Tetrahedron: *Asymmetry* 25 (2014) 568–577

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

New class of bifunctional thioureas from L-proline: highly enantioselective Michael addition of 1,3-dicarbonyls to nitroolefins

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ARTICLE INFO

Article history:
Received 5 February 2014
Accepted 26 February 2014

ABSTRACT

A new class of bifunctional tertiary amine thiourea was synthesized from L-proline. The reported thiourea is amenable to steric and electronic modifications at the stereogenic center bearing a thiourea moiety. Excellent enantioselectivity was obtained in the Michael addition of 2,4-pentanedione to various nitro olefins using the new organocatalyst. The construction of contiguous stereocenters via the Michael reaction of substituted 1,3-dicarbonyls to nitro olefins was also carried out with very good yield, enantioselectivity, and diastereoselectivity.

1. Introduction

In recent years, asymmetric organocatalysis has grown rapidly as an indispensable tool for the synthesis of chiral organic molecules.[1] Multipoint recognition and the activation of reactants by weak enthalpic binding is the main advantage in non-covalent catalysis. Chiral thioureas play a vital role as non-covalent organocatalysts in enantioselective transformations. The development of thiourea organocatalysts is an expanding research area in the field of asymmetric catalysis.[2]

Jacobsen et al. reported on the first example of thiourea catalyzed asymmetric Mannich reactions.[3] In 2003, Takemoto reported on a bifunctional thiourea, which comprized of tertiary amine and a thiourea moiety for the concurrent activation of both a nucleophile and an electrophile.[4] Among the numerous reported thioureas, only a few can be termed as privileged organocatalysts, which can catalyze different asymmetric transformations. More precisely tertiary amine thiourea catalysts derived from privileged chiral building blocks such as cyclohexyl diamine, chincona alkaloid amine, and chiral BINAM belong to this category (see Fig. 1).[5]

The lack of effective bifunctional organocatalysts stimulated us to develop a new class of bifunctional tertiary amine thioureas from L-proline. L-Proline and its derivatives are well known for their efficiency as organocatalysts in performing various enantioselective transformations *via* covalent catalysis.[6] The Yong Tong pyrrolidine–thiourea derived from L-proline also belongs to this category.[7] Due to our interest in generating new chiral ligands from an inexpensive chiral pool for example, tartaric acid,[8] we continued our efforts to develop new organocatalysts from L-proline. We hoped that proline derived non-covalent organocatalysts containing tertiary amines and a thiourea will emulate the catalytic efficiency of proline and its derivatives in various enantioselective reactions. The modularity of organocatalyst **1**, allows the possibility of changing the electronic and steric environment at the stereogenic center bearing the thiourea functionality when compared to other known thioureas. Herein we report the development of L-proline derived novel bifunctional thiourea **1** and its application in conjugate additions of 1,3-diketones and β-ketoesters to nitroolefins.

2. Results and discussion

Starting from L-proline (Scheme 1), *N*-trityl prolinal **3** was obtained using Chemla's strategy with a change in the oxidation step (i.e. a Parikh–Doering oxidation was performed instead of a Swern oxidation).[9] The addition of a Grignard reagent to aldehyde **3** afforded phenyl substituted *N*-trityl prolinol **4**, which was transformed into its corresponding azide **5** under Mitsunobu conditions. Detritylation and N-alkylation provided the phenyl substituted azido compound **7** in good yield. Azide **7** was reduced using $LiAlH_4$ to yield the amine, which was converted in situ into thiourea **1** by treatment with 1-isothiocyanato-3,5-bis(trifluoromethyl) benzene isothiocyanate.

Andres et al. observed a low yield and poor enantioselectivity when organocatalyst **1d** (Fig. 2) was used, in which the thiourea moiety was attached to a non-stereogenic carbon atom.[10] Similar results were obtained for various Michael addition reactions using organocatalyst **1d**.[11] To further prove the requirement of a

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http://dx.doi.org/10.1016/j.tetasy.2014.02.011
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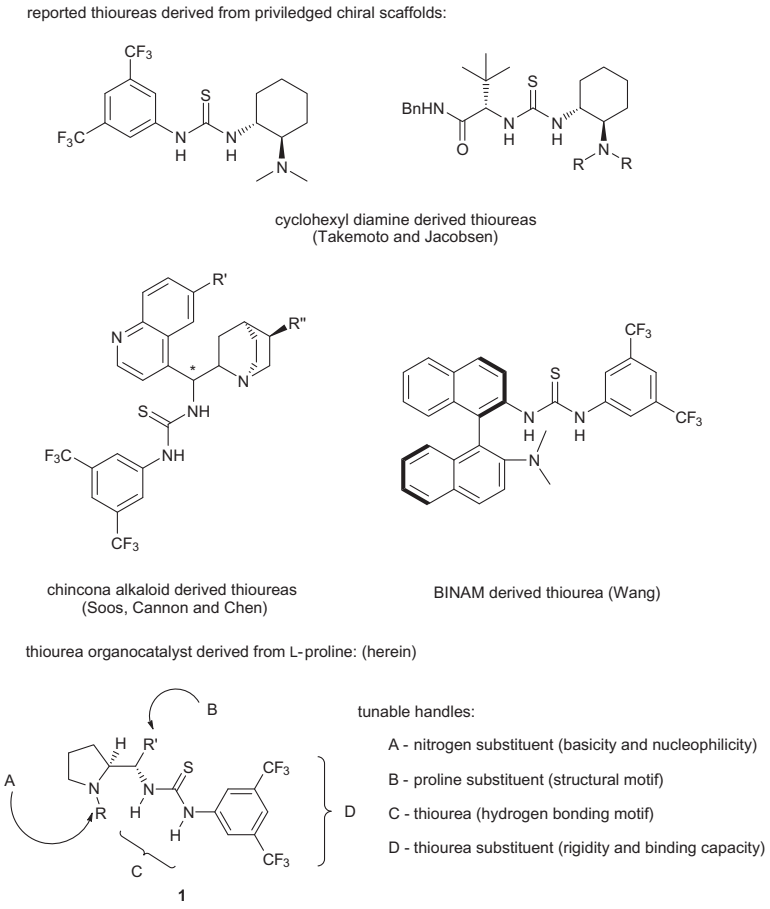
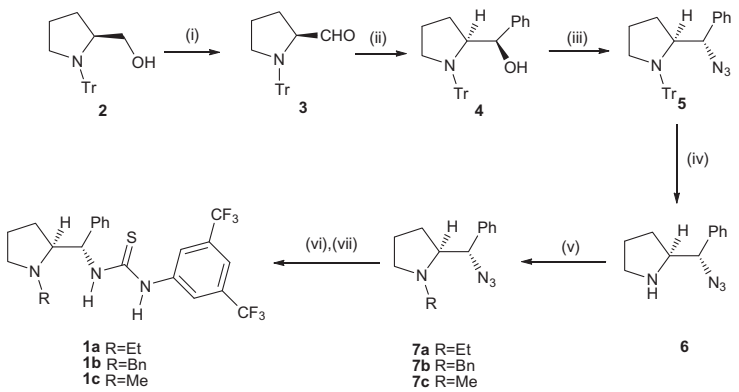


Figure 1. Various bifunctional thiourea organocatalysis.



Scheme 1. Synthesis of L-proline derived bifunctional thiourea. Reagents and conditions: (i) pyridine–SO_3 complex, dry DIEA, dry DMSO, dry DCM, 0 °C, 82% ; (ii) PhMgBr, dry THF, −78 °C, dr = 98:2, 58% ; (iii) PPh_3, DEAD, DPPA, dry THF, rt, 80% ; (iv) 4 M HCl, ether, rt, 85%; (v) (a) EtBr, K_2CO_3, dry DMF, rt, 77%; (b) BnBr, K_2CO_3, dry DMF, rt, 80%; (c) HCOOH, HCHO, H_2O, 100 °C, 62%; (vi) $LiAlH_4$, dry THF, rt; (vii) 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene, dry DCM, rt, 56–70%, over two steps.

