmetric Michael addition of ketones to chalcones. Among them, C_2-symmetric proline-derived tetraamine **2** was proved to be high efficiency for the reaction providing good yield with excellent diastereo- and enantioselectivity.

Results and discussion

Our investigation began with screening the organocatalysts shown in Table 1 for their ability to promote the asymmetric Michael addition reaction of cyclohexanone **5a** with 4-chlorochalcone **6a**. The initial reactions were performed by using 20 mol% of the catalysts at room temperature in $CHCl_3$. Examination of the results from this survey revealed that their catalytic activities varied significantly. For example, catalyst **1** and **3** are not effective catalysts for this process (entries 1 and 3). Although catalyst **4** afforded the product in good diastereoselectivity, it gave low yield and enantioselectivity (97 : 3 dr, 38% yield, 59% ee, entry 4). Catalysts **2** can promote the addition smoothly with good diastereoselectivity, higher yield and enantioselectivity (96 : 4 dr, 51% yield, 70% ee, entry 2), and this catalyst was

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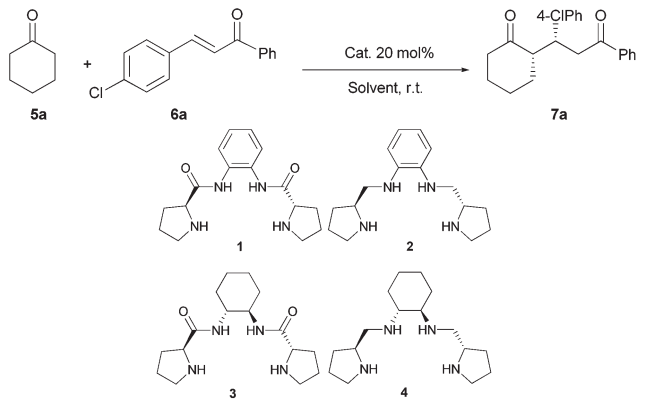
Table 1 The screen of different chiral catalysts **1–4** and solvents[a]



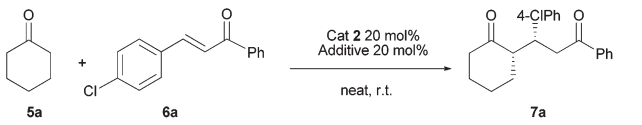
Entry	Cat.	Solvent	*T*/d	Yield (%)[b]	dr [*syn*/*anti*][c]	ee (%)[d]
1	**1**	$CHCl_3$	3	<5	nd	Nd
2	**2**	$CHCl_3$	3	51	96 : 4	70
3	**3**	$CHCl_3$	3	<5	nd	Nd
4	**4**	$CHCl_3$	3	38	97 : 3	59
5	**2**	CH_2Cl_2	3	50	99 : 1	67
6	**2**	i-PrOH	3	55	99 : 1	42
7	**2**	*t*-BuOH	3	31	99 : 1	56
8	**2**	CH_3OH	3	49	99 : 1	50
9	**2**	THF	3	54	98 : 2	63
10[e]	**2**	Neat	3	65	99 : 1	80
11	**2**	CH_3CN	3	47	98 : 2	75

[a] Unless otherwise specified, all reactions were carried out using **5a** (0.2 mL, 2.0 mmol), **6a** (0.2 mmol) and the catalysts (0.04 mmol, 20 mol%) in different solvents (0.5 mL) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] **5a** (0.4 mL, 4.0 mmol) was used.

selected for further studies. Therefore, the screening of different organic solvents with catalyst **2** was carried out (entries 5–11). From all the conditions tested, we found that the yields and enantioselectivities of the product differed significantly. When the reaction performed in less polar solvents such as CH_2Cl_2 and THF, no improvement was obtained in yields and enantioselectivities (entries 5 and 9). When the reaction proceed in CH_3OH, i-PrOH or *t*-BuOH, the products were formed in much lower enantioselectivities (entries 6–8). Higher enantioselectivity was obtained when CH_3CN was used, but the yield was low (47% yield, 75% ee, entry 11). The reaction was also performed under neat conditions, to our delight, it afforded the product in best yield with highest enantioselectivity and diastereoselectivity (65% yield, 99 : 1 dr, 80% ee, entry 10).

With the hope of improving the yield and selectivity, we next examined the effect of various acid additives. As illustrated in Table 2, the strong acid such as 2,4-dinitrobenzoic acid and TFA cannot promote the reaction, probably due to the poisoning of catalyst through salt formation (entries 2 and 12). The enantioselectivities are higher with benzoic acid or its derivatives with electron-donating substituents in the *para* position of the benzene ring (entries 6–8) than other weak acids such as 4-fluorobenzoic acid, phenol or 3,5-dimethylphenol. Finally, we found that 4-methoxybenzoic acid was the best additive in combination with catalyst **2** (81% yield, 98 : 2 dr, 89% ee, entry 8), and it was selected as the additive for further investigation.

Table 2 The effect of different acid additives[a]



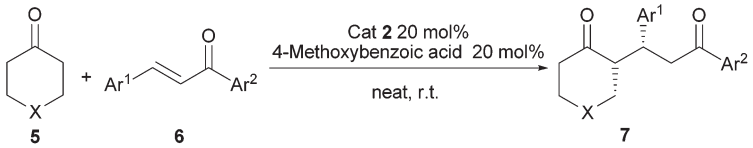
Entry	Additive	*T*/d	Yield (%)[b]	dr [*syn*/*anti*][c]	ee (%)[d]
1	Benzoic acid	3	71	99 : 1	87
2	2,4-Dinitrobenzoic acid	5	—	—	—
3	4-Fluorobenzoic acid	3	59	>99 : 1	79
4	4-Chlorobenzoic acid	3	64	>99 : 1	76
5	4-Bromobenzoic acid	3	61	98 : 2	80
6	2-Hydroxybenzoic acid	3	75	95 : 5	84
7	4-Hydroxybenzoic acid	3	78	97 : 3	86
8	4-Methoxybenzoic acid	3	81	98 : 2	89
9	Phenol	3	74	98 : 2	80
10	3,5-Dimethylphenol	3	69	98 : 2	83
11	4-Nitrophenol	3	85	96 : 4	86
12	TFA	5	—	—	—

[a] Unless otherwise specified, all reactions were carried out using **5a** (0.4 mL, 4.0 mmol), **6a** (0.2 mmol), catalysts **2** (0.04 mmol, 20 mol%) and the additives (0.04 mmol, 20 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis.

