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PAPER

Camphor-derived C_1-symmetric chiral diamine organocatalysts for asymmetric Michael addition of nitroalkanes to enones†

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A series of stable C_1-symmetric chiral diamines (**2a–2l**) were conveniently synthesized by condensing *exo*-(−)-bornylamine or (+)-(1*S*,2*S*,5*R*)-menthylamine with various commercially available Cbz-protected amino acids. Among them, **2a** can efficiently promote the Michael addition of nitroalkanes to a broad scope of enones with high yields (up to 96%) and excellent enantioselectivities (up to 98%) under mild conditions.

Introduction

Over the past decade, asymmetric organocatalysis has become a more and more important complement to traditional metal catalysis and biocatalysis, and has found broad utility in organic synthesis.[1] For a long period of time, chiral secondary amines have been undoubtedly the dominant organocatalysts for their efficient activation of the carbonyl group, especially aliphatic aldehydes and α,β-unsaturated aldehydes, *via* enamine or iminium activation.[1d,2f] However, primary amines have not attracted much attention until very recently.[2] Compared with the various well-developed chiral secondary amine organocatalyst systems, novel chiral primary amines having strong asymmetric induction ability for a wide substrate scope are still in high demand.

The asymmetric Michael addition of nitroalkanes to enones, as one of the most powerful atom-economical carbon–carbon bond-constructing methods, furnishes useful adducts which can be transformed into a wide variety of valuable optically active building blocks, such as multi-substituted pyrrolidines and unnatural amino acids.[3] Therefore, the development of catalytic asymmetric reaction variants have focused great interest and both metal catalysis[4] and organocatalysis systems have been successfully developed.[5–7] The asymmetric additions of nitroalkanes to chalcones[5] or cyclic enones[6] have already achieved excellent ee values up to 99%. Nevertheless, there are few reports about "cinnamones",[7] especially in the case of bulkier 2-nitropropane, and the highest ee reported to date has been 91%.[7f] Meanwhile, the nitromethane adducts can also be delivered by the conjugate addition of acetone or acetophenone to nitroalkenes. However, the production of 2-nitropropanes bearing a quaternary carbon atom are otherwise difficult to access. In light of the knowledge of effective mechanism of iminium activation of enones by chiral primary amines[2,3e,f] and our previous success in developing a group of C_1-symmetric chiral secondary diamines from L-proline and D-camphor,[8a,9] we assumed that chiral primary–secondary diamines bearing a camphor skeleton may partially circumvent the existing limitations and enhance the enantioselectivity. Herein, we disclose a highly asymmetric Michael addition of nitroalkanes to enones catalyzed by a novel C_1-symmetric chiral primary–secondary diamine **2a** derived from L-phenylalanine and *exo*-(−)-bornylamine.

Results and discussion

Very recently, we prepared *exo*-(−)-bornylamine from D-camphor and applied it to constructing a new chiral secondary diamine **2f** (Fig. 1) as a potential catalyst for enantioselective Henry reactions.[8] In our continued synthetic efforts toward the development of new chiral diamine catalysts, we designed and synthesized a class of novel C_1-symmetric chiral primary–secondary diamines from primary amino acids and *exo*-(−)-bornylamine through the route outlined in Scheme 1. Firstly, Cbz-protected L-phenylalanine was condensed with *exo*-(−)-bornylamine. Then the desired amide compound **1a** was obtained after the deprotection of the Cbz group. Subsequent reduction of **1a** using $LiAlH_4$ in THF provided the desired chiral primary–secondary diamine **2a**. Using the above three-step practical protocol, a series of chiral diamines (**2a–2l**) were conveniently prepared in moderate to good yields under mild reaction conditions. This synthetic route is quite simple and straightforward and can be operable on a gram scale.

Initially, the Michael addition of 2-nitropropane (**4**) to 4-chlorobenzylideneacetone (**3a**) was chosen as a model reaction using 20 mol% **2a** as the catalyst to optimize the reaction conditions

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†Electronic supplementary information (ESI) available: Detailed information for optimization of the reaction as well as NMR spectra and HPLC traces. See DOI: 10.1039/c2ob25922b

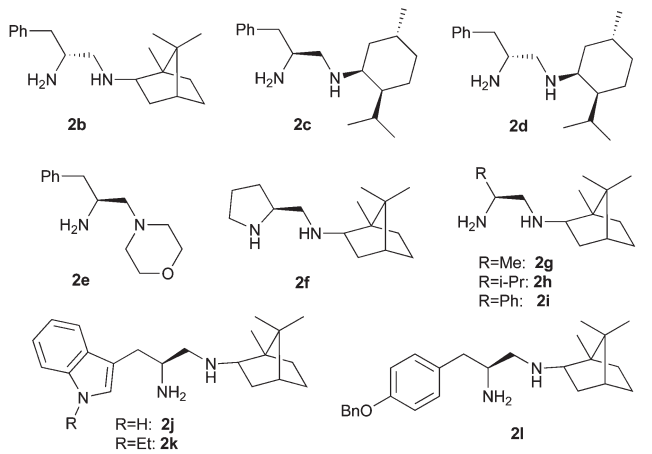
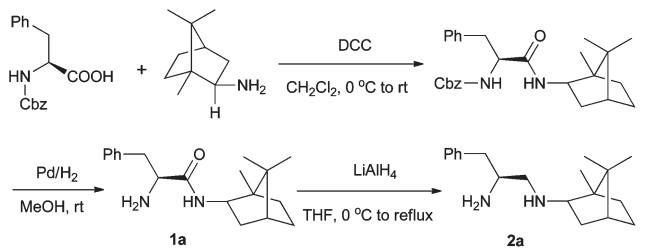


Fig. 1 Structures of other C_1-symmetric chiral diamine organocatalysts.

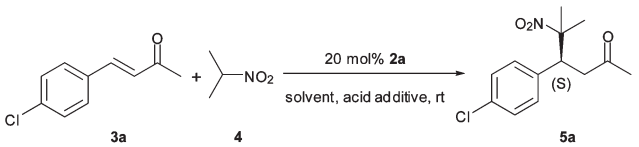


Scheme 1 General synthesis route of the C_1-symmetric chiral diamine organocatalyst.

including the acid additives and solvents at room temperature. The results are summarized in Table 1. To our delight, the diamine **2a** show high efficiency in promoting the transformation with the assistance of various acid additives. Electron-rich benzoic acids gave poorer enantioselectivity than electron-poor benzoic acids (entries 1–4). When 3,5-diNO_2-PhCOOH was used, the reaction rate became much slower albeit with a higher ee value of 94%. The reaction could not even proceed in the presence of stronger acids such as *p*-TsOH and TFA, probably due to their interaction with the basic amine moieties of the catalyst **2a** being too strong.[10] To further improve the reactivity and enantioselectivity, several chiral acids deriving from amino acids were examined for there may exist some synergistic effects between the catalyst and acid additive (entries 5–8). Gratifyingly, Boc-L-PheOH proved to be the best one in terms of yield and enantioselectivity. Both Boc-L-PhgOH and Cbz-L-PheOH gave similar results. When Boc-D-PheOH was utilized, the reaction became sluggish and was accompanied by decreasing enantioselectivity. Next, a group of solvents were further assessed (entries 9–15).[10] Halogenated solvents such as dichloromethane and chloroform gave better results than other solvents including alcohols, ethers and alkanes. When performed in neat 2-nitropropane, the reaction went to completion within 24 h with 92% ee. Accordingly, after the above extensive screening, the optimized system was established as **2a** used in combination with Boc-L-PheOH in chloroform.