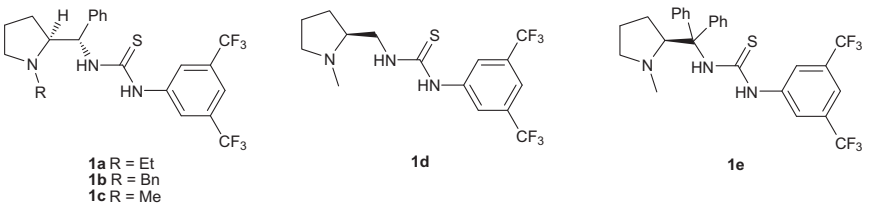
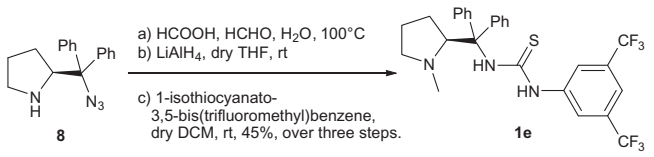


Figure 2. Various L-proline based bifunctional organocatalysts used for screening.

stereogenic center at the carbon bearing a thiourea moiety, we synthesized organocatalyst **1e**, as shown in Scheme 2. N-Methylation of amino azide **8**,[12] followed by reduction using $LiAlH_4$ gave the amine, which was treated in situ with isothiocyanate to afford the desired organocatalyst **1e**.



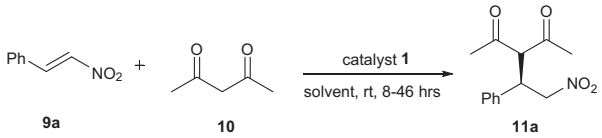
Scheme 2. Synthesis of organocatalyst **1e**.

In the literature, conjugate additions were found to be suitable reactions for examining the catalytic efficacy of new thiourea organocatalytic systems.[13] Hence, the Michael addition of 2,4-pentanedione to nitrostyrene was chosen as the model reaction to evaluate the efficiency of **1** as an organocatalyst. A solution of nitrostyrene **9a** in toluene was treated with 10 mol % of *N*-ethyl thiourea **1a** at room temperature, followed by the addition of 2,4-pentanedione **10**. Michael adduct **11a** was isolated in 72% yield with 90% ee in 46 h (Table 1, entry 1). The *N*-benzyl substituted thiourea **1b** did not catalyze the reaction under identical conditions (Table 1, entry 2). *N*-Methyl thiourea **1c** catalyzed the Michael addition of 2,4-pentanedione to nitrostyrene with great efficiency to yield the product in 92% yield and with 91% enantioselectivity (Table 1, entry 3). Organocatalyst **1d** in which thiourea moiety attached to the non-stereogenic carbon atom afforded Michael adduct in 83% yield with poor enantioselectivity of 9% (Table 1, entry 4). Only trace amounts of the Michael adduct were observed when a similar type of organocatalyst **1e** was employed hence, no further attempts were made either to isolate or determine the enantioselectivity of the product (Table 1, entry 5). These results demonstrate unequivocally the requirement of a stereogenic center at the carbon bearing a thiourea moiety in organocatalyst **1** scaffold for its effective asymmetric induction.

Encouraged by this observation, we screened various polar and non-polar solvents, in which methyl *tert*-butyl ether was identified as the most suitable reaction medium (Table 1, entries 6–11). Using 10 mol % of catalyst **1c**, Michael adduct **11a** was isolated in 98% yield with 96% enantioselectivity within 12 h at ambient temperature in methyl *tert*-butyl ether. Lowering the catalyst loading to 5 mol % did not affect either the yield or the enantioselectivity (Table 1; entry 12). Further lowering of the catalyst loading to 2 mol % resulted in reduction of enantioselectivity to 61% (Table 1, entry 13). Thus the Michael addition of 2,4-pentanedione with nitrostyrene was achieved with quantitative yield and excellent enantioselectivity using 5 mol % of the newly designed thiourea organocatalyst **1c**.

A number of nitroolefins **9** were subjected to a Michael addition with 2,4-pentanedione **10** in the presence of 5 mol % of catalyst **1c** at room temperature. The results are summarized in Table 2. The presence of halogens such as Cl or Br atoms at the *ortho*-, *meta* and *para*-positions, had no influence on either the yield or the enantioselectivity. Quantitative yields and excellent enantioselectivities were obtained for Michael adducts **11b–g** (Table 2; entries 2–7). Similar results were observed for 4-fluoro substituted nitrostyrene which afforded the corresponding Michael adduct **11h** (Table 2; entry 8). An electron donating group, such as a methoxy group, lowered the yield of the reaction but the enantioselectivity (94% ee) remained the same (Table 2; entries 9 and 10). The presence of an electron donating methyl group at the *para*-position had no negative effect on the yield or the enantiomeric excess (Table 2; entry 11). A nitroolefin containing a heteroaromatic moiety such as a thiophene, underwent Michael addition with 2,4-pentanedione in very good yield and enantioselectivity (Table 2; entry 12). An electron withdrawing nitro group at the *ortho*-position **9m** also provided the corresponding product in good yield and excellent enantioselectivity (Table 2; entry 13). Various disubstituted nitroolefins yielded the corresponding Michael adducts in good to very good yields, whereas the enantioselectivity was comparable with mono substituted nitroolefins (Table 2; entries 14–16). It is noteworthy that the presence of an –OH in disubstituted nitrostyrene **9n** lowered the yield as did

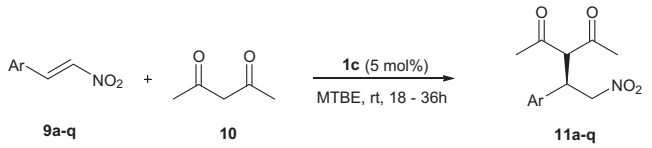
Table 1
Optimization of reaction conditions[a]



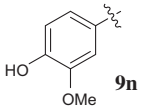
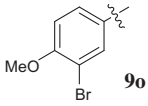
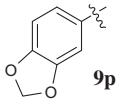
Entry	Organocatalyst (mol %)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a** (10)	$PhCH_3$	46	72	90
2	**1b** (10)	$PhCH_3$	48	25	–
3	**1c** (10)	$PhCH_3$	26	92	91
4	**1d** (10)	$PhCH_3$	30	83	09
5	**1e** (10)	$PhCH_3$	48	Trace	–
6	**1c** (10)	$CHCl_3$	30	95	84
7	**1c** (10)	CH_2Cl_2	32	92	79
8	**1c** (10)	Hexane	24	90	86
9	**1c** (10)	Diethyl ether	48	84	82
10	**1c** (10)	Cyclohexane	28	65	92
11	**1c** (10)	THF	36	68	89
11	**1c** (10)	MTBE	12	98	96
12	**1c** (5)	MTBE	18	95	96
13	**1c** (2)	MTBE	20	71	61

[a] Reaction conditions: 2,4-pentanedione **10** (0.5 mmol) was added to an agitated solution of nitroalkene **9a** (0.15 mmol) and catalyst **1** (x mol %) in 1.5 mL of MTBE at ambient temperature for the time mentioned.
[b] Isolated yields.
[c] Enantiomeric excess was determined by chiral HPLC analysis.

Table 2
Asymmetric Michael addition of 2,4-pentanedione to nitro olefins **8** catalyzed by organocatalyst **1c**[a]



9a-q 10 11a-q

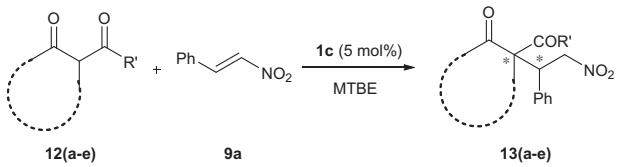
Entry	R	11	Yield[b] (%)	ee[c,d] (%),
1	Ph **9a**	**11a**	98	96
2	2-ClC_6H_4 **9b**	**11b**	90	98
3	3-ClC_6H_4 **9c**	**11c**	85	99
4	4-ClC_6H_4 **9d**	**11d**	92	98
5	2-BrC_6H_4 **9e**	**11e**	92	99
6	3-BrC_6H_4 **9f**	**11f**	94	96
7	4-BrC_6H_4 **9g**	**11g**	94	97
8	4-FC_6H_4 **9h**	**11h**	93	97
9	2-$MeOC_6H_4$ **9i**	**11i**	53	94
10	4-$MeOC_6H_4$ **9j**	**11j**	67	94
11	4-MeC_6H_4 **9k**	**11k**	89	96
12	2-Thiophenyl **9l**	**11l**	88	94
13	2-$NO_2C_6H_4$ **9m**	**11m**	93	98
14[e]	 **9n**	**11n**	68	95
15[e]	 **9o**	**11o**	89	95
16[e]	 **9p**	**11p**	80	95

[a] Reaction conditions: 2,4-pentanedione **10** (0.5 mmol) was added to an agitated solution of nitroalkene **9** (0.15 mmol) and catalyst **1c** (3.45 mg, 0.0075 mmol, 5 mol %) in 1.5 mL of MTBE at ambient temperature for 8–20 h.
[b] Isolated yields.
[c] Enantiomeric excess was determined by chiral HPLC analysis.
[d] The absolute configuration of the product was determined as (*R*) by comparing the specific rotation and HPLC data with the reported literatures.
[e] The absolute configuration was assigned on (*R*) by analogy.