Having established the optimal reaction conditions, the scope and the limitation of this Michael reaction with different ketones **5** and chalcones **6** were examined. As shown in Table 3, structural variation in the α,β-unsaturated ketones was found to be tolerated in Michael addition reactions of cyclohexanone **5a** to chalcones **6** (entries 1–13). The catalyst-promoted processes were successful with aromatic systems (Ar^1) possessing electron-withdrawing substituents (85–93% ee, entries 3–7). Although electron-donating functionalities on Ar^1 resulted in excellent diastereoselectivity, a small decrease in enantioselectivity occurred (82% ee, entry 9). Good to excellent levels of enantioselectivities (85–92% ee) and diastereoselectivities (≥95 : 5) were obtained for reactions of chalcones containing different aromatic substituents (Ar^2) (entries 10–13). To further study the scope of catalyst **2** in Michael reaction, other cyclic ketones were also examined as the donor (entries 14–19). Reactions with 6-membered ring ketones such as 1,4-cyclohexanedione monoethylene acetal, tetrahydro-4*H*-thiopyran-4-one and tetrahydro-4*H*-pyran-4-one gave the Michael adducts in good yields (71–81%) with excellent enantioselectivities (88–92% ee) and diastereoselectivities (≥90 : 10) (entries 14, 15 and 18). Although 4-methyl cyclohexanone and *N*-methyl-4-piperidone gave high diastereoselectivities (≥95 : 5), only moderate enantioselectivities (67–75% ee) were obtained (entries 16–17). Reaction with cyclopentanone took place at a higher rate (1.5 d) and in high yield (90%), but the diastereoselectivity was low (80 : 20), and the major isomer had a comparably lower ee (60%) (entry 19).

After the above success, we sought to extend the catalytic activity of C_2-symmetric proline-derived tetraamine **2** in Michael reaction of 4-hydroxy coumarin **8** to benzylideneacetone **9**. The results of the reaction are shown in eqn (1), it proceeded

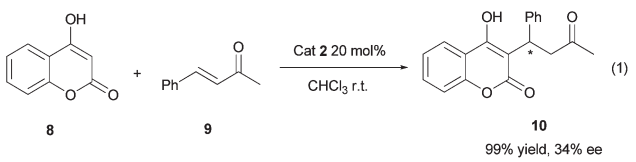
Table 3 Michael reaction of ketones to chalcones[a]



Entry	X	Ar^1	Ar^2	Product	*T*/d	Yield (%)[b]	dr [*syn*/*anti*][c]	ee (%)[d]
1	CH_2	4-ClC_6H_4	Ph	**7a**	3	81	98 : 2	89
2	CH_2	Ph	Ph	**7b**	3	77	>99 : 1	89
3	CH_2	2-ClC_6H_4	Ph	**7c**	3	86	83 : 17	85
4	CH_2	3-ClC_6H_4	Ph	**7d**	3	84	>99 : 1	90
5	CH_2	4-FC_6H_4	Ph	**7e**	3	88	>99 : 1	93
6	CH_2	4-BrC_6H_4	Ph	**7f**	3	90	91 : 9	90
7	CH_2	4-$NO_2C_6H_4$	Ph	**7g**	1.5	96	98 : 2	92
8	CH_2	1-Naphthyl	Ph	**7h**	3	73	>99 : 1	86
9	CH_2	4-MeC_6H_4	Ph	**7i**	4	76	99 : 1	82
10	CH_2	Ph	4-ClC_6H_4	**7j**	3	91	99 : 1	90
11	CH_2	Ph	4-$OMeC_6H_4$	**7k**	5	61	95 : 5	85
12	CH_2	Ph	4-$NH_2C_6H_4$	**7l**	5	67	98 : 2	87
13	CH_2	2-ClC_6H_4	4-$OMeC_6H_4$	**7m**	3	64	>99 : 1	92
14[e]	C[$O(CH_2)_2O$]	4-ClC_6H_4	Ph	**7n**	3	76	90 : 10	92
15[e]	S	4-ClC_6H_4	Ph	**7o**	3	71	98 : 2	90
16	$C(CH_3)$	Ph	Ph	**7p**	5	46	>99 : 1	75
17	$N(CH_3)$	Ph	Ph	**7q**	3	84	95 : 5	67
18	O	Ph	Ph	**7r**	3	81	97 : 3	88
19	None	Ph	Ph	**7s**	1.5	90	80 : 20	60

[a] Unless otherwise specified, all reactions were carried out using **5** (4.0 mmol), **6** (0.2 mmol), catalyst **2** (0.04 mmol, 20 mol%) and 4-methoxybenzoic acid (0.04 mmol, 20 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis. [e] CH_3CN (0.5 mL) as a solvent.

efficiently to give the corresponding product **10** in high yield (99%). However, the enantioselectivity of this reaction was low (34% ee).



(1)

The stereochemistries of the major products **7** were determined by comparison of their HPLC spectra with other previous studies.[8–10] To account for the stereochemical outcome of the Michael reaction, a plausible mechanism is shown in Fig. 2. The protonated catalyst **2** first forms a chiral enamine **I** with ketones **5**, and then a Michael reaction between the enamine-activated **I** and the chalcones **6** leads to the formation of the corresponding products **7** *via* transition state A. The protonated catalyst **2** is regenerated for use in the subsequent catalytic cycle. In transition state A, the NH protons provide stabilization through hydrogen bonding interaction with the chalcones carbonyl group, the enamine intermediate add to the *Si*-face of chalcones, thereby predicting the high enantioselectivity observed in the reaction. The existence of the intermediates **I** and **II** in the reaction mixture was confirmed by ESI-MS (Fig. 3 and 4) (reaction of cyclohexanone **5a** with 4-chlorochalcone **6a** as an example).