In addition, 4 Å molecular sieves, water, brine and quaternary ammonium salt were also evaluated. The results are given in

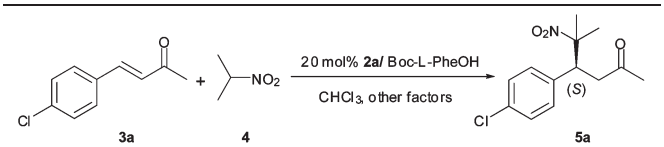
Table 1 Optimization of reaction conditions[a]



Entry	Acid additive	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	PhCOOH	CH_2Cl_2	60	84	83
2	4-MeO-PhCOOH	CH_2Cl_2	60	80	78
3	4-NO_2-PhCOOH	CH_2Cl_2	60	91	92
4	3,5-diNO_2-PhCOOH	CH_2Cl_2	100	84	94
5	Boc-L-PhgOH	CH_2Cl_2	48	95	93
6	Boc-L-PheOH	CH_2Cl_2	48	94	95
7	Cbz-L-PheOH	CH_2Cl_2	48	92	94
8	Boc-D-PheOH	CH_2Cl_2	60	88	90
9	Boc-L-PheOH	$CHCl_3$	48	96	96
10	Boc-L-PheOH	*i*-PrOH	30	90	75
11	Boc-L-PheOH	Et_2O	48	85	90
12	Boc-L-PheOH	MeCN	30	96	89
13	Boc-L-PheOH	PhMe	55	94	92
14	Boc-L-PheOH	Hexane	55	91	91
15	Boc-L-PheOH	Neat	24	98	92

[a] Reactions were carried out with 0.2 mmol of **3a** and 0.5 mL of **4** in 0.5 mL of solvent in the presence of 20 mol% catalyst **2a** and acid additive at room temperature for the specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis using Chiracel AS-H as a column; the absolute configuration was established as *S* by comparison of the optical rotation with literature data.

Table 2 Influence of other factors[a]



Entry	Other factors	Time (h)	Yield[b] (%)	ee[c] (%)
1	30 mg 4 Å molecular sieves	48	94	96
2	0.2 eq H_2O	48	88	96
3	0.2 eq brine	48	91	96
4	1.0 eq H_2O	96	83	96
5	0.2 eq TFA*Morphine	48	92	96

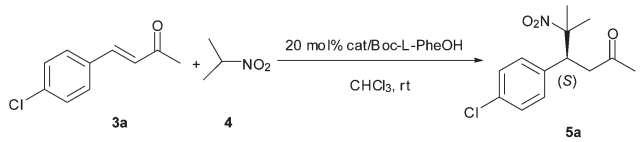
[a] Reactions were carried out with 0.2 mmol of **3a** and 0.5 mL of **4** in 0.5 mL of $CHCl_3$ in the presence of 20 mol% catalyst **2a** and Boc-L-PheOH with some other factors at room temperature for the specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

Table 2. All these factors did not have any apparent influence on the asymmetric catalytic process, while too much water may slow down the reaction rate (entry 4). These results mean this organocatalytic asymmetric conjugated addition is a robust system with good condition-tolerance ability.

Encouraged by these preliminary results, we turned our attention to investigating the effect of different chiral diamines as the organocatalyst and hoped to improve the enantioselectivity. The results are listed in Table 3. On the basis of our previous work,[8a] different combinations were built by employing *exo*-(−)-bornylamine or (+)-(1*S*,2*S*,5*R*)-menthylamine with L or D-phenylalanine

(entries 1–4). Evidently, the stereoselectivity was controlled by the absolute configuration of the phenylalanine part and the camphor scaffold showed better chiral induction than menthone.

Table 3 Catalyst screening[a]



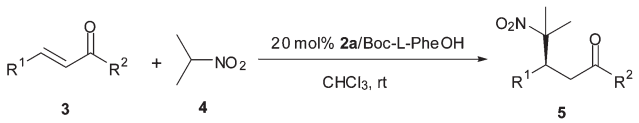
Entry	Catalyst	Acid additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	Boc-L-PheOH	48	96	96
2	**2b**	Boc-D-PheOH	48	91	−80
3	**2c**	Boc-L-PheOH	48	89	79
4	**2d**	Boc-D-PheOH	48	85	−77
5	**1a**	Boc-L-PheOH	100	trace	nd[f]
6	**2e**	Boc-L-PheOH	60	81	50
7	**2f**	Boc-L-PheOH	60	82	4
8	**2g**	Boc-L-PheOH	48	90	80
9	**2h**	Boc-L-PheOH	48	93	94
10	**2i**	Boc-L-PheOH	60	85	93
11	**2j**	Boc-L-PheOH	48	91	96
12	**2k**	Boc-L-PheOH	48	94	95
13	**2l**	Boc-L-PheOH	48	90	94
14[d]	**2a**	Boc-L-PheOH	60	84	95
15[e]	**2a**	Boc-L-PheOH	72	82	95

[a] Reactions were carried out with 0.2 mmol of **3a** and 0.5 mL of **4** in 0.5 mL of $CHCl_3$ in the presence of 20 mol% catalyst and acid additive at room temperature for the specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] 15 mol% catalyst and Boc-L-PheOH was used. [e] 10 mol% catalyst and Boc-L-PheOH was used. [f] Not determined.

Meanwhile, there does exist some cooperation between the two chiral parts, which is responsible for the excellent enantioselectivity. Amide compound **1a** was found to be completely inert for the Michael addition as the amide group may be unfavorable for the formation of iminium ion the with α,β-unsaturated ketone (entry 5). Primary–tertiary diamine **2e** only afforded moderate enantiomeric excess (entry 6). And surprisingly, chiral secondary diamine **2f** even gave almost racemic adduct (entry 7). All these results clearly indicate that both the primary amine and the secondary amine motifs are pivotal for the outcome of high efficiency and enantioselectivity. As a consequence, several commercially available primary amine amino acids were employed to construct a series of chiral primary–secondary diamines (**2g–2l**). Different R substituents on the chiral primary amine position did not make obvious differences and all these catalysts delivered comparable results (entries 9–13). Even when R was replaced by the much smaller methyl group which was derived from alanine, a good ee value of 80% could be produced (entry 8). The catalyst **2k** where the N position of the indole ring was blocked by an ethyl group, showed almost the same efficiency as **2j** (entry 12 *versus* 11). This phenomenon indicates that the R substituent just serves as steric function. Finally, we tried to decrease the catalyst loading for high catalyst loading is always an inherent shortcoming of organocatalysis. When 15 mol% or 10 mol% catalyst **2a** and Boc-L-PheOH were used, the enantioselectivity was not influenced but a longer time was required for the reaction to complete (entries 14–15).

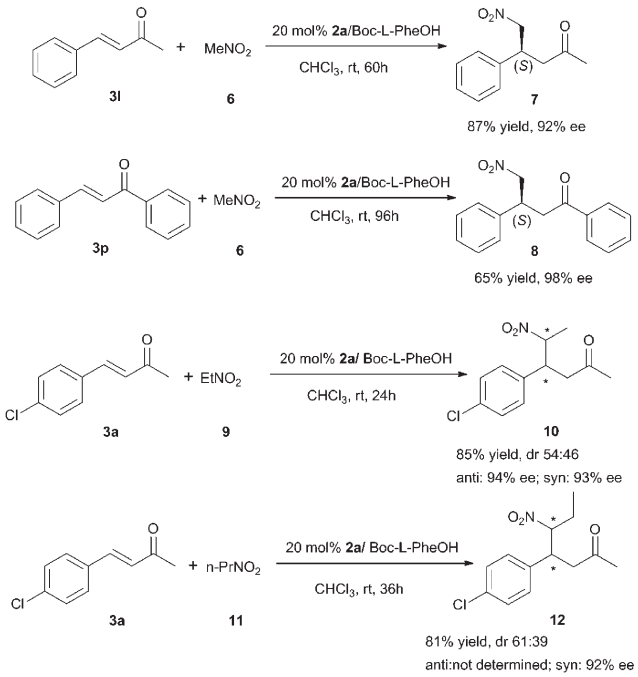
With the optimized reaction parameters in hand, the substrate scope was probed, and the results are presented in Table 4. In general, the electronic nature and positions of the substituent on the aromatic ring do not exert any significant influence on the asymmetric catalytic progress (entries 1–12). All these enones