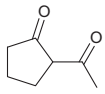
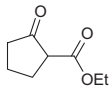
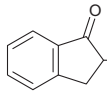
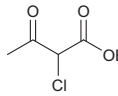
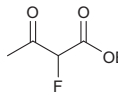
the –OMe substituent in **9i**, although the enantioselectivty was unchanged. These disubstituted niroolefins **9n**–**9p** are the first examples in the literature for asymmetric Michael additions with 2,4-pentanedione. In summary, various substituents such as halogens, electron withdrawing and electron donating groups are well tolerated under the reaction conditions to afford the corresponding Michael adducts with excellent enantioselectivity.

To further expand upon the scope of bifunctional thiourea **1c** in generating contiguous stereogenic centers, the Michael addition of various substituted 1,3-dicarbonyls to nitrostyrene **9a** was performed. It is evident that, Michael addition of 2-acetyl cyclopentanone **12a** with nitrostyrene **9a** proceeded (Table 3; entry 1) with ease to yield the product in good enantioselectivity and diastereoselectivity (90:10). Encouraged by this result, various substituted β-ketoesters were subjected to Michael additions with nitrostyrene **9a**. Among them, ethyl-2-oxocyclopentane carboxylate **12b** afforded the corresponding Michael adduct in excellent diastereoselctivity (99:1) and enantioselectivity (Table 3; entry 2). In the cases of other nucleophiles, only a variation in diastereoselectivity was observed while the enantioselectivity remained as high as 98–99% ee. Substituted β-ketoesters, such as fluoro and chloro (Table 3; entries 3-5) facilitated the reaction effectively to yield the corresponding Michael adducts in very good yields. It is noteworthy that separate optimization was not carried out for these nucleophiles other than changing the temperature.

Table 3
Asymmetric Michael addition of various nucleophiles to nitrostyrene **9a** using organocatalyst **1c**[a]



12(a-e) 9a 13(a-e)

Entry	12	Yield[b] (%)	dr[c]	ee[d]
1[e]	 **12a**	92	90:10	95
2[f]	 **12b**	95	99:1	99
3[f]	 **12c**	87	80:20	98
4[f]	 **12d**	91	58:42	99/98
5[f]	 **12e**	89	65:35	99/99

[a] Reaction conditions: 1,3-dicarbonyl **12** (0.17 mmol) was added to an agitated solution of nitroalkene **9a** (0.15 mmol) and catalyst **1c** (3.45 mg, 0.0075 mmol, 5 mol %) in 1.5 mL of MTBE at the temperature mentioned for 8–12 h.
[b] Isolated yields.
[c] Diastereomeric ratio was determined by ^1H NMR analysis.
[d] Enantiomeric excess was determined by chiral HPLC analysis.
[e] Reaction was carried out at 0 °C.
[f] Reactions were carried out at −15 °C.

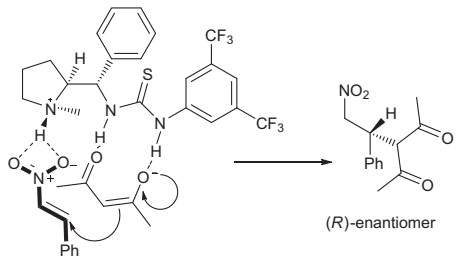


Figure 3. Plausible transition states for Michael addition using organocatalyst **1c**.

On the basis of stereoisomeric outcome, synergistic activation model for the Michael reaction of 2,4-pentanedione to phenyl nitrostyrene is proposed. The possible transition state for the substrate-organocatalyst interaction is shown in Figure 3. Deprotonation of the acidic proton from acetyl acetone by the tertiary amino group of the catalyst, led to the formation of an ammonium ion and the activation of nitrostyrene **9a** occurs through this ammonium moiety while the thiourea engages in H-bonding with the enolate.[14] From the absolute configuration of **11a**, the new C–C bond was formed by the nucleophilic attack on the '*Re*' face of nitrostyrene **9a**.

3. Conclusion

In conclusion, we have developed a new class of bifunctional thiourea from L-proline, an inexpensive chiral pool material.

Organocatalyst **1c** was successfully applied to the Michael addition of 1,3-dicarbonyl compounds and β-ketoesters to nitrostyrene with excellent enantioinduction. Exploration of the newly developed thiourea in other asymmetric transformations is in progress in our laboratory. Further efforts are also being undertaken to obtain the organocatalyst **1c** in fewer synthetic steps. We expect that it is poised to play an active role in the field of asymmetric catalysis, which is currently being explored in our laboratory.

4. Experimental

4.1. Materials and methods

All reactions were carried out in an oven dried flask. The solvents used for the reactions and column chromatography were of commercial grade and distilled prior to use. Toluene and THF were dried over sodium/benzophenone, CH_2Cl_2 and $CHCl_3$ over CaH_2. Solvents for HPLC were bought as analytical grade and used without further purification. TLC was performed on pre-coated silica gel aluminum plates with 60_F254 indicator, visualized by irradiation with UV light. Column chromatography was performed using silica gel 60–100 mesh. ^1H NMR and ^{13}C NMR were recorded on a 500 MHz spectrometer using CD_3OD-d_4 and $CDCl_3$ as the solvent; multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet) br s (broad singlet). Coupling constants *J* were reported in Hertz. High resolution mass spectra were obtained by ESI using a Q-TOF mass spectrometer. IR spectra were recorded in terms of frequency of absorption (cm^{-1}). The enantiomeric excess was obtained by HPLC analysis using a chiral stationary phase column (CHIRALPAK AD-H, AS-H and OD-H). Optical rotations were recorded using a polarimeter at a wavelength of 589 nm.

4.2. Synthesis of organocatalyst 1a, 1b, 1c, and 1e

4.2.1. (*S*)-1-Tritylpyrrolidine-2-carbaldehyde 3[9]

A solution of (*S*)-(1-tritylpyrrolidin-2-yl)methanol **2** (6 g, 17.4 mmol) in 20 mL of dry CH_2Cl_2 and 60 mL of dry DMSO (1:3) was cooled to 0 °C under a nitrogen atmosphere. Dry diethyl isopropyl amine (9.1 mL, 52.4 mmol) was added, then pyridine–SO_3 complex (active SO_3 48–50%, 157.2 mmol) was added portionwise and allowed to stir at the same temperature for 6 h, after which it was diluted with 60 mL of CH_2Cl_2 and 80 mL of water. The organic layer was washed repeatedly using water and finally with a brine solution. The organic phase was separated and dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified through silica gel column using hexane/Et_3N (99.5:0.5) as eluent to afford product **3** (4.9 g, 82%) as a white solid. Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 9.88 (d, *J* = 3.0 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 6H), 7.30 (t, *J* = 7.5 Hz, 6H), 7.20 (t, *J* = 7.5 Hz, 3H), 3.79 (dt, *J* = 9.0, 3.3 Hz, 1H), 3.31 (dt, *J* = 11.5, 7.0 Hz, 1H), 2.94 (ddd, *J* = 11.5, 7.0, 4.0 Hz, 1H), 1.62 (ddd, *J* = 17.0, 8.0, 4.0 Hz, 1H), 1.39–1.49 (m, 1H), 1,14 (ddd, *J* = 17.0, 12.5, 8.5 Hz, 1H), 0.76–0.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.4, 144.5, 129.5, 127.8, 126.5, 77.0, 68.5, 50.7, 28.1, 24.4.