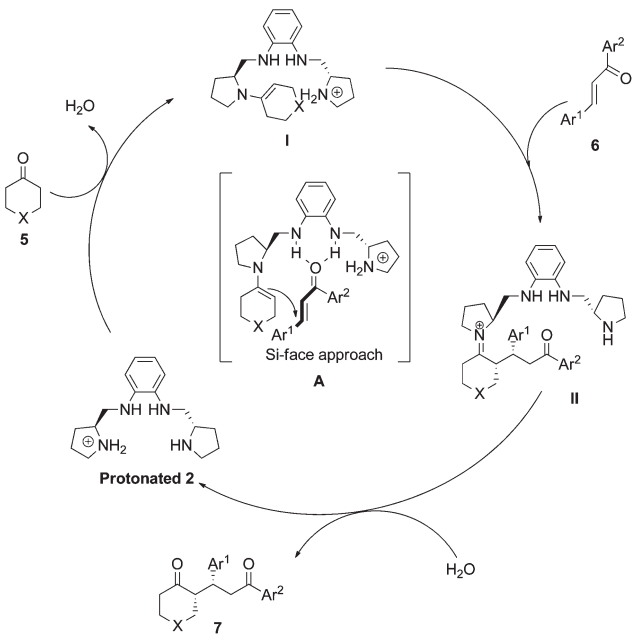


Fig. 2 Proposed mechanism for the **2**-catalyzed Michael reaction.

Conclusion

In summary, we have first presented a C_2-symmetric proline-derived tetraamine **2** as highly effective catalyst for asymmetric Michael addition reactions of ketones with chalcones. The

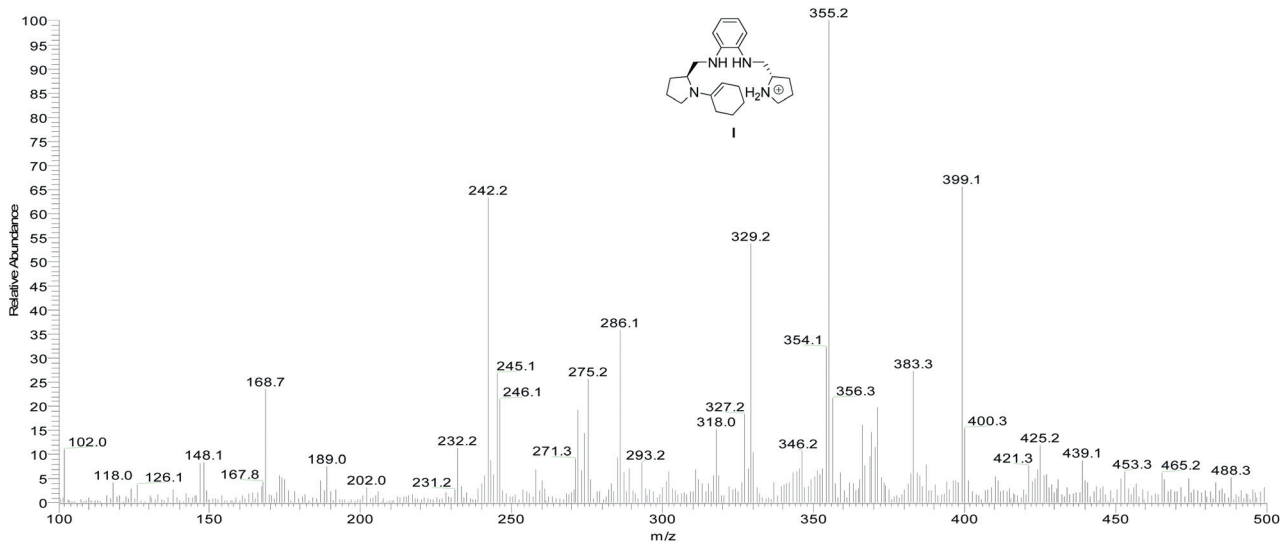


Fig. 3 ESI-MS spectra of the intermediate I (before adding the chalcones).

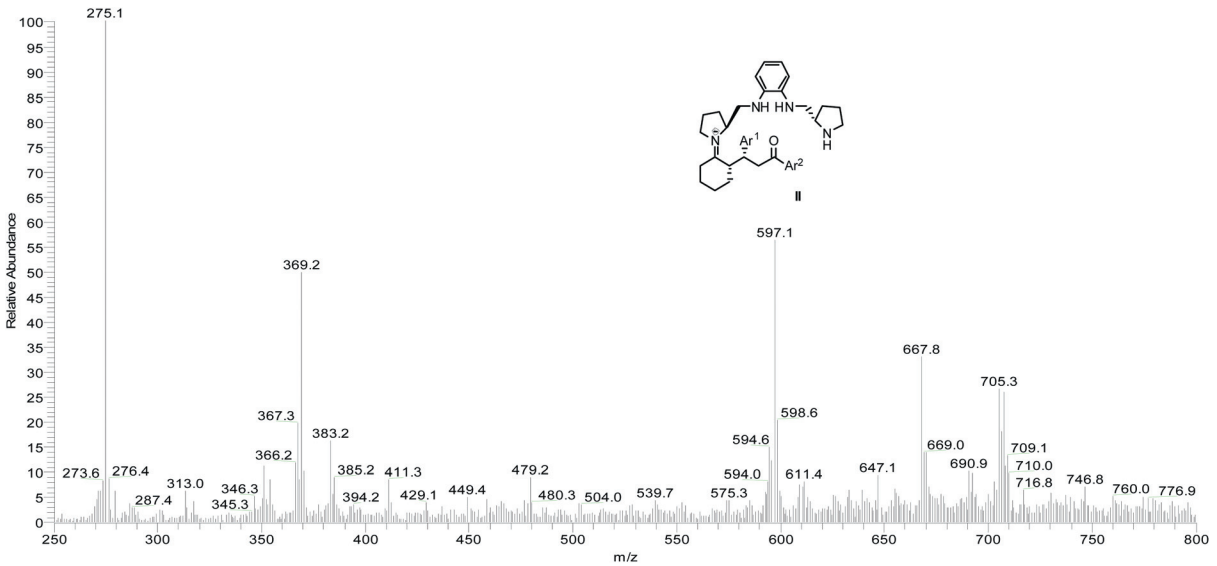


Fig. 4 ESI-MS spectra of the intermediate II (after 3 hours of reaction).

process is carried out under mild conditions to afford synthetically useful 1,5-dicarbonyl compounds in good to high yields with high to excellent levels of diastereoselectivities and enantioselectivities. Based on the experimental results and ESI-MS analysis of the intermediates, the mode of activity of the organocatalyst with the substrate was deduced. Further investigation of synthetic applications of this valuable reaction and the use of these organocatalysts in asymmetric catalysis are still in progress.