Table 4 Enantioselective Michael addition of nitroalkanes to various enones[a]

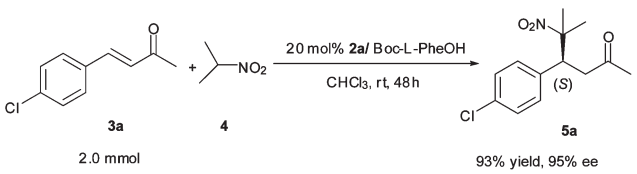


Entry	R^1	R^2	Enone	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-ClC_6H_4	Me	**3a**	**5a**	48	96	96
2	4-FC_6H_4	Me	**3b**	**5b**	48	92	96
3	4-$NO_2C_6H_4$	Me	**3c**	**5c**	48	93	92
4	4-MeC_6H_4	Me	**3d**	**5d**	48	95	93
5	4-$MeOC_6H_4$	Me	**3e**	**5e**	48	90	92
6	4-$MeSC_6H_4$	Me	**3f**	**5f**	48	93	94
7	2-$NO_2C_6H_4$	Me	**3g**	**5g**	60	88	96
8	3-$NO_2C_6H_4$	Me	**3h**	**5h**	48	92	90
9	3-$MeOC_6H_4$	Me	**3i**	**5i**	48	94	91
10	2,4-diClC_6H_3	Me	**3j**	**5j**	60	86	95
11	3,4-$(OCH_2O)C_6H_3$	Me	**3k**	**5k**	60	90	92
12	Ph	Me	**3l**	**5l**	48	96	94
13	2-furyl	Me	**3m**	**5m**	55	93	94
14	$Ph(CH)_2$	Me	**3n**	**5n**	80	75	91
15	$Ph(CH_2)_2$	Me	**3o**	**5o**	80	68	95
16	Ph	Ph	**3p**	**5p**	96	76	95
17	Ph	2-pyridyl	**3q**	**5q**	96	61	90

[a] Reactions were carried out with 0.2 mmol of **3** and 0.5 mL of **4** in 0.5 mL of $CHCl_3$ in the presence of 20 mol% catalyst **2a** and Boc-L-PheOH at room temperature for the specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis.



Scheme 2 Further investigation of the nitroalkane substrate scope.



Scheme 3 Enlarged scale reaction.

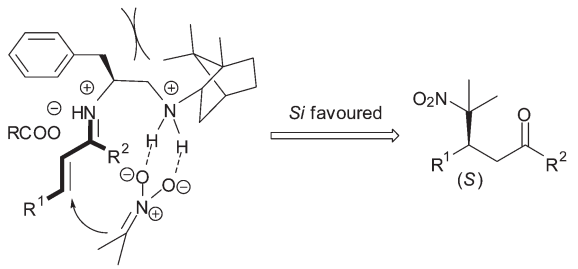


Fig. 2 Possible transition state model.

with a considerable degree of structural variation could undergo the asymmetric Michael addition smoothly to afford the expected products with useful levels of enantiocontrol (above 90% ee) under the specified reaction conditions. Heterocyclic 2-furyl enone **3m** can be tolerated and a satisfying result was generated (entry 13). It was noteworthy that in the case of enone **3n** that derived from cinnamaldehyde bearing two conjugated carbon–carbon double bonds, the Michael addition occurred on the 1,4 position regioselectively (entry 14).[4g,5d,g,7d,11] Moreover, aliphatic substrate **3o** and chalcones **3p**, **3q**, can all work well in this system with high ee values albeit with moderate yields (entries 15–17).

In addition, other nitroalkanes including nitromethane **6**, nitroethane **9** and 1-nitropropane **11** were investigated under the same catalytic conditions (Scheme 2). Nitromethane **6** reacted well with **3l** and **3p**, the transformation proceeding smoothly to afford the expected products in good yield and high enantioselectivities. Nitroethane **9** and 1-nitropropane **11** also proved to be good substrates to react with **3a** in high yields and enantioselectivities albeit with poor diastereoselectivities. The low diastereoselectivities can be partially circumvented as both the diastereomers can be easily separated by silica gel column chromatography.

Finally, in order to examine the synthetic potential of this strategy, the model reaction of **3a** with **4** was performed on a 2.0 mmol scale (10 times enlarged), and the same good result was produced without any loss of yield or enantiomeric excess (Scheme 3). Due to its stable diamine moiety, after completion of the reaction, the catalyst **2a** could be recovered in 86% yield by simple aqueous acid/base workup.

On the basis of the previous work reported by Jørgensen's and Zhao's groups,[7a,b,f] a similar possible transition state model as illustrated in Fig. 2 was proposed to account for the observed stereochemical results. We envisioned that the primary–secondary diamine organocatalyst acts in a bifunctional fashion. The primary amine moiety is a well-known efficient functional group to activate the enone though the iminium activation model. Because of the steric repulsion from the camphor skeleton, the rigid phenyl group of the L-phenylalanine prefers to shield the *Re* face of the enone. On the other hand, the secondary amine can effectively deprotonate the 2-nitropropane and then fix the nucleophilic nitronate by H-bonding interaction to make it attack the enone from the exposed *Si* face. Thus, the corresponding Michael adduct was generated with *S* configuration. At the same time, the acid additive may facilitate the formation of the iminium ion and its hydrolyzation process to regenerate the organocatalyst. This proposal was hypothesized based on the preliminary experimental results for all the three parts: primary amine, secondary amine and chiral acid additive were responsible for the high efficiency of the asymmetric catalytic Michael reaction. However, the exact synergistic effects between the catalyst and acid additive are difficult to be determined in the catalytic transformation.

Conclusions

In summary, starting from commercially available D-camphor and natural amino acids, a small library of novel C_1-symmetric chiral primary–secondary diamines (**2a–2l**) have been successfully constructed with three practical protocols in moderate to good yields. Among them, **2a** as organocatalyst in combination with acid additive Boc-L-PheOH shows high efficiency for the asymmetric Michael addition of nitroalkanes to a wide range of enones with high yields (up to 96%) and excellent enantioselectivities (up to 98%) under mild conditions. Due to its stable diamine moiety, the chemically and optically pure catalyst **2a** could be recovered by simple aqueous acid/base workup. Further studies of asymmetric applications of these new chiral diamines are currently underway in our laboratory.

Experimental

General methods

All the enones substrates were prepared according to the literature.[12] All solvents were dried and purified prior to use. Nitroalkanes were dried over anhydrous $CaCl_2$ and distilled prior to use. Reactions were monitored by TLC analysis using silica gel 60 Å F-254 thin layer plates. Flash column chromatography was performed on silica gel 60 Å, 10–40 μm. Optical rotations were measured by polarimeter in the solvent indicated. Melting points were recorded without correction. ^{1}H NMR spectra were recorded on instruments (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). HRMS was measured on an Apex III (7.0 T) Fourier transform ion cyclotron resonance (FTICR) mass spectrometer equipped with an ESI or EI source. Enantiomer ratios were determined by chiral HPLC analysis on Daicel Chiralcel AS-H, AD-H, OD-H and OJ-H in comparison with the authentic racemates. Retention times are given in minutes. The absolute configuration was assigned by comparison of the optical rotation with literature data or by analogy to other compounds.