4.2.2. (*R*)-Phenyl ((*S*)-1-tritylpyrrolidin-2-yl)methanol 4[9]

To aldehyde **3** (3.41 g, 10 mmol) in dry Et_2O (100 mL) under argon was added PhMgBr solution (30 mmol) at −80 °C. The reaction was followed by TLC. After 5 h of stirring, the reaction was hydrolyzed at −80 °C with a 2:1 mixture of a saturated aqueous NH_4Cl solution and NH_3 (28% in water). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over anhydrous sodium sulfate and the solvents removed in vacuo. The resulting solid was purified by column chromatography on silica gel (Hexane/EtOAc/Et_3N, 9:1:0.2) to afford compound **4** (2.4 g, 58%) as a white foamy solid. Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 6H), 7.18–7.34 (m, 12H), 7.14 (d, *J* = 7.0 Hz, 2H), 5.17 (d, *J* = 3.5 Hz, 1H), 3.78 (ddd, *J* = 8.5, 5.0, 3.5 Hz, 1H), 3.34 (br s, 1H), 3.34 (ddd, *J* = 12.0, 9.0, 7.0 Hz, 1H), 3.09 (ddd, *J* = 11.5, 8.0, 3.5 Hz, 1H), 1.49 (ddt, *J* = 12.0, 8.0, 5.0 Hz, 1H), 1.32–1.40 (m, 1H), 0.084 (ddt, *J* = 13.0, 8.5, 4.5 Hz, 1H), 0.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.7, 142.4, 130.0, 128.1, 127.7, 126.6, 126.5, 125.5, 78.3, 75.7, 66.2, 53.4, 25.9, 24.9.

4.2.3. (*S*)-2-((*S*)-Azido (phenyl)methyl)-1-tritylpyrrolidine 5

To a solution of compound **4** (1 g, 2.25 mmol) and PPh_3 (1.2 g, 4.5 mmol) in dry THF (10 mL), diethyl azodicarboxylate (0.78 mL, 4.5 mmol) was added dropwise at 0 °C followed by a similar addition of diphenyl phosphoryl azide (0.6 mL, 2.7 mmol) under an argon atmosphere. The resulting solution was allowed to warm and stirred for 8 h at ambient temperature. The reaction mixture was concentrated through in vacuo, after which water was added and extracted using EtOAc. The organic phase was separated, dried over sodium sulfate, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel using Hexane/Et_3N (99.5:0.5) as eluent to obtain the product **5** (0.76 g, 80%) as white solid. Mp: 123–126 °C; $[\alpha]_D^{25} = -99.3$ (*c* 1.0, $CHCl_3$); IR(KBr): *ν* = 3349, 2985, 2958, 2895, 2102, 1599, 1487, 1446, 1359, 1301, 1277, 1027, 747, 707, 698, 648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7 Hz, 6H), 7.27 (t, *J* = 7.5 Hz, 6H), 7.15–7.21(m, 6H), 6.86 (d, *J* = 7 Hz, 1H), 5.26 (d, *J* = 2.5 Hz, 1H), 3.76 (dt, *J* = 8.5, 3 Hz, 1H), 3.38–3.44 (m,1H), 3.02–3.07 (m, 1H), 1.36–1.49 (m, 2H), 0.80–0.88 (m, 1H), 0.14–0.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 138.9, 129.9, 128.2, 127.6, 127.2, 126.3, 126.0, 78.4, 70.9, 67.3, 51.9, 25.5, 24.9; HRMS (ESI): *m*/*z* calculated for $C_{30}H_{28}N_4$+Na^+: 467.2212, found: 467.2226.

4.2.4. (*S*)-2-((*S*)-Azido(phenyl)methyl)pyrrolidine 6

To a solution of **5** (1 g, 4.9 mmol) in Et_2O (10 mL) was added HCl (4 M aqueous solution, 10 mL). After 3 h of vigorous stirring, the two phases were separated, and the aqueous layer was washed three times with Et_2O (3 × 5 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by extraction with $CHCl_3$ (3 × 10 mL). The extract was dried over anhydrous sodium sulfate and the solvents were evaporated in vacuo. Purification was carried out by column chromatography using silica gel (Hexane/EtOAc–75:25) to afford the title compound **6** (0.389 g, 85%) as a yellow oil. $[\alpha]_D^{25} = -184.6$ (*c* 1.0, $CHCl_3$); IR(KBr): *ν* = 3062, 2965, 2794, 2101, 1494, 1452, 1288, 1123, 741, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.40 (m, 2H), 7.31–7.35 (m, 3H), 4.36 (d, *J* = 8 Hz, 1H), 3.33 (q, *J* = 7 Hz, 1H), 2.94–2.99 (m, 1H), 2.80–2.85 (m, 1H), 1.88–1.94 (m, 1H), 1.78–1.86 (m, 1H), 1.63–1.77 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 128.8, 128.3, 127.4, 70.3, 62.9, 46.4, 28.3, 25.0; HRMS (ESI): *m*/*z* calculated for $C_{11}H_{15}N_4$+H^+: 203.1297, found: 203.1290.

4.2.5. (*S*)-2-((*S*)-Azido (phenyl)methyl)-1-ethylpyrrolidine 7a

To a solution of compound **6** (0.5 g, 2.1 mmol) in dry DMF, K_2CO_3 (0.348 g, 2.5 mmol) was added and stirred for a few minutes, after which ethyl bromide (0.19 mL, 2.5 mmol) was added and stirred overnight at ambient temperature. The reaction mixture was diluted with water and extracted using CH_2Cl_2. The organic phase was washed three times with water, separated, dried over sodium sulfate, and concentrated. Purification was carried out by column chromatography using silica gel (Hexane/EtOAc–97:3) to give compound **7a** (0.438 g, 77%) as a colorless liquid. $[\alpha]_D^{25} = -165.3$ (*c* 1.0, $CHCl_3$); IR (KBr): *ν* = 3421, 2924, 2854,

2106, 1628, 1444, 1377, 1275, 1110, 770, 703, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.36 (m, 2H), 7.27.7.32 (m, 3H), 4.70 (d, J = 3.5 Hz, 1H), 3.23 (td, J = 9, 2 Hz, 1H), 2.79–2.88 (m, 1H), 2.71–2.75 (m, 1H), 2.27–2.34 (m, 1H), 2.16–2.21 (m, 1H), 1.84–1.91 (m, 1H), 1.75–1.83 (m, 1H), 1.64–1.70 (m, 1H), 1.50–1.58 (m, 1H), 1.10 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 128.4, 127.6, 126.9, 69.7, 67.0, 53.6, 48.6, 25.7, 23.2, 13.8; HRMS (ESI): m/z calculated for $C_{13}H_{18}N_4$+H^+: 231.1610, found: 231.1615.

4.2.6. (*S*)-2-((*S*)-Azido(phenyl)methyl)-1-benzylpyrrolidine 7b

To a solution of compound **6** (0.5 g, 2.1 mmol) in dry DMF, K_2CO_3 (0.348 g, 2.5 mmol) was added and stirred for a few minutes, after which benzyl bromide (0.29 mL, 2.5 mmol) was added and stirred overnight at ambient temperature. The reaction mixture was diluted with water and extracted using CH_2Cl_2. The organic phase was washed three times with water, separated, dried over sodium sulfate, and concentrated. Purification was carried out by column chromatography using silica gel (Hexane/EtOAc–98:2) to give compound **7b** (0.585 g, 81%) as a colorless liquid. $[\alpha]_D^{25} = -105.0$ (c 1.0, $CHCl_3$); IR (KBr): ν = 3295, 2965, 2794, 2101, 1494, 1452, 1288, 1123, 741, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.36 (m, 6H), 7.25.7.29 (m, 4H), 4.59 (d, J = 2 Hz, 1H), 3.95 (d, J = 13 Hz, 1H), 3.51 (d, J = 13 Hz, 1H), 3.05 (t, J = 7.5 Hz, 1H), 2.95–2.97 (m, 1H), 2.26–2.30 (m, 1H), 1.91–1.96 (m, 1H), 1.76–1.86 (m, 1H), 1.60–1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 138.5, 128.9, 128.4, 128.3, 127.6, 127.1, 127.0, 69.7, 67.3, 59.8, 54.9, 26.1, 23.6; HRMS (ESI): m/z calculated for $C_{18}H_{20}N_4$+H^+: 293.1766, found: 293.1766.