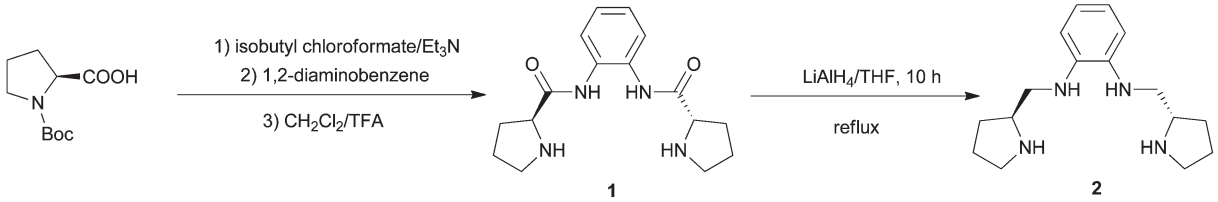
Experimental section

General information

All the solvents were purified according to standard procedures. The ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 75 MHz. ^{1}H and ^{13}C NMR chemical shifts were calibrated to tetramethylsilane as an external reference. Coupling constants are given in hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, double; t, triplet; m, multiplet. HR-MS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. HPLC analysis was performed on Shimadzu CTO-10AS by using a Chiralpak AD-H, OD-H or AS-H column purchased from Daicel Chemical Industries. The chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China), and were used without purification prior to use. All reactions were carried out directly under air unless otherwise noted.

General procedure for the synthesis of catalysts 1–4

Boc-protected L-proline (4.3 g, 20 mmol) and TEA (3.1 mL, 20 mmol) were dissolved in CH_2Cl_2 (25 mL). Isobutyl



Scheme 1 Synthesis of catalysts **1** and **2**.

chloroformate (2.6 mL, 20 mmol) was added to the solution dropwise at 0 °C. After the solution was stirred for 30 min, *o*-phenylenediamine (1.08 g, 10 mmol) in 10 mL CH_2Cl_2 was added over 15 min. The resulting solution was stirred at room temperature for 12 h and detected by TLC. The reaction mixture was washed with saturated aqueous $NaHSO_4$ (30 mL), water (30 mL), and dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and TFA (6.2 mL, 80 mmol) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred overnight. After removal of the organic solvents under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and treated with saturated Na_2CO_3 solution (30 mL) for 1 h at room temperature. The aqueous layer was extracted with CH_2Cl_2 three times (15 mL × 3) and the combined extracts were washed with brine (15 mL), then dried over anhydrous Na_2SO_4. Concentration *in vacuo* after filtration, the crude product was purified by column chromatography with CH_2Cl_2–MeOH (20 : 1) to afford 2.14 g (71%) of **1** as a white solid.

A solution of **1** (0.86 g, 2.85 mmol) in 15 mL anhydrous THF was added dropwise to a suspension of lithium aluminum hydride (0.54 g, 14.2 mmol) in 25 mL anhydrous THF in an ice bath, the mixture was stirred and heated to reflux for 10 h. The reaction mixture was chilled and 0.5 g (28 mmol) of water was added dropwise with vigorous stirring at 0 °C. The precipitated mass was filtered off and washed with THF. The combined filtrate and washings were dried over anhydrous Na_2SO_4, followed by evaporation of the solvent under vacuum to give 0.53 g (67%) catalyst **2** as a dark oil.

Catalysts **3** and **4** are prepared according the above procedure using (1*R*,2*R*)-1,2-diaminocyclohexane as starting material. The catalyst **3** obtained in 81% yield as a white solid, **4** 62% yield as a colorless oil.

***N*,*N*′-Bis[(*S*)-prolyl]phenylenediamine (1).**[14] White solid, mp 151–152 °C, 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.69–1.82 (m, 4H), 1.97–2.06 (m, 2H), 2.13–2.37 (m, 2H), 2.93–2.97 (m, 2H), 2.99–3.07 (m, 2H), 3.86 (dd, 2H, J_1 = 5.3 Hz, J_2 = 9.2 Hz), 7.11–7.21 (m, 2H), 7.63–7.68 (m, 2H), 9.59–9.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 26.27, 30.85, 47.37, 61.04, 123.99, 125.60, 129.76, 174.17; MS *m*/*z* = 302 ([M^+]).

***N*,*N*′-Bis{[(*S*)-pyrrolidin-2-yl]methyl}-phenylenediamine (2).**[14] Dark oil, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.49–1.58 (m, 2H), 1.73–2.02 (m, 6H), 2.91–3.12 (m, 6H), 3.24–3.29 (dd, 2H, J_1 = 5.6 Hz, J_2 = 4.0 Hz), 3.49–3.54 (m, 2H), 6.59–6.63 (m, 2H), 6.71–6.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 25.14, 29.19, 45.58, 48.03, 57.97, 111.34, 118.77, 136.87; MS *m*/*z* = 275 ([M^+ + 1]).

***N*,*N*′-Bis[(*S*)-prolyl]-(1*R*,2*R*)-1,2-diaminocyclohexane (3).**[15] White solid, mp 159–162 °C, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.87–0.96 (m, 1H), 1.09–1.18 (m, 4H), 1.29–1.41 (m, 6H), 1.95–2.15 (m, 3H), 2.90–3.10 (m, 4H), 3.58–3.69 (m, 4H), 7.66 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.73, 26.17, 30.80, 32.60, 47.12, 52.56, 60.58, 174.95; MS *m*/*z* = 308 ([M^+]).

***N*,*N*′-Bis{[(*S*)-pyrrolidin-2-yl]methyl}-(1*R*,2*R*)-1,2-diaminocyclohexane (4).**[15] Colorless oil, 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.98–1.03 (m, 1H), 1.09–1.40 (m, 4H), 1.64–1.79 (m, 5H), 1.80–1.98 (m, 2H), 1.99–2.20 (m, 3H), 2.27–2.35 (m, 2H), 2.68–3.09 (m, 8H), 3.11–3.29 (m, 2H), 3.50–3.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 25.03, 25.48, 29.65, 31.74, 46.34, 52.18, 52.88, 62.10; MS *m*/*z* = 281 ([M^+ + 1]).