Synthesis and characterization of the chiral diamine organocatalysts

Exo-(−)-bornylamine and (+)-(1*S*,2*S*,5*R*)-menthylamine were prepared according to our previous work.[8a]

General synthesis route

1a. To a stirred mixture of (*S*)-*N*-benzyloxycarbonylphenylalanine (2.99 g, 10 mmol) in anhydrous dichloromethane (40 mL), a dichloromethane (30 mL) solution of dicyclohexylcarbodiimide (DCC) (2.18 g, 10.5 mmol) at 0 °C was added dropwise followed by a dichloromethane (30 mL) solution of *exo*-(−)-bornylamine (1.53 g, 10 mmol). The mixture was stirred at 0 °C for 30 minutes, and then warmed to room temperature for another few hours. After the reaction completed, 0.5 mL acetic acid was added and the mixture was stirred for additional 30 minutes. Insoluble dicyclohexylurea (DCU) was removed by filtration. After removing the solvent, the residue was dissolved in ether, and then filtered again. The filtrate was washed by saturated $NaHCO_3$ aqueous solution (2 × 50 mL) and brine (2 × 50 mL), and the organic phase was dried over anhydrous Na_2SO_4. Evaporation of the organic solvent afforded the product as colorless oil (4.12 g, 95% yield), which was used directly in the next steps without further purification. To a stirred solution of the residue in MeOH (80 mL), Pd/C (0.41 g, 10% w/w) was added and the resulting suspension was stirred under H_2 atmosphere (1 atm.) at room temperature. After stirring overnight, the reaction mixture was filtered through a pad of celite and washed with MeOH. Then the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford **1a** as Colorless solid (2.62 g, 92% yield). m.p. 66–68 °C; $[\alpha]_D^{20}$ = −71.5 (*c* = 1.0 in EtOH; lit[8a]: $[\alpha]_D^{25}$ = −65.7, *c* = 0.9 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.79 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 1.13–1.20 (m, 1H), 1.27–1.34 (m, 1H), 1.36 (br s, 2H), 1.50–1.60 (m, 2H), 1.66–1.73 (m, 2H), 1.83 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.68 (dd, *J* = 13.8, 9.4 Hz, 1H), 3.28 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.57 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.88 (td, *J* = 9.4, 5.0 Hz, 1H), 7.22–7.25 (m, 3H), 7.27–7.33 (m, 2H), 7.38–7.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.7, 20.0, 20.2, 27.0, 35.9, 39.0, 41.2, 44.9, 47.0, 48.4, 56.0, 56.5, 126.7, 128.6, 129.2, 138.0, 173.1; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{29}N_2O$ $[M + H]^+$: 301.2275; found: 301.2272.

2a. To a stirred mixture of $LiAlH_4$ (0.91 g, 24 mmol) in anhydrous THF (30 mL) was added a THF (40 mL) solution of **1a** (2.40 g, 8 mmol) at 0 °C dropwise. The mixture was warmed to room temperature and then heated to reflux for a few hours. After the reaction completed, saturated Na_2SO_4 aqueous solution was added dropwise to quench the reaction at 0 °C. The resulting white precipitation was removed by filtration. The filtrate was dried over anhydrous K_2CO_3, and then concentrated under reduced pressure. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford **2a** as light yellow oil (1.56 g, 68% yield). $[\alpha]_D^{20}$ = −48.6 (*c* = 1.3 in EtOH; lit[8a]: $[\alpha]_D^{25}$ = −44.5, *c* = 0.9 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.88 (s, 3H), 1.02 (s, 3H), 1.04–1.08 (m, 2H), 1.32 (br s, 3H), 1.48–1.58 (m, 3H), 1.65–1.68 (m, 2H), 2.37 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.44–2.49 (m, 2H), 2.65 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.80 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.98–3.05 (m, 1H), 7.19–7.22 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.3, 20.5, 20.6, 27.3, 36.9, 39.4, 42.8, 45.2, 46.6, 48.5, 53.1, 55.5, 67.2, 126.1, 128.4, 129.2, 139.5; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{31}N_2$ $[M + H]^+$: 287.2482; found: 287.2472.

2b. Light yellow oil (1.33 g, 62% yield). $[\alpha]_D^{20}$ = −89.1 (*c* = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.85 (s, 3H), 1.02 (s, 3H), 1.01–1.08 (m, 2H), 1.46 (br s, 3H), 1.52–1.54 (m, 1H), 1.55–1.56 (m, 2H), 1.67–1.68 (m, 2H), 2.36 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.50–2.55 (m, 2H), 2.58 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.73 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.00–3.06 (m, 1H), 7.19–7.22 (m, 3H), 7.27–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.1, 20.5, 27.3, 36.9, 38.7, 42.5, 45.2, 46.6, 48.2, 52.7, 54.4, 66.6, 126.1, 128.3, 129.2, 139.4; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{31}N_2$ $[M + H]^+$: 287.2482; found: 287.2473.

2c. Light yellow oil (1.46 g, 55% yield). $[\alpha]_D^{20}$ = +26.0 (*c* = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.84–0.90 (m, 12H), 1.18 (qd, *J* = 12.8, 3.2 Hz, 1H), 1.36 (br s, 3H), 1.49–1.57 (m, 1H), 1.61–1.72 (m, 3H), 1.89 (ddd, *J* = 13.4, 5.6, 3.2 Hz, 1H), 2.47–2.54 (m, 2H), 2.55 (s, 1H), 2.79 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.86 (d, *J* = 3.2 Hz, 1H), 3.01–3.07 (m, 1H), 7.20–7.22 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.8, 21.4, 22.5, 24.9, 25.6, 28.9, 35.4, 38.2, 42.5, 48.4, 52.9, 53.4, 53.5, 126.1, 128.4, 129.2,

139.6; HRMS (ESI): *m/z* calcd for $C_{19}H_{33}N_2$ $[M + H]^+$: 289.2638; found: 289.2635.

2d. Light yellow oil (1.09 g, 60% yield). $[\alpha]_D^{20} = +9.5$ ($c = 1.0$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.84–0.90 (m, 12H), 1.18 (qd, J = 12.8, 3.2 Hz, 1H), 1.38 (br s, 3H), 1.49–1.57 (m, 1H), 1.61–1.72 (m, 3H), 1.89 (ddd, J = 13.4, 5.6, 3.2 Hz, 1H), 2.47–2.54 (m, 2H), 2.56 (s, 1H), 2.78 (dd, J = 13.4, 5.0 Hz, 1H), 2.86 (d, J = 3.2 Hz, 1H), 3.01–3.17 (m, 1H), 7.19–7.22 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.7, 21.4, 22.5, 24.8, 25.5, 28.9, 35.4, 38.1, 42.5, 48.3, 52.8, 53.3, 53.5, 126.1, 128.3, 129.2, 139.5; HRMS (ESI): *m/z* calcd for $C_{19}H_{33}N_2$ $[M + H]^+$: 289.2638; found: 289.2634.

2e. Yellow solid (0.45 g, 65% yield). m.p. 58–60 °C; $[\alpha]_D^{20}$ = +17.8 ($c = 1.0$ in EtOH; lit[13]: $[\alpha]_D^{25}$ = +21, $c = 1.0$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.68 (br s, 2H), 2.23–2.30 (m, 2H), 2.32–2.38 (m, 2H), 2.47–2.56 (m, 3H), 2.73 (dd, J = 13.4, 4.6 Hz, 1H), 3.17–3.24 (m, 1H), 3.65–3.74 (m, 4H), 7.20–7.23 (m, 3H), 7.28–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 42.1, 48.8, 53.9, 65.3, 67.0, 126.1, 128.3, 129.1, 139.0; HRMS (ESI): *m/z* calcd for $C_{13}H_{21}N_2O$ $[M + H]^+$: 221.1649; found: 221.1643.