4.2.7. (*S*)-2-((*S*)-Azido(phenyl)methyl)-1-methylpyrrolidine 7c

Amino azide **6** (0.5 g, 2.1 mmol) was dissolved in water (2 mL), and HCOOH (98%, 1 mL) and HCHO (37% aqueous solution, 1.5 mL) were added. The reaction mixture was stirred for 3 h at reflux and then cooled and made alkaline with concentrated aqueous NaOH, followed by extraction with CH_2Cl_2. The extract was dried over sodium sulfate and the solvent evaporated in vacuo. The residue was purified over silica gel hexane/EtOAc (92:8) as eluent to afford the title compound **7c** (0.331 g, 62%) as a slightly yellow oil. $[\alpha]_D^{25} = -119.0$ (c 1.0, $CHCl_3$); IR (KBr): ν = 3417, 2854, 2102, 1633, 1453, 1277, 1176, 1136, 742, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.38 (m, 2H), 7.28.7.33 (m, 3H), 4.71 (d, J = 4 Hz, 1H), 3.11–3.14 (m, 1H), 2.48–2.51 (m, 1H), 2.34 (s, 3H), 2.21–2.26 (m, 1H), 1.88–1.94 (m, 1H), 1.74–1.83 (m, 1H), 1.62–1.68 (m, 1H), 1.56–1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 128.6, 127.8, 127.0, 71.0, 66.6, 57.5, 40.9, 25.9, 22.8; HRMS (ESI): m/z calculated for $C_{12}H_{16}N_4$+H^+: 217.1453, found: 217.1450.

4.2.8. General procedure for synthesis of thiourea 1a, 1b, and 1c from the corresponding *N*-alkyl azide 7

To $LiAlH_4$ (38 mg, 1 mmol) in 1 mL of dry THF, a solution of compound **7** (1 mmol) in 2 mL of dry THF was slowly added under ice cold conditions under an argon atmosphere. The resulting mixture was stirred at room temperature for 1.5 h and then quenched using 5% aqueous sodium potassium tartarate solution. The reaction mixture was filtered through a short Celite pad, dried using sodium sulfate, and concentrated in vacuo. The resulting yellowish liquid was dissolved in dry CH_2Cl_2 (3 mL), after which 1-isothiocyanato-3,5-bis (trifluoromethyl) benzene (0.22 mL, 1.2 mmol) was added and allowed to stir for 18 h at room temperature. Volatiles are removed in vacuo and purified by column chromatography using silica gel.

4.2.9. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-((*S*)-1-ethyl pyrrolidin-2-yl)(phenyl)methyl)thiourea 1a

Prepared according to general procedure using compound **7a** (231.31 mg, 1 mmol). Purification was carried out by column chromatography using silica gel (Hexane/EtOAc–85:15) to afford the title compound **1a** (0.266 g, 56%) as a colorless foamy solid. Mp: 73–76 °C; $[\alpha]_D^{25} = -82.2$ (c 1.0, $CHCl_3$); IR (KBr): ν = 3251, 2972, 1600, 1543, 1473, 1384, 1273, 1176, 1134, 1000, 960, 885, 700, 681 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 8.22 (s, 2H), 7.63 (s, 1H), 7.25–7.34 (m, 5H), 5.71 (s,1H), 3.25 (t, J = 4.0 Hz, 1H), 2.94–3.01 (m, 2H), 2.3(br s, 2H), 1.76 (br s, 4H), 1.10 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 183.2, 143.4, 141.5, 132.7 (q, J = 33.75 Hz), 129.6, 128.0, 17.5, 124.7 (q, J = 270 Hz), 121.5, 117.8, 70.2, 59.2, 54.1, 49.6, 26.9, 23.0, 13.6; HRMS (ESI): m/z calculated for $C_{22}H_{23}F_6N_3S$+H^+: 476.1595, found: 476.1591.

4.2.10. 1-((*S*)-((*S*)-1-Benzylpyrrolidin-2-yl)(phenyl)methyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea 1b

Prepared according to general procedure using compound **7b** (293.2 mg, 1 mmol). Purification was carried out by column chromatography using silica gel (Hexane/EtOAc–90:10) to afford the title compound **1b** (0.349 g, 65%) as a colorless foamy solid. Mp: 52–55 °C; $[\alpha]_D^{25} = -127.2$ (c 1.0, $CHCl_3$); IR (KBr): ν = 3251, 3030, 2969, 1599, 1538, 1473, 1384, 1277, 1175, 1133, 1075, 885, 847, 699 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 8.11 (s, 2H), 7.53(s, 1H), 7.07–7.24(m, 10H), 5.73(s, 1H), 4.00(br, d, J = 12.5 Hz, 1H), 3.20(br, 1H), 2.85–2.93(m, 2H), 2.20(br, 1H), 1.57–1.72(m, 4H); ^{13}C NMR (125 MHz, CD_3OD): δ 182.0, 161.9, 141.9, 140.2, 138.6, 131.3(q, J = 32.5 Hz), 129.0, 128.3, 128.1, 126.9, 125.2(q, J = 298 Hz), 120.1, 116.6, 68.0, 58.2, 53.6, 26.5, 25.7, 21.7; HRMS (ESI): m/z calculated for $C_{27}H_{25}F_6N_3S$+H^+: 538.1752, found: 538.1750.

4.2.11. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-((*S*)-1-methyl pyrrolidin-2-yl)(phenyl)methyl)thiourea 1c

Prepared according to general procedure using compound **7c** (217.2 mg, 1 mmol). Purification was carried out by column chromatography using silica gel (Hexane/EtOAc–85:15) to afford the title compound **1c** (0.325 g, 70%) as a colorless foamy solid. Mp: 56–59 °C; $[\alpha]_D^{25} = -43.5$ (c 1.0, $CHCl_3$); IR (KBr): ν = 3287, 2924, 2854, 1744, 1470, 1384, 1277, 1176, 1134, 885, 700, 681 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 8.23 (s, 2H), 7.62 (s, 1H), 7.33–7.36 (m, 4H), 7.24–7.27 (m, 1H), 5.75 (s, 1H), 3.12 (t, J = 7.0 Hz, 1H), 2.71 (s, 1H), 2.41 (s, 3H), 2.31 (d, J = 7.0 Hz, 1H), 1.64–1.78 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD): δ 183.1, 143.4, 141.6, 132.7 (q, J = 32.5 Hz), 129.5, 128.3, 127.9, 124.7 (q, J = 270 Hz), 133.4, 117.7, 71.6, 58.9, 58.1, 41.1, 27.0, 22.9 ; HRMS (ESI): m/z calculated for $C_{21}H_{21}F_6N_3S$+H^+: 462.1439, found: 462.1434.

4.2.12. Synthesis and characterization of thiourea organano catalyst 1e

Amino azide **8** (0.5 mg, 1.8 mmol) was dissolved in water (2 mL), after which HCOOH (98%, 1 mL) and HCHO (37% aqueous solution, 1.5 mL) were added. The reaction mixture was stirred for 3 h at reflux, cooled, and then made alkaline with concentrated aqueous NaOH, followed by extraction with CH_2Cl_2. To $LiAlH_4$ (68.4 mg, 1.8 mmol) in 1 mL of dry THF, a solution of crude product in 2 mL of dry THF was slowly added under ice cold conditions under an argon atmosphere. The resulting mixture was stirred at room temperature for 1.5 h, and then quenched using 5% aqueous sodium potassium tartarate solution. The reaction mixture was filtered through a short Celite pad, dried over sodium sulfate, and concentrated in vacuo. The resulting yellowish liquid was dissolved in dry CH_2Cl_2 (4 mL), after which 1-isothiocyanato-3,5-bis(trifluoromethyl) benzene (0.33 mL, 1.8 mmol) was added and allowed to stir for 18 h at room temperature. The volatiles are removed in vacuo and purified by column chromatography using silica gel. The residue was purified over silica gel (Hexane/EtOAc–98:2) to afford compound **1e** (0.434 g, 45% yield) as a foamy

white paste. $[\alpha]_D^{26}$ = +300.0 (*c* 1.0, $CHCl_3$); IR (KBr): *v* = 3263, 2989, 2832, 1732, 1510, 1311, 1239, 1102, 1176, 879, 721, 679 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.93 (s, 2H), 7.59 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 4.68 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.10–3.06 (m, 1H), 2.71 (m, 1H), 2.49 (s, 3H), 2.40–2.32 (m, 1H), 2.03–2.01 (m, 1H), 1.91–1.85 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 183.6, 147.2, 143.9, 143.4, 132.8 (q, *J* = 33 Hz), 130.1, 129.4, 128.7, 128.4, 128.2, 127.4, 124.7 (q, *J* = 270 Hz), 123.4, 118.0, 75.9, 72.4, 59.3, 45.1, 31.4, 25.5; HRMS (ESI): *m*/*z* calculated for $C_{27}H_{25}F_6N_3S+H^+$: 538.1746, found: 538.1761.

4.2.13. General procedure A for the enantioselective Michael addition of 2,4-pentanedione to nitroolefins

To a stirred solution of **1c** (3.45 mg, 0.0075 mmol, 5 mol %) and nitroalkene **9** (0.15 mmol) in MTBE (1.5 mL), 2,4-pentanedione **10** (0.5 mmol) was added under argon. The solution was stirred at ambient temperature for 8–20 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give the product.