Typical procedure for Michael reaction of ketones with chalcones

Catalyst **2** (11 mg, 0.04 mmol) and 4-methoxybenzoic acid (6 mg, 0.04 mmol) were added to a vial containing ketones **5** (4 mmol) and chalcones **6** (0.2 mmol) at room temperature. The mixture was stirred vigorously and monitored by TLC. When the reaction was finished, the mixture was purified by flash silica gel chromatography eluting with various mixtures of petroleum ether : EtOAc to afford the desired products **7**.

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7a).[10] 81% yield; *syn*/*anti* = 98 : 2 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.20–1.29 (m, 1H), 1.62–1.81 (m, 4H), 1.95–2.05 (m, 1H), 2.31–2.53 (m, 2H), 2.69 (m, 1H), 3.19 (dd, 1H, J_1 = 9.9 Hz, J_2 = 16.5 Hz), 3.50 (dd, 1H, J_1 = 4.2 Hz, J_2 = 16.5 Hz), 3.71 (dt, 1H, J_1 = 9.6 Hz, J_2 = 3.9 Hz), 7.10–7.13 (m, 2H), 7.20–7.23 (m, 2H), 7.40–7.44 (m, 2H), 7.51–7.54 (m, 1H), 7.90 (d, 2H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.34, 28.51, 32.51, 40.53, 42.46, 43.94, 55.61, 128.15, 128.54, 128.63, 129.76, 132.29, 132.99, 136.89, 140.58, 198.50, 213.12. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 13.4 min (minor) and 17.25 min (major), 89% ee.

(*S*)-2-((*R*)-3-Oxo-1,3-diphenylpropyl)-cyclohexanone (7b).[8] 77% yield; *syn*/*anti* = >99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23–1.30 (m, 1H), 1.59–1.81 (m, 4H), 1.95–2.03 (m, 1H), 2.36–2.49 (m, 1H), 2.52–2.58 (m, 1H), 2.75 (dt, 1H, J_1 = 10.2 Hz, J_2 = 4.8 Hz), 3.25 (dd, 1H, J_1 = 9.9 Hz, J_2 = 16.5 Hz), 3.51 (dd, 1H, J_1 = 4.2 Hz, J_2 = 16.5 Hz), 3.75 (dt, 1H, J_1 = 9.6 Hz, J_2 = 3.9 Hz), 7.12–7.16 (m, 3H),

7.22–7.32 (m, 2H), 7.40–7.49 (m, 2H), 7.50–7.57 (m, 1H), 7.89 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.11, 28.55, 32.46, 41.13, 42.33, 44.24, 55.84, 126.62, 128.18, 128.37, 128.46, 132.82, 137.07, 142.05, 198.79, 213.64. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 13.63 min (minor) and 20.83 min (major), 89% ee.

(*S*)-2-((*R*)-1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7c).[8] 86% yield; *syn*/*anti* = 83 : 17 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.20–1.39 (m, 1H), 1.57–1.83 (m, 4H), 2.00–2.09 (m, 1H), 2.36–2.43 (m, 1H), 2.56–2.58 (m, 1H), 2.89 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz), 3.38 (dd, 1H, J_1 = 10.0 Hz, J_2 = 15.6 Hz), 3.57 (dd, 1H, J_1 = 4.0 Hz, J_2 = 16.0 Hz), 4.22 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.0 Hz), 7.09 (t, 1H, J = 7.2 Hz), 7.17 (t, 1H, J = 7.2 Hz), 7.26–7.31 (m, 2H), 7.41 (t, 2H, J = 7.2 Hz), 7.51 (t, 1H, J = 7.2 Hz), 7.93 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.78, 28.66, 29.72, 32.62, 42.72, 42.93, 55.14, 127.02, 127.69, 128.22, 128.46, 129.89, 132.85, 134.65, 136.95, 139.61, 198.61, 213.16. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 12.26 min (minor) and 19.34 min (major), 85% ee.

(*S*)-2-((*R*)-1-(3-Chlorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7d).[10] 84% yield; *syn*/*anti* = >99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21–1.29 (m, 1H), 1.53–1.81 (m, 4H), 1.99–2.04 (m, 1H), 2.34–2.42 (m, 1H), 2.46–2.52 (m, 1H), 2.70 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz), 3.22 (dd, 1H, J_1 = 9.6 Hz, J_2 = 16.4 Hz), 3.49 (dd, 1H, J_1 = 3.6 Hz, J_2 = 16.4 Hz), 3.71 (dt, 1H, J_1 = 9.6 Hz, J_2 = 3.6 Hz), 7.08–7.20 (m, 4H), 7.42 (t, 2H, J = 7.6 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.90 (d, 2H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.36, 28.49, 32.55, 40.76, 42.46, 43.84, 55.51, 126.86, 128.14, 128.35, 128.53, 129.71, 132.98, 134.27, 136.90, 144.40, 198.29, 212.97. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 10.57 min (minor) and 20.07 min (major), 90% ee.

(*S*)-2-((*R*)-1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7e).[8] 88% yield; *syn*/*anti* = >99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21–1.28 (m, 1H), 1.53–1.81 (m, 4H), 1.97–2.05 (m, 1H), 2.37–2.47 (m, 1H), 2.50–2.56 (m, 1H), 2.72 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz), 3.20 (dd, 1H, J_1 = 10.0 Hz, J_2 = 16.0 Hz), 3.51 (dd, 1H, J_1 = 4.0 Hz, J_2 = 16.0 Hz), 3.74 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.0 Hz), 6.94–6.98 (t, 2H), 7.14–7.18 (t, 2H), 7.42–7.57 (t, 2H),7.52–7.56 (t, 1H), 7.92–7.94 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.29, 28.55, 32.50, 40.40, 42.45, 44.19, 55.79, 115.20, 128.16, 128.53, 129.74, 129.81, 132.97, 136.88, 137.62, 198.68, 213.38. HPLC analysis: Chiralpak OD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 7.48 min (minor) and 8.02 min (major), 93% ee.

