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PAPER

Asymmetric Michael addition reactions of 3-substituted benzofuran-2(3*H*)-ones to nitroolefins catalyzed by a bifunctional tertiary-amine thiourea†

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The current work reports an organocatalytic strategy for the asymmetric catalysis of chiral benzofuran-2(3*H*)-ones bearing 3-position all-carbon quaternary stereocenters. Accordingly, highly enantioselective Michael addition reactions of 3-substituted benzofuran-2(3*H*)-ones to nitroolefins have been developed by utilizing a bifunctional tertiary-amine thiourea catalyst. The reactions accommodate a number of nitroolefins and 3-substituted benzofuran-2(3*H*)-ones to give the desired chiral benzofuran-2(3*H*)-one products with moderate to excellent yields (up to 98%) and moderate to very good selectivities (up to 19 : 1 dr and up to 91% ee). Theoretical calculations using the DFT method on the origin of the stereoselectivity were conducted. The effect of the nitroolefin substituent position on the stereoselectivity of the Michael addition reaction was also theoretically rationalized.

Introduction

The development of novel and highly enantioselective transformations is one of the most exciting goals for organic chemists involved in the competitive and stimulating field of asymmetric organocatalysis.[1] In this area, asymmetric hydrogen-bonding catalysis, especially using a bifunctional chiral thiourea/urea, which has a combination of thiourea/urea and tertiary-amine group, has been recognized as an impactful strategy to realize a number of important asymmetric C–C bond-forming reactions.[2,3] Among the multitudinous realized asymmetric reactions promoted by bifunctional tertiary-amine thiourea/ureas, the Michael addition reaction takes up the considerably dominant status.[4] Several impressive Michael acceptors, which can be activated through the double hydrogen-bonding interaction of the N–H of thiourea/urea to realize a specific role in efficient enantiocontrol, have been successfully applied. Among them, nitroolefins have attracted special attention by virtue of their high activity and diversiform synthetic application, in which the resulting nitroalkanes can readily be transformed into many useful building blocks, such as amines, nitrile oxides and ketones. In this context, a number of influential bifunctional tertiary-amine thiourea catalyzed Michael additions, in which nitroolefins are used as electrophiles, have left a deep impression.[5]

3,3′-Disubstituted benzofuran-2(3*H*)-ones and their derivatives have received extensive attention, since the structural motif of this type of compound, which has in its construction a quaternary chiral center, is a prominent feature in a number of biologically and pharmaceutically active natural products.[6] In this context, great efforts have been focused toward the total synthesis of corresponding benzofuran-2(3*H*)-one type compounds in recent years.[7] However, direct and valuable strategies for the asymmetric synthesis of the 3,3′-disubstituted benzofuran-2(3*H*)-one framework have been less studied and only a few examples based on organocatalytic protocols have been investigated to date.[5h,5l,8] Therefore, the development of new and efficient organocatalytic methodologies to obtain chiral 3,3′-disubstituted benzofuran-2(3*H*)-ones is still of remarked importance, and is strongly desired.

Continuing our recent research program towards a new strategy for synthesis of chiral 3,3′-disubstituted benzofuran-2(3*H*)-ones by asymmetric organocatalysis[5h,5l,8c] and based on our experience using bifunctional tertiary-amine thiourea catalysts,[5h–5l] herein, we report a highly enantioselective Michael addition reaction of 3-substituted benzofuran-2(3*H*)-ones to nitroolefins promoted by a bifunctional tertiary-amine thiourea catalyst (Fig. 1). A number of nitroolefins and 3-substituted benzofuran-2(3*H*)-ones are favored in this synthetic strategy for chiral 3,3′-substituted benzofuran-2(3*H*)-one type compounds. In addition, we have sought to explain the stereoselectivity results using a DFT theoretical study. And the results are presented in the following.