2f. Light yellow oil (0.99 g, 48% yield). $[\alpha]_D^{25} = -61.1$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.87 (s, 3H), 1.02 (s, 3H), 1.04–1.08 (m, 2H), 1.28–1.37 (m, 1H), 1.45–1.56 (m, 3H), 1.65–1.74 (m, 4H), 1.81–1.89 (m, 1H), 2.11 (br s, 2H), 2.39 (dd, J = 11.4, 7.8 Hz, 1H), 2.50 (t, J = 6.6 Hz, 1H), 2.59 (dd, J = 11.4, 5.0 Hz, 1H), 2.84–2.98 (m, 2H), 3.11–3.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.2, 20.5, 20.6, 25.6, 27.4, 29.7, 36.9, 39.1, 45.3, 46.5, 46.7, 48.4, 53.8, 58.9, 67.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{29}N_2$ $[M + H]^+$: 237.2325; found: 237.2315.

2g. Light yellow oil (1.12 g, 51% yield). $[\alpha]_D^{25} = -51.9$ (c = 1.1 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.88 (s, 3H), 1.01 (s, 3H), 1.03–1.09 (m, 5H), 1.48–1.69 (m, 9H), 2.27 (dd, J = 11.6, 8.0 Hz, 1H), 2.48 (dd, J = 8.0, 5.2 Hz, 1H), 2.55 (dd, J = 11.8, 4.6 Hz, 1H), 2.86–2.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.3, 20.5, 20.7, 21.9, 27.4, 36.9, 39.5, 45.3, 46.7, 47.2, 48.5, 57.7, 67.2; HRMS (ESI): *m/z* calcd for $C_{13}H_{27}N_2$ $[M + H]^+$: 211.2169; found: 211.2161.

2h. Light yellow oil (1.52 g, 56% yield). $[\alpha]_D^{20} = -42.4$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.90 (s, 3H), 0.88–0.92 (m, 6H), 1.01 (s, 3H), 1.05–1.09 (m, 2H), 1.48–1.54 (m, 2H), 1.55–1.58 (m, 2H), 1.59–1.62 (m, 3H), 1.65–1.69 (m, 3H), 2.26 (dd, J = 11.4, 9.0 Hz, 1H), 2.46–2.53 (m, 2H), 2.65 (dd, J = 11.4, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.3, 17.8, 19.4, 20.4, 20.5, 27.3, 32.1, 36.9, 39.4, 45.2, 46.6, 48.5, 53.5, 57.0, 67.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{31}N_2$ $[M + H]^+$: 239.2482; found: 239.2477.

2i. Light yellow oil (1.08 g, 63% yield). $[\alpha]_D^{20} = -56.7$ (c = 1.1 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.79 (s, 3H), 0.83 (s, 3H), 0.97 (s, 3H), 1.01–1.04 (m, 2H), 1.46–1.51 (m, 1H), 1.54–1.59 (m, 5H), 1.65–1.69 (m, 2H), 2.50 (t, J = 6.6 Hz, 1H), 2.59 (dd, J = 11.6, 7.8 Hz, 1H), 2.79 (dd, J = 11.6, 4.4 Hz, 1H), 3.98 (dd, J = 7.8, 4.6 Hz, 1H), 7.22–7.26 (m, 1H), 7.32–7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.1, 20.4, 20.5, 27.3, 36.8, 39.2, 45.2, 46.6, 48.4, 55.9, 56.7, 66.8, 126.3, 126.9, 128.3, 145.0; HRMS (ESI): *m/z* calcd for $C_{18}H_{29}N_2$ $[M + H]^+$: 273.2325; found: 273.2323.

2j. Light yellow oil (0.49 g, 45% yield). $[\alpha]_D^{20} = -45.0$ (c = 1.1 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.88 (s, 3H), 1.01 (s, 3H), 0.99–1.07 (m, 2H), 1.47–1.49 (m, 1H), 1.54–1.58 (m, 2H), 1.65–1.66 (m, 2H), 1.86 (br s, 3H), 2.42 (dd, J = 11.6, 8.0 Hz, 1H), 2.49 (dd, J = 7.6, 5.6 Hz, 1H), 2.62 (dd, J = 14.2, 8.6 Hz, 1H), 2.72 (dd, J = 11.6, 4.4 Hz, 1H), 2.94 (dd, J = 14.2, 4.6 Hz, 1H), 3.10–3.15 (m, 1H), 6.98 (s, 1H), 7.07–7.11 (m, 1H), 7.14–7.18 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 8.88 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.2, 20.4, 20.5, 27.3, 31.8, 36.8, 39.4, 45.2, 46.6, 48.5, 51.9, 55.5, 67.2, 111.2, 112.8, 118.8, 119.0, 121.7, 122.6, 127.6, 136.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{32}N_3$ $[M + H]^+$: 326.2591; found: 326.2585.

2k. Light yellow oil (0.67 g, 46% yield). $[\alpha]_D^{20} = -48.8$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.88 (s, 3H), 1.02 (s, 3H), 1.04–1.08 (m, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.50–1.52 (m, 1H), 1.56–1.58 (m, 2H), 1.59–1.66 (m, 2H), 1.79 (br s, 3H), 2.43 (dd, J = 11.6, 7.6 Hz, 1H), 2.50 (dd, J = 7.2, 6.0 Hz, 1H), 2.63 (dd, J = 14.2, 8.6 Hz, 1H), 2.73 (dd, J = 11.6, 4.4 Hz, 1H), 2.95 (dd, J = 14.2, 4.6 Hz, 1H), 3.10–3.17 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 6.98 (s, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.3, 15.4, 20.5, 20.6, 27.3, 31.9, 36.9, 39.3, 40.7, 45.2, 46.6, 48.5, 51.9, 55.5, 67.2, 109.2, 111.8, 118.6, 119.1, 121.4, 125.4, 128.2, 136.1; HRMS (ESI): *m/z* calcd for $C_{23}H_{36}N_3$ $[M + H]^+$: 354.2904; found: 354.2897.

2l. Light yellow oil (0.52 g, 50% yield). $[\alpha]_D^{20} = -34.5$ (c = 0.9 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.80 (s, 3H), 0.88 (s, 3H), 1.01 (s, 3H), 1.03–1.08 (m, 2H), 1.47–1.66 (m, 8H), 2.35 (dd, J = 11.6, 7.8 Hz, 1H), 2.42 (dd, J = 13.4, 8.6 Hz, 1H), 2.47 (dd, J = 7.8, 5.4 Hz, 1H), 2.64 (dd, J = 11.6, 4.4 Hz, 1H), 2.72 (dd, J = 13.8, 4.8 Hz, 1H), 2.93–3.00 (m, 1H), 5.02 (s, 2H), 6.88–6.92 (m, 2H), 7.09–7.24 (m, 2H), 7.28–7.32 (m, 1H), 7.34–7.39 (m, 2H), 7.41–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 12.2, 20.4, 20.5, 27.2, 36.8, 39.3, 41.6, 45.1, 46.6, 48.4, 53.1, 55.2, 67.1, 69.9, 114.7, 127.3, 127.8, 128.4, 130.0, 131.5, 137.0, 157.2; HRMS (ESI): *m/z* calcd for $C_{26}H_{37}N_2O$ $[M + H]^+$: 393.2901; found: 393.2893.

General procedure for the catalytic Michael addition

To a mixture of enone **3** (0.2 mmol), catalyst **2a** (0.04 mmol, 20 mol%) and Boc-L-PheOH (0.04 mmol, 20 mol%) in $CHCl_3$ (0.5 mL) was added 2-nitropropane **4** (0.5 mL) under an aerobic atmosphere, taking no precaution to exclude moisture. After 48 h of stirring at room temperature (about 25 °C), the reaction mixture was quenched with 1 mL 1 M aqueous HCl solution and extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the corresponding Michael adduct **5** after purification by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate.