(*S*)-2-((*R*)-1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7f).[9] 90% yield; *syn*/*anti* = 91 : 9 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26–1.29 (m, 1H), 1.62–1.81 (m, 4H), 1.97–2.03 (m, 1H), 2.35–2.55 (m, 2H), 2.71 (dt, 1H, J_1 = 10.0 Hz, J_2 = 10.0 Hz, J_3 = 4.8 Hz), 3.20 (dd, 1H, J_1 = 16.37 Hz, J_2 = 9.79 Hz), 3.51 (dd, 1H, J_1 = 16.4 Hz, J_2 = 3.9 Hz), 3.70 (dt, 1H, J_1 = 9.8 Hz, J_2 = 9.8 Hz, J_3 = 3.9 Hz), 7.09 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H J = 8.4 Hz), 7.45 (d, 2H, J = 7.8 Hz), 7.56 (t, 1H, J = 7.3 Hz),7.92 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.37, 28.52, 32.54, 40.57, 42.48, 43.88, 55.54, 120.38, 128.15, 128.54, 130.18, 131.57, 133.01, 136.86, 141.15, 198.45, 213.08. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 0.9 mL min^{-1}, λ = 254 nm, retention time: 16.26 min (minor) and 20.31 min (major), 90% ee.

(*S*)-2-((*R*)-1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7g).[8] 96% yield; *syn*/*anti* = 98 : 2 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21–1.27 (m, 1H), 1.58–1.90 (m, 4H), 2.06–2.10 (m, 1H), 2.39–2.55 (m, 2H), 2.79 (dt, 1H, J_1 = 10.8 Hz, J_2 = 5.2 Hz), 3.34 (dd, 1H, J_1 = 10.0 Hz, J_2 = 16.8 Hz), 3.62 (dd, 1H, J_1 = 3.6 Hz, J_2 = 16.8 Hz), 3.90 (dt, 1H, J_1 = 9.6 Hz, J_2 = 4.0 Hz), 7.41–7.47 (m, 4H), 7.56 (t, 1H, J = 7.2 Hz), 7.92 (d, 2H, J = 8.0 Hz), 8.15 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.70, 28.45, 32.75, 40.91, 42.67, 43.44, 55.15, 123.67, 128.09, 128.64, 129.45, 133.25, 136.59, 146.64, 150.35, 197.93, 212.25. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.6 mL min^{-1}, λ = 254 nm, retention time: 17.56 min (minor) and 30.72 min (major), 92% ee.

(*S*)-2-((*R*)-1-(Naphthalen-1-yl)-3-oxo-3-phenylpropyl)-cyclohexanone (7h).[10] 73% yield; *syn*/*anti* = >99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25–1.30 (m, 1H), 1.42–1.75 (m, 4H), 1.95–2.04 (m, 1H), 2.37–2.47 (m, 1H), 2.50–2.59 (m, 1H), 2.87 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz), 3.45 (dd, 1H, J_1 = 10.0 Hz, J_2 = 16.0 Hz), 3.69 (dd, 1H, J_1 = 3.6 Hz, J_2 = 16.4 Hz), 3.68 (dt, 1H, J_1 = 9.6 Hz, J_2 = 3.6 Hz), 7.34–7.47 (m, 7H), 7.67–7.72 (m, 1H), 7.78–7.88 (m, 3H), 8.11–8.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.67, 28.74, 32.81, 34.05, 42.68, 44.76, 57.10, 123.59, 125.48, 126.00, 127.03, 128.14, 128.41, 128.82, 132.77, 137.03, 198.83, 213.93. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 11.41 min (minor) and 23.32 min (major), 86% ee.

(*S*)-2-((*R*)-3-Oxo-3-phenyl-1-*p*-tolylpropyl)-cyclohexanone (7i).[10] 76% yield; *syn*/*anti* = 99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21–1.40 (m, 1H), 1.56–1.87 (m, 4H), 1.96–2.06 (m, 1H), 2.30 (s, 3H), 2.30–2.43 (m, 1H), 2.49–2.57 (m, 1H), 2.69 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz), 3.19 (dd, 1H, J_1 = 9.2 Hz, J_2 = 15.6 Hz), 3.47 (dd, 1H, J_1 = 2.8 Hz, J_2 = 16.0 Hz), 3.67 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.0 Hz), 7.07 (d, 4H, J = 7.2 Hz), 7.43 (t, 2H, J = 6.8 Hz), 7.52 (t, 1H, J = 6.0 Hz), 7.93 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.08, 28.57, 32.44, 40.76, 42.31, 44.33, 50.84, 55.93, 128.18, 128.21, 128.45, 129.18, 132.81, 136.09, 137.05, 138.84, 199.01, 213.94. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 11.23 min (minor) and 16.25 min (major), 82% ee.

(*S*)-2-((*R*)-1-(4-Phenyl)-3-oxo-3-(4′-chlorophenyl)-propyl)-cyclohexanone (7j).[8] 91% yield; *syn*/*anti* = 99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.22–1.27(m, 1H), 1.62–1.80

(m, 4H), 1.97–2.05 (m, 1H), 2.35–2.55 (m, 2H), 2.73 (dt, 1H, J_1 = 10.2 Hz, J_2 = 10.0 Hz, J_3 = 4.9 Hz), 3.15 (dd, 1H, J_1 = 15.9 Hz, J_2 = 9.6 Hz), 3.50 (dd, 1H, J_1 = 15.9 Hz, J_2 = 4.0 Hz), 3.70 (dt, 1H, J_1 = 9.9 Hz, J_2 = 9.9 Hz, J_3 = 4.0 Hz), 7.11–7.20 (m, 3H), 7.26 (d, 2H, J = 7.5 Hz), 7.39 (d, 2H, J = 8.6 Hz), 7.86 (d, 2H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.31, 28.65, 32.72, 41.41, 42.51, 44.41, 55.79, 126.74, 128.27, 128.55, 128.77, 129.68, 135.27, 139.22, 141.71, 197.70, 213.74. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 12.86 min (minor) and 17.30 min (major), 90% ee.