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† Electronic supplementary information (ESI) available: NMR and HPLC spectra for all the new compounds, details of theoretical calculations. CCDC reference number 810503 (**3h**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06518a

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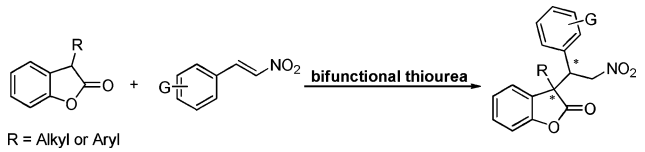


Fig. 1 Strategy for bifunctional tertiary-amine thiourea catalyzed Michael reactions of benzofuran-2(3*H*)-ones to nitroolefins.

Results and discussion

Bifunctional tertiary-amine thiourea catalyzed Michael addition reaction of 3-alkyl substituted benzofuran-2(3*H*)-ones to nitroolefins

The Michael addition reaction of 3-methylbenzofuran-2(3*H*)-one **1a** to nitrostyrene was first selected as our initial testing reaction. The Michael addition reaction cannot progress when no catalyst is added. Although a simple alkali **4a** can completely promote the Michael addition (entry 2 in Table 1), the obtained product is racemic. Then six widely used bifunctional tertiary-amine thiourea/urea catalysts **4b–4g**[5] (Fig. 2) with different chiral scaffolds were screened in the current model reaction at 20 °C. To our delight, all of the chiral bifunctional hydrogen-bonding catalysts **4b–4g** exhibited high catalytic activity. As a result, the Michael addition products were cleanly isolated with quantitative yields and moderate selectivities (entries 3–8 in Table 1). It is obvious that the activation effect of the double hydrogen-bonding of thiourea or urea on benzofuran-2(3*H*)-one is of significant importance for the inducement of enantioselectivity. In comparison, catalyst **4g**, was found to give the optimal enantioselectivity (98% yield, 3 : 1 dr and 53% ee, entry 8 in Table 1). In order to further improve the catalytic results, we then examined the catalysts **4h–4j**, which are chiral scaffolds based on the predominate structure of (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-ethanediamine. To our disappointment, the obtained three enantioselectivities catalyzed by **4h–4j** are all lower than the corresponding result catalyzed by **4g**.

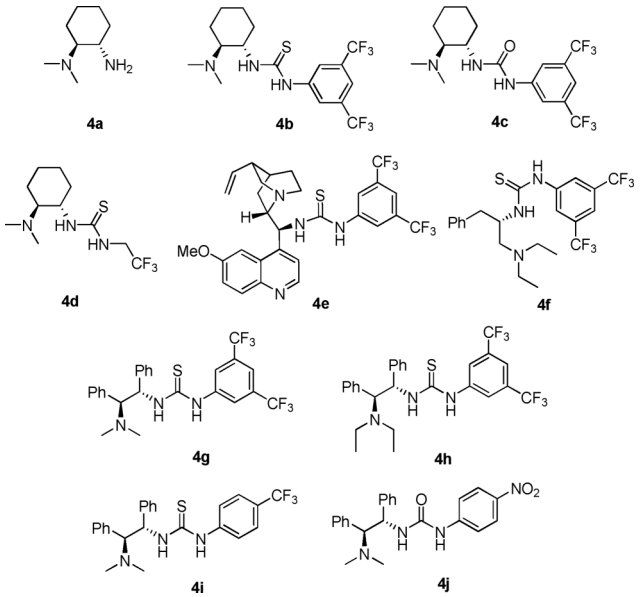
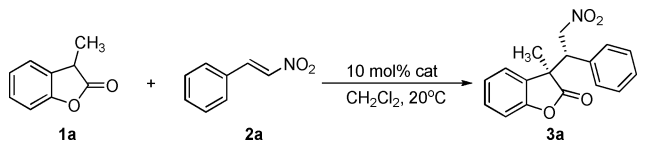


Fig. 2 Examined catalysts.