4.2.14. General procedure B for the enantioselective Michael addition of substituted 1,3-dicarbonyls to nitrostyrene

To a stirred solution of **1c** (3.45 mg, 0.0075 mmol, 5 mol %) and nitroalkene **9a** (0.15 mmol) in MTBE (1.5 mL), substituted 1,3-dicarbonyl **12** (0.17 mmol) was added under argon. The solution was stirred at the mentioned temperature for 8–12 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel.

4.2.15. (*R*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione 11a[13a,15]

Prepared according to general procedure A using β-nitrostyrene **9a** (22.37 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 10 h. After column chromatography, the desired product was obtained as a white solid (36.62 mg, 98% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.36 (m, 3H), 7.16–7.21 (m, 2H), 4.65 (dd, *J* = 12.5, 7.5 Hz, 1H), 4.60 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.16–4.27 (m, 2 H), 4.37 (d, *J* = 11 Hz, 1H), 4.19–4.27 (m, 1H), 2.29 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 200.9, 135.8,129.3, 128.6, 127.8, 78.2, 70.7, 42.8, 30.4, 29.5; HPLC (AD-H, hexane/IPA = 90/10, flow rate-1.0 mL/min, 210 nm): t_{minor} = 9.2 min, t_{major} = 12.1 min; ee = 96%.

4.2.16. (*R*)-3-(1-(2-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione 11b[13b]

Prepared according to general procedure A using β-nitrostyrene **9b** (27.5 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 10 h. After column chromatography, the desired product was obtained as a white solid (38.30 mg, 90% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.44 (t, *J* = 2.0 Hz, 1H), 7.21–7.30 (m, 2H), 7.14–7.18 (m, 1H), 4.81–4.87 (dd, *J* = 6.5 Hz, 11.5 Hz, 2H), 4.72–4.78 (m, 1H), 4.59–4.69 (m, 1H), 2.30 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 200.9, 133.8, 133.4, 130.7 129.7, 129.0, 127.7, 76.2, 69.0, 38.8, 30.9, 28.4; HPLC (AS-H, hexane/IPA = 90/10, flow rate-0.6 mL/min, 210 nm): t_{minor} = 20.6 min, t_{major} = 22.3 min, ee = 98%.

4.2.17. (*R*)-3-(1-(3-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione 11c[13b,16]

Prepared according to general procedure A using β-nitrostyrene **9c** (27.5 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 12 h. After column chromatography, the desired product was obtained as a white solid (36.18 mg, 85% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.44 (t, *J* = 2.0 Hz, 1H), 7.22–7.31(m, 2H), 7.15–7.19 (m, 1H), 4.82–4.88 (dd, *J* = 6.5 Hz, 11.5 Hz, 1H), 4.73–4.79 (m, 1H), 4.69–4.70 (d, *J* = 3.5 Hz, 1H), 4.61–4.66 (dd, *J* = 3.5 Hz, 7.5 Hz, 1H), 2.31 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 200.9, 133.8, 133.4, 130.7, 129.7, 129.0, 127.7, 76.2, 69.0, 38.8, 30.9, 28.4; HPLC (AD-H, hexane/2-propanol = 97/3, flow rate-0.8 mL/min, 210 nm): t_{minor} = 23.6 min, t_{major} = 26.8 min, ee = 99%.

4.2.18. (*R*)-3-(1-(4-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione 11d[13b]

Prepared according to general procedure A using β-nitrostyrene **9d** (27.5 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 11 h. After column chromatography, the desired product was obtained as a white solid (39.16 mg, 92% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.33(m, 2H), 7.12–7.16(m, 2H), 4.60–4.62(t, *J* = 2 Hz, 2H), 4.32–4.35(d, *J* = 11 Hz, 1H), 4.19–4.27(m, 1H), 2.30(s, 3H), 1.98(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 200.6, 134.6, 134.5, 129.6, 129.3, 77.9, 70.5, 42.1, 30.5, 29.7; HPLC (AS-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 210 nm): t_{minor} = 12.8 min, t_{major} = 23.2 min, ee = 98%.

4.2.19. (*R*)-3-[1-(2-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione 11e[13i,18]

Prepared according to general procedure A using β-nitrostyrene **9e** (34.21 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 8 h. After column chromatography, the desired product was obtained as a pale brown solid (45.3 mg, 92% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 8, 1.5 Hz, 1H), 7.29 (td, *J* = 7.5, 1.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 7.14 (dd, *J* = 8, 1.5 Hz, 1H), 4.84 (dd, *J* = 12.0, 6.5 Hz, 1H), 4.75 (ddd, *J* = 10, 6.5, 4.0 Hz, 1H), 4.68 (dd, *J* = 12.5, 4.0 Hz, 1H), 4.61 (d, *J* = 9.5 Hz, 1H), 2.32 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.0, 200.9, 134.0, 130.0, 128.7, 128.3, 124.6, 76.2, 69.1, 41.0, 31.0, 28.3; HPLC (OD-H, hexane/2-propanol = 95/5, flow rate-0.8 mL/min, 254 nm): t_{minor} = 37.5 min, t_{major} = 46.7 min, ee = 99%.

4.2.20. (*R*)-3-[1-(3-Bromophenyl)-2-nitroethyl]-pentane-2,4-dione 11f[17,18]

Prepared according to general procedure A using β-nitrostyrene **9f** (34.21 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 9 h. After column chromatography, the desired product was obtained as a white solid (46.28 mg, 94% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.42 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H), 7.34 (t, *J* = 1.5 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.11 (dt, *J* = 7.0, 1.0 Hz, 1H), 4.63 (dd, *J* = 13.0, 7.5 Hz, 1H), 4.59 (dd, *J* = 13.0, 5.0 Hz, 1H), 4.33 (d, *J* = 10.5 Hz, 1H), 4.19 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 1H), 2.28 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.2, 200.4, 138.4, 131.7, 131.0, 130.8, 126.5, 123.3, 77.7, 70.3, 42.2, 30.5, 29.8; HPLC (AS-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 210 nm): t_{minor} = 14.6 min, t_{major} = 26.4 min, ee = 96%.

4.2.21. 3-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)pentane-2,4-dione 11g[13h,23]

Prepared according to general procedure A using β-nitrostyrene **9g** (34.21 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 8 h. After column chromatography, the desired product was obtained as a white solid (46.28 mg, 94% yield). Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.5 Hz, 2H),

7.08 (d, J = 8.5 Hz, 2H), 4.66–4.59 (m, 2H), 4.33 (d, J = 10.5 Hz, 1H), 4.26–4.19 (m, 1H), 2.29 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.3, 200.5, 135.0, 132.5, 129.6, 122.6, 77.8, 70.4, 42.1, 30.4, 29.7; HPLC (AS-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 210 nm): t_{minor} = 14.6 min, t_{major} = 26.4 min, ee = 97%.

4.2.22. (*R*)-3-(1-(4-Fluorophenyl)-2-nitroethyl)pentane-2,4-dione 11h[13b]

Prepared according to general procedure A using β-nitrostyrene **9h** (25.07 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 8 h. After column chromatography, the desired product was obtained as a white solid (37.29 mg, 93% yield). Analytical data matched with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15–7.20 (m, 2H), 7.00–7.06 (m, 2H), 4.60–4.62 (t, J = 1.0 Hz, 2H), 4.32–4.36 (d, J = 10.5 Hz, 1H), 4.20–4.28 (m, 1H), 2.30 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 200.9, 133.8, 133.4, 130.7, 129.7, 129.0, 127.7, 76.2, 69.0, 38.8, 30.9, 28.4; HPLC (OD-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 210 nm): t_{minor} = 14.1 min, t_{major} = 15.6 min, ee = 97%.

4.2.23. 3-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione 11i[16,23]

Prepared according to general procedure A using β-nitrostyrene **9i** (26.87 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 20 h. After column chromatography, the desired product was obtained as an oil (22.20 mg, 53% yield). Analytical data matched with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (dd, J = 16.0 Hz, 1.5 Hz, 1H), 7.07(dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.94–6.85 (m, 2H), 4.77 (dd, J = 12.5 Hz, 8.0 Hz, 1H), 4.62–4.55 (m, 2H), 4.51–4.45 (m, 1H), 3.87 (s, 3H), 2.27 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 201.6, 157.0, 130.2, 129.7, 123.4, 121.1, 111.2, 76.5, 68.9, 55.4, 38.9, 30.4, 28.7; HPLC (AD-H, hexane/2-propanol = 99/1, flow rate-0.5 mL/min, 210 nm): t_{minor} = 61.7 min, t_{major} = 96.7 min, ee = 94%.