(*S*)-2-((*R*)-3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)-cyclohexanone (7k).[8] 61% yield; *syn*/*anti* = 95 : 5 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25–1.30 (m, 1H), 1.58–1.88 (m, 4H), 1.97–2.04 (m, 1H), 2.38–2.45 (m, 1H), 2.49–2.55 (m, 1H), 2.75 (dt, 1H, J_1 = 10.0 Hz, J_2 = 5.2 Hz), 3.20 (dd, 1H, J_1 = 9.6 Hz, J_2 = 16.0 Hz), 3.45 (dd, 1H, J_1 = 4.4 Hz, J_2 = 16.0 Hz), 3.75 (dt, 1H, J_1 = 9.6 Hz, J_2 = 4.0 Hz), 3.88 (s, 3H), 6.90 (d, 2H, J = 8.8 Hz), 7.14–7.17 (m, 3H), 7.23–7.26 (m, 3H), 7.92 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.03, 28.56, 32.40, 41.32, 42.28, 43.87, 55.43, 55.89, 113.60, 126.58, 128.38, 128.46, 130.47, 142.09, 163.28, 197.33, 213.76. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 16.87 min (minor) and 22.85 min (major), 85% ee.

(*S*)-2-((*R*)-1-(4-Phenyl)-3-oxo-3-(4′-aminophenyl)-propyl)-cyclohexanone (7l).[9] 67% yield; *syn*/*anti* = 99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30–1.34 (m, 1H), 1.58–1.64 (m, 3H), 1.76–1.84 (m, 2H), 1.96–2.04 (m, 1H), 2.38–2.60 (m, 2H), 2.78 (dt, 1H, J_1 = 10.1 Hz, J_2 = 9.8 Hz, J_3 = 4.8 Hz), 3.34 (dd, 1H, J_1 = 15.9 Hz, J_2 = 9.6 Hz), 3.63 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.0 Hz), 3.79 (dt, 1H, J_1 = 9.8 Hz, J_2 = 9.8 Hz, J_3 = 4.0 Hz), 7.18–7.23 (m, 3H), 7.50–7.60 (m, 2H), 7.81–7.84 (m, 2H), 7.92–7.97 (m, 2H), 8.5 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.16, 28.63, 32.57, 41.42, 42.41, 44.38, 55.93, 124.03, 126.62, 127.72, 128.38, 128.53, 129.67, 129.98, 132.52, 134.29, 135.49, 141.97, 198.79, 213.86. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 23.59 min (major) and 28.43 min (minor), 87% ee.

(*S*)-2-((*R*)-1-(2-Chlorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl)-cyclohexanone (7m).[10] 64% yield; *syn*/*anti* = >99 : 1 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29–1.39 (m, 1H), 1.57–1.85 (m, 4H), 2.01–2.06 (m, 1H), 2.36–2.44 (m, 1H), 2.48–2.54 (m, 1H), 2.89 (dt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz), 3.32 (dd, 1H, J_1 = 10.0 Hz, J_2 = 16.0 Hz), 3.84 (s, 3H), 3.54 (dd, 1H, J_1 = 4.0 Hz, J_2 = 16.4 Hz), 4.24 (dt, 1H, J_1 = 9.6 Hz, J_2 = 3.6 Hz), 6.90 (d, 2H, J = 8.8 Hz), 7.09 (t, 1H, J = 6.8 Hz), 7.18 (t, 1H, J = 7.2 Hz), 7.27–7.32 (m, 2H), 7.95 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.73, 28.69, 32.62, 42.60, 42.70, 55.42, 113.59, 126.98, 127.64, 129.85, 130.08, 130.53, 134.65, 139.65, 163.30, 197.15, 213.29. HPLC analysis: Chiralpak OD-H column, i-PrOH–hexane 30 : 70, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 5.89 min (minor) and 7.57 min (major), 92% ee.

(*R*)-2-((*R*)-1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-1,4-cyclohexanedione monoethylene acetal (7n).[8] 76% yield; *syn*/*anti* = 90 : 10 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.54 (t, 1H, J = 12.5 Hz), 1.65–1.73 (m, 1H), 1.85–2.10 (m, 2H), 2.45–2.53 (m, 1H), 2.63–2.72 (m, 1H), 3.00–3.10 (m, 1H), 3.19 (dd, 1H, J_1 = 16.0 Hz, J_2 = 10.0 Hz), 3.52 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.0 Hz), 3.78 (dt, 1H, J_1 = 13.5 Hz, J_2 = 4.0 Hz), 3.75–4.01 (m, 4H), 7.12 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.42 (t, 2H, J = 7.5 Hz), 7.53 (t, 1H, J = 7.5 Hz), 7.91 (d, 2H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 35.15, 38.67, 39.12, 40.09, 43.97, 51.13, 64.52, 64.77, 107.28, 128.13, 128.55, 128.66, 129.87, 132.31, 133.01, 136.83, 140.22, 198.28, 211.35. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 15.27 min (minor) and 30.29 min (major), 92% ee.

(*S*)-3-((*R*)-1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-tetrahydrothiopyran-4-one (7o).[8] 71% yield; *syn*/*anti* = 98 : 2 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.4 (dd, 1H, J_1 = 14.0 Hz, J_2 = 7.5 Hz), 2.65–2.77 (m, 2H), 2.87–3.03 (m, 4H), 3.30 (d, 2H, J = 6.5 Hz), 4.08, (dd, 1H, J_1 = 13.5 Hz, J_2 = 7.0 Hz), 7.19 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 7.42 (t, 2H, J = 7.5 Hz), 7.53 (d, 1H, J = 7.5 Hz), 7.86 (d, 2H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 31.38, 34.63, 39.71, 43.36, 43.69, 57.72, 128.04, 128.59, 129.01, 129.72, 132.79, 133.19, 136.69, 139.59, 197.73, 210.71. HPLC analysis: Chiralpak AS-H column, i-PrOH–hexane 40 : 60, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time: 20.70 min (minor) and 30.78 min (major), 90% ee.

(*S*)-2-((*R*)-3-Oxo-1,3-diphenylpropyl)-4-methyl-cyclohexanone (7p).[10] 46% yield; *syn*/*anti* = >99 : 1 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88 (d, 3H, J = 6.6 Hz), 1.25–1.35 (m, 1H), 1.40–1.54 (m, 2H), 2.00–2.09 (m, 1H), 2.11–2.21 (m, 1H), 2.63–2.74 (m, 2H), 3.19 (dd, 1H, J_1 = 4.5 Hz, J_2 = 17.4 Hz), 3.35 (dd, 1H, J_1 = 8.4 Hz, J_2 = 17.4 Hz), 3.82–3.90 (m, 1H), 7.16–7.31 (m, 5H), 7.35–7.40 (m, 2H), 7.47–7.52 (m, 1H), 7.83 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.75, 26.22, 35.32, 37.83, 38.85, 40.78, 43.91, 54.98, 126.82, 128.02, 128.11, 128.49, 128.71, 133.01, 136.90, 142.11, 198.27, 215.32. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 10 : 90, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 12.19 min (major) and 12.78 min (minor), 75% ee.