With thiourea **4g** as the optimal catalyst, the reaction was further optimized by screening different solvents (Table 2). Highly polar solvents such as DMSO and DMF were not applicable solvents leading to totally depleted activity (entries 1 and 2 in Table 2). The reactions generally proceeded smoothly in less polar solvent such as CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, THF, C_6H_6 and $PhCH_3$. Among a number of solvents examined, $PhCH_3$ was the optimal one, furnishing the best enantioselectivity (entry 10 in Table 2, 96% yield, 3.5 : 1 dr and 57% ee). Further improvement could be achieved by lowering the reaction temperature (entries 10–12 in Table 2). Addition of 4 Å molecular sieves to the reaction mixture slightly increased both the diastereoselectivity

Table 1 Catalyst screening[a]

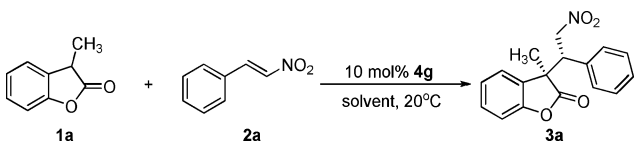


1a 2a 3a

Entry	Catalyst	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	No catalyst	72	No reaction	nd[e]	nd[e]
2	**4a**	24	80	1 : 1	rac
3	**4b**	4	91	2 : 1	33
4	**4c**	4	95	2 : 1	28
5	**4d**	4	93	3 : 1	40
6	**4e**	4	99	3 : 1	39
7	**4f**	4	90	2 : 1	31
8	**4g**	4	98	3 : 1	53
9	**4h**	4	83	3 : 1	50
10	**4i**	4	87	3 : 1	51
11	**4j**	4	94	3 : 1	48

[a] The reaction was carried out on a 0.1 mmol scale in 400 uL CH_2Cl_2 at 20 °C, and the molar ratio of **1a**/nitrostyrene is 1/1.5. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by HPLC. [e] Not determined.

Table 2 Screening of solvent[a]

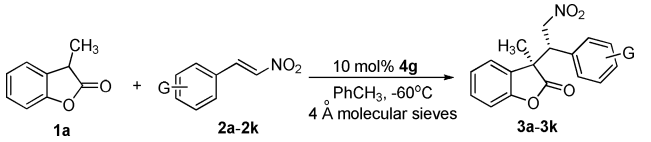


1a 2a 3a

Entry	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	DMSO	4	trace	nd	nd
2	DMF	4	trace	nd	nd
3	Et_2O	4	30	2 : 1	35
4	CH_3CN	4	85	2 : 1	30
5	CH_2Cl_2	4	98	3 : 1	53
6	$CHCl_3$	4	97	2 : 1	44
7	$ClCH_2CH_2Cl$	4	91	3 : 1	47
8	THF	4	90	3 : 1	57
9	C_6H_6	4	95	3 : 1	52
10	$PhCH_3$	4	96	3.5 : 1	57
11[e]	$PhCH_3$	12	85	3.5 : 1	62
12[f]	$PhCH_3$	48	90	4 : 1	64
13[g]	$PhCH_3$	48	95	4 : 1	66

[a] The reaction was carried out on a 0.1 mmol scale in 400 uL of solvent at 20 °C, and the molar ratio of **1a**/nitrostyrene is 1/1.5. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by HPLC. [e] Conducted at −20 °C. [f] Conducted at −60 °C. [g] Conducted at −60 °C with 40 mg 4 Å molecular sieves.

Table 3 Asymmetric Michael addition reaction of 3-methylbenzofuran-2(3*H*)-one to different substituted nitrostyrenes[a]



entry	G =	Time	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	H	48	**3a**: 96	4 : 1	66
2	4-MeO	72	**3b**: 92	3 : 1	65
3	4-F	48	**3c**: 90	3 : 1	64
4	4-Ph	60	**3d**: 90	3 : 1	58
5	4-Cl	48	**3e**: 87	2 : 1	52
6	3,4-2Cl	48	**3f**: 87	3 : 1	fd[e]
7	3-NO_2	72	**3g**: 91	1 : 1	75/15
8	2-Cl	48	**3h**:: 95	19 : 1	86
9	2-Br	48	**3i**: 98	19 : 1	80
10	2-F-6-Cl	72	**3j**: 85	4 : 1	82
11	2,6-2Cl	72	**3k**: 87	11 : 1	91

[a] The reaction was carried out on a 0.1 mmol scale in 400 uL $PhCH_3$ at −60 °C with 40 mg 4 Å molecular sieves, and the molar ratio of **1a**/nitroolefin is 1/1.5. [b] Isolated yield. [c] Determined by ^1H NMR of crude products. [d] Determined by HPLC. [e] fd = Failed to determine the ee because the two enantiomers could not be separated on the Daicel chiralpak columns.

and enantioselectivity (entry 13 in Table 2). Collectively, the best results with respect to yield and stereoselectivity were obtained by performing the reaction at −60 °C in $PhCH_3$ in the presence of 4 Å molecular sieves. Under this condition, the reaction provided the desired product with 95% yield in 4 : 1 dr and 66% ee.