The large scale reaction (Scheme 3) was carried out on a scale of 2.0 mmol of **3a** under identical conditions. After the reaction completed, 1 M HCl aqueous solution was added and stirred for a few minutes. The mixture was then extracted with EtOAc, and the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the corresponding Michael adduct **5a** after purification by column chromatography on silica gel. The water layer was neutralized by 4 M NaOH aqueous solution until pH = 11 and subsequently extracted by CH_2Cl_2, and the organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude recovered catalyst **2a** (86% yield) was directly characterized by NMR, and the ^1H and ^{13}C NMR spectra are also enclosed in the ESI.†

(*S*)-4-(4-Chlorophenyl)-5-methyl-5-nitrohexan-2-one (5a). Colorless oil (Table 4, entry 1, 96% yield, 96% ee). $[\alpha]_D^{20} = -31.2$ (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{18} = -35.2$, c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.48 (s, 3H), 1.54 (s, 3H), 2.04 (s, 3H), 2.74 (dd, J = 17.4, 3.4 Hz, 1H), 3.04 (dd, J = 17.4, 10.6 Hz, 1H), 3.90 (dd, J = 10.6, 3.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.6, 25.5, 30.3, 43.9, 48.1, 90.7, 128.7, 130.4, 133.7, 136.2, 204.7; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 34.87 min, $t_{R(minor)}$ = 29.68 min.

(*S*)-4-(4-Fluorophenyl)-5-methyl-5-nitrohexan-2-one (5b). Colorless oil (Table 4, entry 2, 92% yield, 96% ee). $[\alpha]_D^{20} = -34.1$ (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{22} = -32.7$, c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.48 (s, 3H), 1.55 (s, 3H), 2.04 (s, 3H), 2.74 (dd, J = 17.2, 3.2 Hz, 1H), 3.05 (dd, J = 17.2, 10.8 Hz, 1H), 3.92 (dd, J = 10.6, 3.4 Hz, 1H), 6.98–7.02 (m, 2H), 7.15–7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.6, 25.5, 30.3, 44.0, 48.0, 90.8, 115.3, 115.5, 130.5, 130.6, 133.3, 133.4, 160.9, 163.4, 204.8; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 54.38 min, $t_{R(minor)}$ = 31.46 min.

(*S*)-5-Methyl-5-nitro-4-(4-nitrophenyl)hexan-2-one (5c). Yellow solid (Table 4, entry 3, 93% yield, 92% ee). m.p. 90–92 °C, lit[7f]: 89–91 °C; $[\alpha]_D^{20} = -40.1$ (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{22} = -43.0$, c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.53 (s, 3H), 1.58 (s, 3H), 2.09 (s, 3H), 2.87 (dd, J = 18.0, 3.2 Hz, 1H), 3.12 (dd, J = 18.0, 10.4 Hz, 1H), 4.03 (dd, J = 10.6, 3.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.6, 25.5, 30.3, 43.9, 48.1, 90.7, 128.7, 130.4, 133.7, 136.2, 204.7; HPLC (Chiralcel AS-H, hexane–isopropanol 70 : 30, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 42.22 min, $t_{R(minor)}$ = 31.59 min.

(*S*)-5-Methyl-5-nitro-4-*p*-tolylhexan-2-one (5d). Colorless oil (Table 4, entry 4, 95% yield, 93% ee). $[\alpha]_D^{20} = -28.0$ (c = 1.0 in EtOH); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.47 (s, 3H), 1.54 (s, 3H), 2.01 (s, 3H), 2.30 (s, 3H), 2.68 (dd, J = 16.8, 3.2 Hz, 1H), 3.07 (dd, J = 16.8, 10.8 Hz, 1H), 3.89 (dd, J = 10.8, 3.6 Hz, 1H), 7.06–7.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.9, 22.3, 25.6, 30.2, 43.9, 48.4, 91.1, 128.9, 129.1, 134.3, 137.4, 205.2; HRMS (ESI): m/z calcd for $C_{14}H_{19}NO_3Na$ $[M + Na]^+$: 272.1257; found: 272.1252; HPLC (Chiralcel OJ-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 45.26 min, $t_{R(minor)}$ = 42.51 min.

(*S*)-4-(4-Methoxyphenyl)-5-methyl-5-nitrohexan-2-one (5e). Colorless oil (Table 4, entry 5, 90% yield, 92% ee). $[\alpha]_D^{20} = -33.0$ (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{22} = -22.7$, c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.47 (s, 3H), 1.54 (s, 3H), 2.02 (s, 3H), 2.67 (dd, J = 16.8, 3.6 Hz, 1H), 3.04 (dd, J = 16.8, 10.8 Hz, 1H), 3.77 (s, 3H), 3.87 (dd, J = 10.8, 3.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.3, 25.6, 30.2, 44.1, 48.1, 55.1, 91.1, 113.8, 129.3, 130.1, 159.0, 205.3; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 34.27 min, $t_{R(minor)}$ = 40.64 min.

(*S*)-5-Methyl-4-(4-(methylthio)phenyl)-5-nitrohexan-2-one (5f). Yellow oil (Table 4, entry 6, 93% yield, 94% ee). $[\alpha]_D^{20} = -29.7$ (c = 1.0 in EtOH); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.48 (s, 3H), 1.54 (s, 3H), 2.03 (s, 3H), 2.46 (s, 3H), 2.69 (dd, J = 17.0, 3.4 Hz, 1H), 3.05 (dd, J = 16.8, 10.8 Hz, 1H), 3.88 (dd, J = 10.8, 3.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 15.4, 22.4, 25.7, 30.3, 43.9, 48.3, 90.9, 126.3, 129.5, 134.1, 138.3, 205.0; HRMS (ESI): m/z calcd for $C_{14}H_{19}NO_3SNa$ $[M + Na]^+$: 304.0978; found: 304.0978; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 40.63 min, $t_{R(minor)}$ = 49.58 min.

(*S*)-5-Methyl-5-nitro-4-(2-nitrophenyl)hexan-2-one (5g). Yellow oil (Table 4, entry 7, 88% yield, 96% ee). $[\alpha]_D^{20} = -65.8$ (c = 1.0 in EtOH); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.57 (s, 3H), 1.67 (s, 3H), 2.05 (s, 3H), 2.97–3.11 (m, 2H), 4.58 (dd, J = 10.0, 4.0 Hz, 1H), 7.23–7.25 (m, 1H), 7.40–7.44 (m, 1H), 7.54 (td, J = 7.8, 1.2 Hz, 1H), 7.82 (dd, J = 8.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.6, 26.5, 29.8, 41.0, 45.3, 90.6, 124.9, 128.1, 128.5, 132.6, 133.0, 151.6, 204.7; HRMS (EI): m/z calcd for $C_{13}H_{16}N_2O_5$ $[M]^+$: 280.1059; found: 280.1055; HPLC (Chiralcel AS-H, hexane–isopropanol 70 : 30, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 21.42 min, $t_{R(minor)}$ = 24.38 min.

(*S*)-5-Methyl-5-nitro-4-(3-nitrophenyl)hexan-2-one (5h). Colorless oil (Table 4, entry 8, 92% yield, 90% ee). $[\alpha]_D^{20} = -31.9$ (c = 1.0 in EtOH); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.53 (s, 3H), 1.59 (s, 3H), 2.10 (s, 3H), 2.86 (dd, J = 17.6, 3.2 Hz, 1H), 3.15 (dd, J = 18.0, 10.8 Hz, 1H), 4.06 (dd, J = 10.4, 3.2 Hz, 1H), 7.49–7.58 (m, 2H), 8.07–8.06 (m, 1H), 8.14–8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.1, 25.3, 31.4, 43.8, 48.1, 90.4, 123.0, 123.3, 129.6, 135.8, 140.2, 148.2, 204.2; HRMS (EI): m/z calcd for $C_{13}H_{16}N_2O_5$ $[M]^+$: 280.1059; found: 280.1054; HPLC (Chiralcel AS-H, hexane–isopropanol 70 : 30, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 31.65 min, $t_{R(minor)}$ = 29.11 min.