(*R*)-3-((*R*)-3-Oxo-1,3-diphenylpropyl)-1-methylpiperidin-4-one (7q).[10] 84% yield; *syn*/*anti* = 95 : 5 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.04–2.14 (m, 1H), 2.20 (s, 3H), 2.34 (s, 1H), 2.37–2.47 (m, 1H), 2.58 (d, 2H, J = 14.2 Hz), 2.71–2.88 (m, 2H), 3.28 (dd, 2H, J_1 = 16.5 Hz, J_1 = 9.3 Hz), 3.48 (d, 1H, J = 14.3 Hz), 3.90 (s, 1H), 7.23 (dd, 3H, J_1 = 14.4 Hz, J_2 = 7.3 Hz), 7.40 (d, 2H, J = 7.4 Hz), 7.88 (d, 2H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 39.68, 41.22, 43.98, 45.27, 55.19, 56.47, 59.66, 126.80, 128.09, 128.29, 128.47, 128.59, 132.86, 137.01, 141.67, 198.29, 211.08. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 20 : 80, flow rate 0.6 mL min^{-1}, λ = 254 nm, retention time: 15.71 min (minor) and 21.32 min (major), 67% ee.

(*R*)-3-((*R*)-3-Oxo-1,3-diphenylpropyl)-tetrahydropyran-4-one (7r).[10] 81% yield; *syn*/*anti* = 97 : 3 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.45–2.59 (m, 1H), 2.69–2.85 (m, 2H), 3.28–3.50 (m, 3H), 3.54–3.66 (m, 1H), 3.82–4.03 (m, 3H), 7.10–7.35 (m, 4H), 7.38–7.49 (m, 2H), 7.48–7.54 (m, 1H), 7.87 (d, 2H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 38.77, 42.40, 43.80, 57.15, 68.89, 71.16, 125.58, 127.05, 128.06, 128.21, 128.51, 128.78, 132.99, 136.92, 141.15, 198.04, 209.05. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 15 : 85, flow rate 0.7 mL min^{-1}, λ = 254 nm, retention time: 24.58 min (minor) and 27.30 min (major), 88% ee.

(*S*)-2-((*R*)-3-Oxo-1,3-diphenylpropyl)-cyclopentanone (7s).[16] 90% yield; *syn*/*anti* = 80 : 20 (by ^{1}H NMR), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.51–1.60 (m, 1H), 1.65–1.75 (m, 1H), 1.87–1.90 (m, 2H), 2.06 (dd, 1H, J_1 = 9.0 Hz, J_2 = 18.6 Hz), 2.21–2.27 (m, 1H), 2.46 (dd, 1H, J_1 = 8.7 Hz, J_2 = 17.1 Hz), 3.36 (dd, 1H, J_1 = 7.5 Hz, J_2 = 16.8 Hz), 3.70 (dd, 1H, J_1 = 7.5 Hz, J_2 = 14.4 Hz), 3.87 (dd, 1H, J_1 = 6.3 Hz, J_2 = 16.5 Hz), 7.17–7.29 (m, 5H), 7.42 (t, 2H, J = 7.5 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.91 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.30, 27.94, 38.89, 40.83, 42.92, 52.95, 126.67, 128.09, 128.32, 128.44, 128.55, 132.99, 137.05, 142.51, 198.72, 220.09. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 50 : 50, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 7.21 min (minor) and 9.67 min (major), 60% ee.

Typical procedure for Michael reaction of 4-hydroxy coumarin to benzylideneacetone

To a stirring solution of catalyst **2** (11 mg, 0.04 mmol) in $CHCl_3$ (0.5 mL), benzylideneacetone **9** (22 mg, 0.15 mmol) was added followed by 4-hydroxy coumarin **8** (16 mg, 0.1 mmol). The mixture was stirred vigorously and monitored by TLC. When the reaction was finished, the solvent was evaporated and the crude product was purified by flash silica gel chromatography (petroleum ether–EtOAc = 2 : 1) to afford the desired product **10** as a white solid.

Warfarin (10).[17b] 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.69 (s, 1.58H), 1.73 (s, 1.73H), 2.03 (dd, 0.89H, J_1 = 22.3 Hz, J_2 = 10.8 Hz), 2.31 (s, 0.39 H), 2.49 (dt, 1.63 H, J_1 = 21.2 Hz, J_2 = 14.2 Hz, J_3 = 5.1 Hz), 3.34 (d, 0.61, J = 16.5 Hz), 3.88 (dd, 0.17H, J_1 = 19.4 Hz, J_2 = 10.1 Hz), 4.16 (m, 0.77 H), 4.31 (m, 0.52 H), 4.73 (d, 0.14 H, J = 8.0 Hz), 7.18–7.40 (m, 7H), 7.51 (t, 0.68H, J = 7.7 Hz), 7.59 (t, 0.55H, J = 7.4 Hz), 7.83 (d, 0.56H, J = 8.2 Hz), 7.92 (d, 0.46H, J = 7.8 Hz), 7.96 (d, 0.16H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 27.72, 28.20, 30.10, 34.20, 34.85, 35.35, 40.00, 42.55, 45.17, 99.01, 100.53, 101.15, 104.19, 115.56, 115.89, 116.21, 116.52, 116.67, 122.73, 123.08, 123.64, 123.96, 126.51, 126.98, 127.05, 127.23, 127.99, 128.19, 128.64, 129.24, 131.57, 132.04, 141.45, 143.22, 152.90, 152.99, 158.82, 159.71, 161.33, 162.19. HPLC analysis: Chiralpak AD-H column, i-PrOH–hexane 20 : 80, flow rate 1.0 mL min^{-1}, λ = 254 nm, retention time: 5.27 min (major) and 13.67 min (minor), 34% ee.

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