With the optimal conditions in hand, the substrate scopes were next explored. Firstly, eleven substituted nitrostyrenes were examined. As shown in Table 3, the reactions worked well with nitrostyrenes bearing either electronic withdrawing or electronic donating groups to give the desired products with high yield (85–96%), moderate to very good diastereoselectivities (3 : 1–19 : 1 dr) and moderate to very good enantioselectivities (52–91% ee). It is obviously found that the stereoselectivity of the reaction is sensitive to the substitution position of the nitrostyrene. Slightly lower selectivities were obtained, when *p*-substituted nitrostyrenes **2a–2e** were used as Michael acceptors (entries 1–5 in Table 3). As a result, the corresponding conjugate addition products **3a–3e** were obtained with 4 : 1–3 : 1 dr and 52–66% ee. On the other hand, higher selectivities were obtained, when *o*-substituted nitrostyrenes **2h–2k** were selected as Michael acceptors (entries 8–11 in Table 3, up to 19 : 1 dr and 80–91% ee).

In order to expand the substrate scope, other types of nitroolefins, such as naphthyl and alkyl substituted nitroolefins were investigated in this study. From the results in Fig. 3 (**3l–3n**), we found that not only the naphthyl nitroolefin, but also the two alkyl type nitroolefins put up very good activities (85–90% yield), moderate to excellent diastereoselectivities (2 : 1–19 : 1 dr) and good enantioselectivities (77–85% ee) in the current bifunctional tertiary-amine thiourea catalytic system. Furthermore, we also explored the influence of Michael donor. As a result, 3-benzylbenzofuran-2(3*H*)-one was reacted with nitrostyrene **2a** under the optimized conditions, in which the desired Michael product **3o** was obtained with high yield (91%), bad diastereoselectivity (1 : 1 dr) and good enantioselectivities (84%/65% ee).

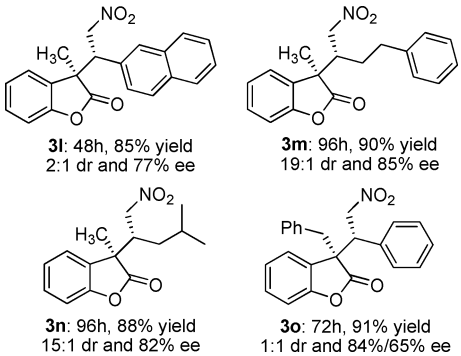


Fig. 3 Investigation of other substrates.

We obtained the X-ray crystal structure of product **3h** (Fig. 4),[9] which proved the absolution configuration for **3h**. The absolute configurations of other products can therefore be determined by analogy.

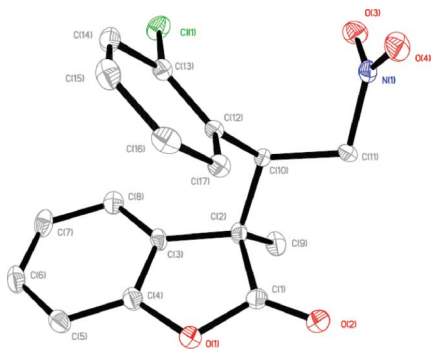


Fig. 4 X-ray crystal structure of **3h**.

Bifunctional tertiary-amine thiourea catalyzed Michael addition reaction of 3-aryl substituted benzofuran-2(3*H*)-ones to nitroolefins

3-Aryl substituted benzofuran-2(3*H*)-ones, were next attempted in the current Michael strategy with the hope of further expanding the substrate scope. Indeed, various 3-aromatic substituted benzofuran-2(3*H*)-ones worked very well with nitrostyrene to give the desired products **3p–3t** in high yields with good stereoselectivities (Fig. 5).