4.2.24. 3-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione 11j[16,23]

Prepared according to general procedure A using β-nitrostyrene **9j** (26.87 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 19 h. After column chromatography, the desired product was obtained as an oil (28.07 mg, 67% yield). Analytical data matched with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.61–4.57 (m, 2H), 4.35 (d, J = 11.0 Hz, 1H), 4.24–4.18 (m, 1H), 3.78 (s, 3H), 2.29 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 201.1, 159.4, 129.0, 127.5, 114.6, 78.4, 70.8, 55.1, 42.0, 30.3, 29.4; HPLC (AD-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 210 nm): t_{minor} = 9.5 min, t_{major} = 14.2 min, ee = 94%.

4.2.25. (*R*)-3-(2-Nitro-1-*p*-tolylethyl)pentane-2,4-dione 11k[13b,16]

Prepared according to general procedure A using β-nitrostyrene **9k** (24.48 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 14 h. After column chromatography, the desired product was obtained as a colorless solid (35.15 mg, 89% yield). Analytical data matched with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.58–4.65 (m, 2H), 4.36 (d, J = 11.0 Hz, 1H), 4.24–4.17 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 201.1, 138.3, 132.7, 130.0, 127.7, 78.3, 70.8, 42.4, 30.4, 29.4, 21.0; HPLC (AD-H, hexane/2-propanol = 90/10, flow rate-0.8 mL/min, 210 nm): t_{minor} = 10.7 min, t_{major} = 17.5 min, ee = 96%.

4.2.26. (*S*)-3-(2-Nitro-1-(thiophen-2-yl)ethyl)pentane-2,4-dione 11l[13b,g]

Prepared according to general procedure A using β-nitrostyrene **9l** (23.27 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 12 h. After column chromatography, the desired product was obtained as a colorless solid (33.70 mg, 88% yield). Analytical data matched with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, J = 5.0, 1.0 Hz, 1H), 6.86 (dd, J = 5.0, 3.5 Hz, 1H), 6.81 (d, J = 3.5 Hz, 1H), 4.58 (m, 2H), 4.47 (m, 1H), 4.32 (d, J = 10.0 Hz, 1H), 2.22 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 199.6, 137.4, 126.4, 126.0, 124.7, 77.5, 70.0, 37.2, 29.5, 28.6; HPLC (AS-H, hexane/2-propanol = 90/10, flow rate-0.6 mL/min, 210 nm): t_{minor} = 32.8 min, t_{major} = 42.4 min, ee = 94%.

4.2.27. (*R*)-3-[2-Nitro-1-(2-nitro-phenyl)-ethyl]-pentane-2,4-dione 11m[18]

Prepared according to general procedure A using β-nitrostyrene **9m** (29.12 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 10 h. After column chromatography, the desired product was obtained as a pale yellow solid (41.05 mg, 93% yield). Analytical data matched with previously reported values.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (dd, J = 8.0, 1.5 Hz, 1H), 7.59 (td, J = 8.0, 1.5 Hz, 1H), 7.49 (td, J = 8.0, 1.5 Hz, 1H), 7.37 (dd, J = 8.0, 1.5 Hz, 1H), 4.98 (dd, J = 13.0, 7.0 Hz, 1H), 4.85 (dd, J = 13.0, 3.5 Hz, 1H), 4.74 (ddd, J = 8.5, 7.0, 3.5 Hz, 1H), 4.68 (d, J = 8.5 Hz, 1H), 2.32 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5, 200.5, 149.8, 133.5, 131.2, 129.3, 129.2, 125.6, 76.5, 69.1, 37.1, 31.3, 29.2; HPLC (OD-H, hexane/2-propanol = 90/10, flow rate-1 mL/min, 230 nm): t_{minor} = 30.0 min, t_{major} = 35.6 min, ee = 98%.

4.2.28. (*R*)-3-(1-(4-Hydroxy-3-methoxyphenyl)-2-nitroethyl) pentane-2,4-dione 11n

Prepared according to general procedure A using β-nitrostyrene **9n** (29.27 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 20 h. After column chromatography, the desired product was obtained as a light yellow paste (30.12 mg, 68% yield). $[\alpha]_D^{25} = -38.1$ (c 0.25, $CHCl_3$); IR (KBr): ν = 3391, 2957, 2925, 2337, 1695, 1637, 1568, 1384, 1333, 846, 769, 741, 702, 590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (d, J = 8.5 Hz, 1H), 6.68 (dd, J = 8.0, 2.0 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 4.55–4.62 (m, 2H), 4.34 (d, J = 11 Hz, 1H), 4.14–4.18 (m, 1H), 3.86 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 201.2, 146.9, 145.8, 127.7, 120.5, 115.1, 110.8, 78.5, 70.9, 56.0, 42.6, 30.3, 29.5; HRMS (ESI): m/z calculated for $C_{14}H_{17}NO_6$+Na$^+$: 318.0954, found: 318.0940; HPLC (AS-H, hexane/2-propanol = 75/25, flow rate-0.3 mL/min, 220 nm): t_{minor} = 59.3 min, t_{major} = 64.6 min, ee = 95%. Configuration assignment: The absolute stereochemistry was assigned as (*R*) by analogy.

4.2.29. (*R*)-3-(1-(3-Bromo-4-methoxyphenyl)-2-nitroethyl) pentane-2,4-dione 11o

Prepared according to general procedure A using β-nitrostyrene **9o** (38.71 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 19 h. After column chromatography, the desired product was obtained as a colorless solid (47.82 mg, 89% yield). Mp: 131–134 °C; $[\alpha]_D^{25} = -118.1$ (c 1.0, $CHCl_3$); IR (KBr): ν = 3397, 3009, 2926, 2839, 2764, 1735, 1705, 1605, 1551, 1504, 1361, 1261, 1138, 1052, 951, 821, 737, 675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 2.5 Hz, 1H), 7.09 (dd, J = 7.5, 2.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 4.58–4.59 (m, 2H), 4.31 (d, J = 11 Hz, 1H), 4.14–4.19 (m, 1H), 3.86 (s, 3H), 2.29 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5, 200.7, 155.9, 132.6, 129.3, 128.2, 112.4, 112.3, 78.1, 70.6, 56.2, 41.7, 30.4, 29.6; HRMS (ESI): m/z calculated for $C_{14}H_{16}NO_5Br$+Na$^+$:

380.0110, found: 380.0117; HPLC (AS-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 220 nm): t_{minor} = 25.7 min, t_{major} = 44.8 -min, ee = 95%. Configuration assignment: The absolute stereochemistry was assigned as (*R*) by analogy

4.2.30. (*R*)-3-(1-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroethyl)pentane-2,4-dione 11p

Prepared according to general procedure A using β-nitrostyrene **9p** (28.97 mg, 0.15 mmol) and 2,4-pentanedione **10** (50 mg, 0.5 mmol), the reaction time was 20 h. After column chromatography, the desired product was obtained as a colorless solid (35.20 mg, 80% yield). Mp: 86–89 °C; $[\alpha]_D^{25} = -102.0$ (*c* 0.5, $CHCl_3$); IR (KBr): ν = cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, *J* = 7.5 Hz, 1H), 6.63–6.65 (m, 2H), 5.95 (s, 2H), 4.56 (d, *J* = 6.5 Hz, 2H), 4.30 (d, *J* = 11 Hz, 1H), 4.14–4.18 (m, 1H), 2.29 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 200.9, 148.4, 147.7, 129.4, 121.4, 108.9, 108.1, 101.4, 78.4, 70.9, 42.6, 30.4, 29.4; HRMS (ESI): *m*/*z* calculated for $C_{14}H_{15}NO_6$+Na^+: 316.0797, found: 316.0811; HPLC (AS-H, hexane/2-propanol = 70/30, flow rate-1 mL/min, 220 nm): t_{minor} = 25.2 min, t_{major} = 45.1 min, ee = 95%. Configuration assignment: The absolute stereochemistry was assigned as (*R*) by analogy.