(*S*)-4-(3-Methoxyphenyl)-5-methyl-5-nitrohexan-2-one (5i). Colorless oil (Table 4, entry 9, 94% yield, 91% ee). $[\alpha]_D^{20} = -23.3$ (c = 1.0 in EtOH); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.49 (s, 3H), 1.56 (s, 3H), 2.03 (s, 3H), 2.69 (dd, J = 17.0, 3.4 Hz, 1H), 3.07 (dd, J = 17.0, 10.6 Hz, 1H), 3.78 (s, 3H), 3.91 (dd, J = 10.8, 3.6 Hz, 1H), 6.77–6.81 (m, 2H),

6.73–6.74 (m, 1H), 7.22 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.4, 25.8, 30.3, 44.0, 48.7, 55.1, 91.0, 112.6, 115.5, 121.4, 129.4, 139.1, 159.4, 205.0; HRMS (ESI): m/z calcd for $C_{14}H_{19}NO_4Na$ $[M + Na]^+$: 288.1206; found: 288.1202; HPLC (Chiralcel AD-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 17.63 min, $t_{R(minor)}$ = 16.32 min.

(*S*)-4-(2,4-Dichlorophenyl)-5-methyl-5-nitrohexan-2-one (5j). Colorless oil (Table 4, entry 10, 86% yield, 95% ee). $[\alpha]_D^{20}$ = −45.7 (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.53 (s, 3H), 1.59 (s, 3H), 2.05 (s, 3H), 2.89 (dd, J = 17.2, 4.0 Hz, 1H), 2.99 (dd, J = 17.2, 10.4 Hz, 1H), 4.55 (dd, J = 10.4, 3.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 8.4, 2.0 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.3, 26.1, 30.0, 42.8, 44.6, 90.9, 127.4, 128.8, 130.0, 134.1, 134.7, 136.8, 204.6; HRMS (EI): m/z calcd for $C_{13}H_{15}Cl_2NO_3$ $[M]^+$: 303.0424; found: 303.0421; HPLC (Chiralcel OJ-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 38.86 min, $t_{R(minor)}$ = 46.97 min.

(*S*)-4-(Benzo[*d*][1,3]dioxol-6-yl)-5-methyl-5-nitrohexan-2-one (5k). Colorless oil (Table 4, entry 11, 90% yield, 92% ee). $[\alpha]_D^{20}$ = −20.5 (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.49 (s, 3H), 1.55 (s, 3H), 2.05 (s, 3H), 2.67 (dd, J = 17.0, 3.4 Hz, 1H), 3.01 (dd, J = 16.8, 10.8 Hz, 1H), 3.84 (dd, J = 10.8, 3.6 Hz, 1H), 5.94 (s, 2H), 6.64–6.67 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.5, 25.6, 30.3, 44.1, 48.5, 91.1, 101.1, 108.2, 109.2, 122.6, 131.1, 147.1, 147.7, 205.1; HRMS (ESI): m/z calcd for $C_{14}H_{17}NO_5Na$ $[M + Na]^+$: 302.0999; found: 302.0992; HPLC (Chiralcel AS-H, hexane–isopropanol 70 : 30, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 30.66 min, $t_{R(minor)}$ = 43.17 min.

(*S*)-5-Methyl-5-nitro-4-phenylhexan-2-one (5l). White solid (Table 4, entry 12, 96% yield, 94% ee). m.p. 90–91 °C, lit[7f]: 92–94 °C; $[\alpha]_D^{20}$ = −26.2 (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{22}$ = −30.9, c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.48 (s, 3H), 1.55 (s, 3H), 2.03 (s, 3H), 2.71 (dd, J = 17.0, 3.4 Hz, 1H), 3.09 (dd, J = 17.0, 10.6 Hz, 1H), 3.93 (dd, J = 10.6, 3.4 Hz, 1H), 7.19–7.21 (m, 2H), 7.27–7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.4, 25.7, 30.3, 44.0, 48.7, 91.0, 127.8, 128.5, 129.1, 137.5, 205.1; HPLC (Chiralcel OD-H, hexane–isopropanol 98 : 2, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 37.09 min, $t_{R(minor)}$ = 39.89 min.

(*R*)-4-(Furan-2-yl)-5-methyl-5-nitrohexan-2-one (5m). Colorless oil (Table 4, entry 13, 93% yield, 94% ee). $[\alpha]_D^{20}$ = −22.9 (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{22}$ = −28.3, c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.51 (s, 3H), 1.58 (s, 3H), 2.08 (s, 3H), 2.53 (dd, J = 17.0, 3.0 Hz, 1H), 3.10 (dd, J = 17.0, 11.0 Hz, 1H), 4.12 (dd, J = 11.0, 3.0 Hz, 1H), 6.18 (d, J = 3.2 Hz, 1H), 6.29–6.31 (m, 1H), 7.32–7.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.3, 25.6, 30.0, 42.0, 42.5, 90.4, 109.1, 110.4, 142.1, 151.1, 204.6; HPLC (Chiralcel OJ-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 41.20 min, $t_{R(minor)}$ = 36.94 min.

(*S*,*E*)-4-(2-Nitropropan-2-yl)-6-phenylhex-5-en-2-one (5n). Colorless oil (Table 4, entry 14, 75% yield, 91% ee). $[\alpha]_D^{20}$ = −11.6 (c = 0.8 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.58 (s, 3H), 1.59 (s, 3H), 2.12 (s, 3H), 2.50 (dd, J = 16.4, 3.2 Hz, 1H), 2.61 (dd, J = 16.6, 9.8 Hz, 1H), 3.44 (td, J = 9.6, 3.2 Hz, 1H), 5.86 (dd, J = 15.8, 9.4 Hz, 1H), 6.55 (d, J = 15.6 Hz, 1H), 7.24–7.26 (m, 1H), 7.30–7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.8, 25.1, 30.5, 43.8, 46.8, 90.4, 125.3, 126.4, 127.9, 128.5, 135.3, 136.2, 205.1; HRMS (EI): m/z calcd for $C_{15}H_{19}NO_3$ $[M]^+$: 261.1359; found: 261.1353; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 22.15 min, $t_{R(minor)}$ = 23.77 min.

(*R*)-4-(2-Nitropropan-2-yl)-6-phenylhexan-2-one (5o). Colorless oil (Table 4, entry 15, 68% yield, 95% ee). $[\alpha]_D^{20}$ = −18.0 (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.36–1.43 (m, 1H), 1.51 (s, 3H), 1.52 (s, 3H), 1.69–1.77 (m, 1H), 2.17 (s, 3H), 2.42 (dd, J = 18.2, 6.2 Hz, 1H), 2.51–2.62 (m, 3H), 2.82–2.88 (m, 1H), 7.12–7.14 (m, 2H), 7.17–7.21 (m, 1H), 7.25–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.6, 24.0, 30.0, 33.4, 34.3, 41.1, 45.0, 91.4, 126.1, 128.3, 128.4, 141.2, 206.0; HRMS (EI): m/z calcd for $C_{15}H_{21}NO_3$ $[M]^+$: 263.1516; found: 263.1512; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 19.38 min, $t_{R(minor)}$ = 18.23 min.

(*S*)-4-Methyl-4-nitro-1,3-diphenylpentan-1-one (5p). White solid (Table 4, entry 16, 76% yield, 95% ee). m.p. 148–150 °C, lit[7f]: 147–149 °C; $[\alpha]_D^{20}$ = −75.3 (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{24}$ = −77.5, c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.54 (s, 3H), 1.63 (s, 3H), 2.57 (dd, J = 17.2, 3.2 Hz, 1H), 3.68 (dd, J = 17.2, 10.4 Hz, 1H), 4.15 (dd, J = 10.4, 3.6 Hz, 1H), 7.21–7.29 (m, 5H), 7.42 (t, J = 3.6 Hz, 2H), 7.52–7.56 (m, 1H), 7.85–7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.6, 26.1, 39.1, 49.0, 91.2, 127.7, 127.9, 128.4, 128.6, 129.2, 133.2, 136.6, 137.9, 196.7; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 26.20 min, $t_{R(minor)}$ = 21.76 min.

(*S*)-4-Methyl-4-nitro-3-phenyl-1-(pyridin-2-yl)pentan-1-one (5q). Yellow oil (Table 4, entry 17, 61% yield, 90% ee). $[\alpha]_D^{20}$ = −77.2 (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.53 (s, 3H), 1.68 (s, 3H), 3.31 (dd, J = 22.8, 12.0 Hz, 1H), 4.16–4.25 (m, 2H), 7.19–7.29 (m, 5H), 7.42–7.45 (m, 1H), 7.74 (td, J = 7.6, 1.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.66–8.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.7, 25.3, 37.8, 48.7, 91.4, 121.8, 127.3, 127.5, 128.2, 129.3, 136.8, 138.0, 148.8, 152.8, 198.4; HRMS (ESI): m/z calcd for $C_{17}H_{19}N_2O_3$ $[M + H]^+$: 299.1390; found: 299.1395; HPLC (Chiralcel AD-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 21.49 min, $t_{R(minor)}$ = 24.50 min.

(*S*)-5-Nitro-4-phenylpentan-2-one (7). 0.5 mL Nitromethane **6** was used instead under the same catalytic conditions described in the general procedure. White solid (Scheme 2, eqn (1), 87% yield, 92% ee). m.p. 113–115 °C, lit[7f]: 109–111 °C; $[\alpha]_D^{20}$ = +2.9 (c = 1.0 in EtOH; lit[7f]: $[\alpha]_D^{18}$ = +3.3, c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.12 (s, 3H), 2.91 (d, J = 7.2 Hz, 2H), 4.01 (p, J = 7.2 Hz, 1H), 4.60 (dd, J = 12.4, 8.0 Hz, 1H), 4.69 (dd, J = 12.4, 6.8 Hz, 1H), 7.20–7.23 (m, 1H), 7.24–7.29 (m, 1H), 7.32–7.35 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$, 25 °C, TMS): δ = 30.3, 39.0, 46.1, 79.4, 127.3, 127.9, 129.0, 138.8, 205.4; HPLC (Chiralcel AD-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 20.98 min, $t_{R(minor)}$ = 22.61 min.

(*S*)-4-Nitro-1,3-diphenylbutan-1-one (8). 0.5 mL Nitromethane **6** was used instead under the same catalytic conditions described in the general procedure. White solid (Scheme 2, eqn (2), 65% yield, 98% ee). m.p. 89–90 °C, lit[5g]: 87–88 °C; $[\alpha]_D^{20}$ = −23.3 (*c* = 1.0 in EtOH; lit[4g]: $[\alpha]_D^{28}$ = −23.2, *c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.53 (s, 3H), 1.68 (s, 3H), 3.38–3.51 (m, 2H), 4.19–4.26 (m, 1H), 4.68 (dd, *J* = 12.4, 8.0 Hz, 1H), 4.82 (dd, *J* = 12.4, 6.4 Hz, 1H), 7.25–7.28 (m, 3H), 7.31–7.35 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.54–7.59 (m, 1H), 7.89–7.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 39.2, 41.5, 79.5, 127.4, 127.8, 128.0, 128.7, 129.0, 133.5, 136.3, 139.1, 196.8; HPLC (Chiralcel AD-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 29.20 min, $t_{R(minor)}$ = 40.06 min.

4-(4-Chlorophenyl)-5-nitrohexan-2-one (10). 0.5 mL Nitroethane **9** was used instead under the same catalytic conditions described in the general procedure. Diastereomers **I** and **II** were isolated by silica gel column chromatography, respectively.[14] Diastereomer **I** (*anti* major): Yellow oil (Scheme 2, eqn (3), 47% yield, 94% ee). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.33 (d, *J* = 6.8 Hz, 3H), 2.03 (s, 3H), 2.75 (dd, *J* = 17.4, 4.2 Hz, 1H), 2.94 (dd, *J* = 17.2, 9.6 Hz, 1H), 3.71 (td, *J* = 9.6, 4.0 Hz, 1H), 4.74 (dq, *J* = 9.6, 6.8 Hz, 1H), 7.13–7.16 (m, 2H), 7.29–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 17.6, 30.3, 44.6, 46.0, 86.7, 129.2, 129.5, 133.7, 136.8, 204.5; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 31.88 min, $t_{R(minor)}$ = 38.51 min. Diastereomer **II** (*syn* minor): Yellow oil (Scheme 2, eqn (3), 40% yield, 93% ee). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.48 (d, *J* = 6.8 Hz, 3H), 2.12 (s, 3H), 2.86 (dd, *J* = 17.6, 7.6 Hz, 1H), 3.02 (dd, *J* = 18.0, 6.4 Hz, 1H), 3.70 (dt, *J* = 7.6, 6.4 Hz, 1H), 4.85 (apparent p, *J* = 6.8 Hz, 1H), 7.07–7.09 (m, 2H), 7.28–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 16.8, 30.5, 43.9, 44.8, 85.7, 128.9, 129.5, 133.8, 136.4, 205.2; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 31.53 min, $t_{R(minor)}$ = 35.25 min.

4-(4-Chlorophenyl)-5-nitroheptan-2-one (12). 0.5 mL 1-Nitropropane **11** was used instead under the same catalytic conditions described in the general procedure. Diastereomers **I** and **II** were isolated by silica gel column chromatography, respectively. Diastereomer **I** (*anti* major): Yellow oil (Scheme 2, eqn (4), 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.85 (t, *J* = 7.4 Hz, 3 H), 1.47 (dqd, *J* = 14.8, 7.4, 3.2 Hz, 1H), 1.77–1.85 (m, 1 H), 2.00 (s, 3H), 2.69 (dd, *J* = 17.4, 3.6 Hz, 1H), 2.94 (dd, *J* = 17.4, 10.0 Hz, 1H), 3.69 (td, *J* = 10.0, 3.6 Hz, 1H), 4.55 (td, *J* = 10.8, 3.2 Hz, 1H), 7.14–7.16 (m, 2H), 7.30–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.2, 25.4, 30.4, 43.8, 46.0, 93.9, 129.2, 129.4, 133.6, 137.1, 204.5; the ee value was not determined for the chiral HPLC separations for the product was not fully resolved. Diastereomer **II** (*syn* minor): Yellow oil (Scheme 2, eqn (4), 32% yield, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.95 (t, *J* = 7.4 Hz, 3 H), 1.77 (dqd, *J* = 14.8, 7.4, 3.6 Hz, 1H), 1.84–1.94(m, 1 H), 2.11 (s, 3H), 2.82 (dd, *J* = 17.6, 7.6 Hz, 1H), 2.99 (dd, *J* = 17.6, 6.4 Hz, 1H), 3.71 (dt, *J* = 7.2, 6.8 Hz, 1H), 4.67 (ddd, *J* = 10.6, 7.2, 3.6 Hz, 1H), 7.07–7.10 (m, 2H), 7.25–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.4, 24.6, 30.6, 43.0, 45.1, 92.8, 128.8, 129.5, 133.7, 136.6, 205.2; HPLC (Chiralcel AS-H, hexane–isopropanol 90 : 10, 0.5 mL min^{-1}, UV λ = 254 nm): $t_{R(major)}$ = 25.89 min, $t_{R(minor)}$ = 27.20 min.

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