4.2.31. ((*S*)-2-Acetyl-2-((*S*)-2-nitro-1-phenylethyl) cyclopentanone 13a[13g,19,21]

Prepared according to general procedure B using nitrostyrene **9a** (22.37 mg, 0.15 mmol) and 2-acetyl cyclopentanaone **12a** (21.45 mg, 0.17 mmol), the reaction time was 12 h. After column chromatography, the desired product was obtained as colorless solid (38 mg, 92% yield); dr = 90:10 (determined by ^1H NMR); Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): 7.20–7.32 (m, 5H), 4.87 (t, *J* = 11.5 Hz, 1H), 4.50 (dd, *J* = 4.0 and 13.0 Hz, 1H), 4.40 (dd, *J* = 4.0 and 11.5 Hz, 1H), 2.56–2.61 (m, 1H), 2.34 (s, 3H), 2.15–2.28 (m, 1H), 1.93–2.03 (m, 1H), 1.65–1.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.3, 203.0, 134.4, 129.7, 129.1, 128.7, 75.8, 71.4, 46.6, 38.9, 27.5, 26.8, 19.7; HPLC (OD-H, hexane/2-propanol = 80/20, flow rate-1 mL/min, 220 nm): Major diastereomer: t_{minor} = 10.8 min, t_{major} = 40.8 min, ee = 95%; Minor diastereomer: t_{minor} = 13.4 min, t_{major} = 18.9 min, ee = 94%.

4.2.32. (*R*)-Ethyl 1-((*S*)-2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate 13b[13b,g]

Prepared according to general procedure B using nitrostyrene **9a** (22.37 mg, 0.15 mmol) and ethyl 2-oxocyclopentanecarboxylate **12b** (26.55 mg, 0.17 mmol), the reaction time was 9 h. After column chromatography, the desired product was obtained as an oil (43.51 mg, 95% yield); dr = 99:1 (determined by ^1H NMR); Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.25–7.34(m, 5 H), 5.18(dd, *J* = 4.0 Hz, 13.5 Hz, 1H), 5.02(dd, *J* = 11.0 Hz, 13.5 Hz, 1H), 4.17–4.24(m, 2H), 4.08 (dd, *J* = 4.0 Hz, 11.0 Hz, 1H), 2.31–2.41(m, 2H), 1.78–2.08(m, 4H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.3, 169.3, 135.3, 129.3, 128.7, 128.2, 76.4, 62.4, 62.1, 46.1, 37.8, 31.2, 19.3, 13.9; HPLC (OD-H, hexane/2-propanol = 90/10, flow rate-0.7 mL/min, 220 nm): Major diastereomer: t_{minor} = 14.1 min, t_{major} = 20.2 min, ee = 99%.

4.2.33. Methyl 2-(2-nitro-1-phenylethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 13c[13e]

Prepared according to general procedure B using nitrostyrene **9a** (22.37 mg, 0.15 mmol) and methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxyla **12c** (32.33 mg, 0.17 mmol), the reaction time was 8 h. After column chromatography, the desired product was obtained as an oil (44.28 mg, 87% yield); dr = 80:20 (determined by ^1H NMR); Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 0.20H), 7.67 (d, *J* = 7.5 Hz, 0.80H), 7.58 (t, *J* = 7.5 Hz, 0.8H), 7.50 (d, *J* = 7.5 Hz, 0.2H), 7.40–7.32 (m, 2H), 7,26–7.14 (m, 5H), 5.44 (dd, *J* = 3.5, 13.5 Hz, 0.8H), 5.24–5.16 (m, 1H), 5.07 (dd, *J* = 3.5, 13.5 Hz, 0.2H), 4.48 (dd, *J* = 3.5, 11.0 Hz, 0.2H), 4.21 (dd, *J* = 3.5, 11.2 Hz, 0.8H), 3.75 (s, 2.4H), 3,70 (s, 0.6H), 3.64 (d, *J* = 17.5 Hz, 0.8H), 3.49 (d, *J* = 17.5 Hz, 0.2H), 3.24–3.13 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 199.9, 171.2, 169.8, 152.3, 152.2, 136.1, 135.8, 135.7, 135.6, 134.8, 134.0, 129.0, 128.9, 128.8, 128.6, 128.3, 128.0, 127.9, 126.05, 126.04, 125.2, 124.4, 77.0, 76.9, 62.7, 61.8, 53.2, 53.1, 47.3, 47.0, 36.5, 35.2; HPLC (OD-H, hexane/2-propanol = 80/20, flow rate-0.8 mL/min, 254 nm): Major diastereomer: t_{minor} = 11.5 min, t_{major} = 59.1 min, ee = 98%; Minor diastereomer: t_{minor} = 13.3 min, t_{major} = 33.6 min, ee = 97%. The absolute stereochemistry was not assigned.

4.2.34. Ethyl 2-acetyl-2-chloro-4-nitro-3-phenylbutanoate 13d

Prepared according to general procedure B using nitrostyrene **9a** (22.37 mg, 0.15 mmol) and ethyl 2-chloro-3-oxobutanoate **12d** (27.98 mg, 0.17 mmol), the reaction time was 10 h. After column chromatography, the desired product was obtained as an oil (42.83 mg, 91% yield); dr = 58:42 (determined by ^1H NMR); Major diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ 7.30–7.33 (m, 5H), 5.13 (dd, *J* = 13.5, 4.0 Hz, 1H), 5.04 (dd, *J* = 13.5, 4.1 Hz, 1H), 4.60 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.20–4.29 (m, 2H), 1.97 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 166.5, 133.0, 129.8, 129.0, 128.8, 76.6, 75.9, 63.6, 48.6, 27.2, 13.7. Minor diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.36 (m, 5H), 4.94 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.87 (dd, *J* = 15.5, 10.5 Hz, 1H), 4.66 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.94–4.07 (m, 2H), 2.31 (s, 3H), 1.08 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.5, 164.8, 133.7, 129.3, 129.0, 128.7, 77.1, 76.9, 63.8, 46.7, 25.6, 13.6; HRMS (ESI): *m*/*z* calculated for $C_{14}H_{16}NO_5Cl$+Na^+: 336.0607, found: 336.0615; HPLC (OD-H, hexane/2-propanol = 90/10, flow rate-0.5 mL/min, 210 nm): Major diastereomer: t_{minor} = 13.9 min, t_{major} = 21.9 min, ee = 99% Minor diastereomer: t_{minor} = 15.1 min, t_{major} = 16.9 min, ee = 98%. The absolute stereochemistry was not assigned.

4.2.35. Ethyl 2-acetyl-2-fluoro-4-nitro-3-phenylbutanoate 13e[20,22]

Prepared according to general procedure B using nitrostyrene **9a** (22.37 mg, 0.15 mmol) and ethyl 2-fluoro-3-oxobutanoate **12e** (25.18 mg, 0.17 mmol), the reaction time was 8 h. After column chromatography, the desired product was obtained as a paste (39.69 mg, 89% yield); dr = 64:36 (determined by ^1H NMR); Analytical data matched with previously reported values. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31–7.26 (m, 8.5H), 4.84–4.88 (m, 2H), 4.74–4.51 (m, 2.8H), 4.31 (dq, *J* = 7.0, 1.5 Hz, 2H) (major), 3.97 (q, *J* = 7.0 Hz, 1.1H) (minor), 2.32 (d, *J* = 4.5 Hz, 1.7H) (minor), 1.85 (d, *J* = 5.5 Hz, 3H) (major), 1.32 (t, *J* = 7.0 Hz, 3H) (major)), 0.98 (t, *J* = 7.0 Hz, 1.7H) (minor); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 201.1, 199.6, 199.4, 164.6, 164.4, 163.8, 163.6, 133.1, 132.4, 129.52, 129.51, 129.18, 129.17, 129.0, 128.9, 128.9, 101.7, 101.3, 100.0, 99.7, 75.3, 75.2, 63.6, 63.1, 47.2, 47.1, 46.5, 46.3, 26.3, 25.7,13.9, 13.6; HPLC (OD-H, hexane/2-propanol = 90/10, flow rate-0.5 mL/min, 210 nm): Major diastereomer: t_{minor} = 19.5 min, t_{major} = 28.9 min, ee = 99%; Minor diastereomer: t_{minor} = 22.1 min, t_{major} = 24.3 min, ee = 99%. The absolute stereochemistry was not assigned.

Acknowledgements

This work was supported by Department of Science & Technology, Government of India, New Delhi (Grant No. SR/S1/OC-60/2006). Vinayagam thanks Council for Scientific and Industrial

Research, India for the research fellowship. We thank Dr. M. S. Moni and Dr. C. Baby at Sophisticated Analytical Instrument Facility (SAIF), IIT Madras for NMR analysis.

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