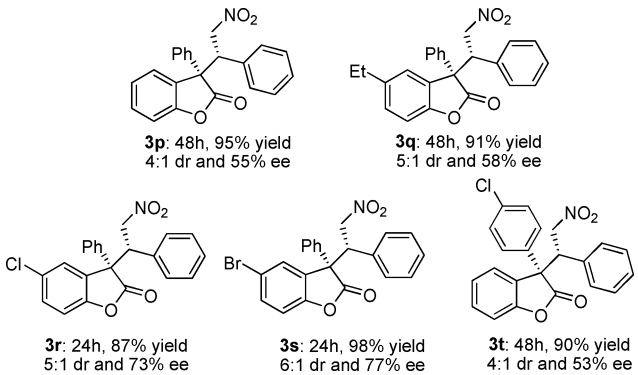


Fig. 5 Results of 3-aryl substituted benzofuran-2(3*H*)-ones as Michael donors.

Theoretical study of the bifunctional tertiary-amine thiourea catalyzed Michael addition reactions of 3-substituted benzofuran-2(3*H*)-ones to nitroolefins

The activation of nitroolefins by tertiary-amine thioureas has been demonstrated earlier in many other mechanism studies and indicated the bifunctional character of this structure in Michael reactions.[5c,10] On the basis of the catalytic results, we assumed that the enantioselectivity of the reaction is controlled during the C–C bond formation between the activated nitroolefin and the nucleophile.

Since nitro compounds are known to form hydrogen bonds with urea and thiourea,[11] nitroolefins have been assumed to interact with the thiourea moiety *via* multiple H-bonds, enhancing the electrophilic character of the reacting carbon center. On the other hand, the enolic forms of benzofuran-2(3*H*)-ones are assumed to interact with the tertiary amine group, and a subsequent deprotonation results in a highly nucleophilic enolate species. According to the above described model, a mechanism based upon catalyst **4g** is proposed to account for the observed diastereo- and enantioselectivity. As shown in Fig. 6, we have studied the approach of 3-methylbenzofuran-2(3*H*)-one (**1a**) and nitrostyrene (**2a**), which have been employed as the model reagents, to both *Re* and *Si* faces of the nitroalkene. For each enantiotopic face, the attack can also arise from two possible orientations of the 3-methylbenzofuran-2(3*H*)-one, leading to four transition states (Fig. 6).

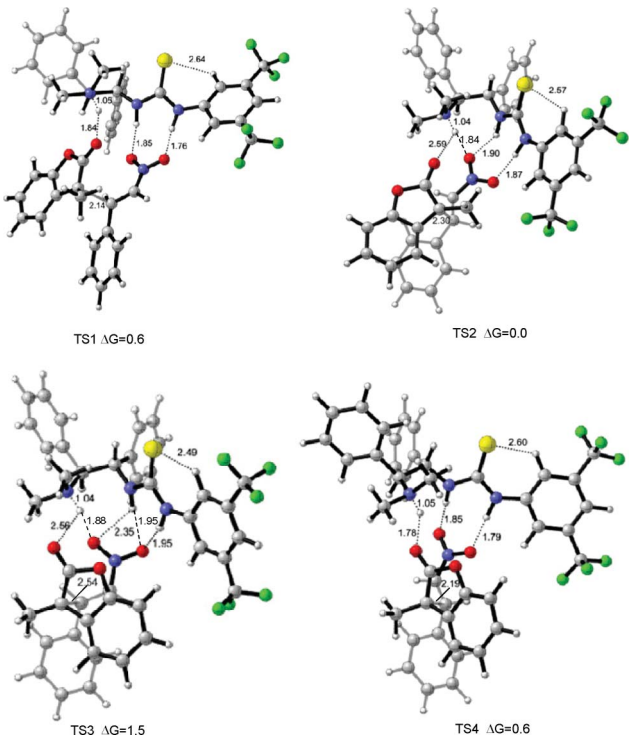


Fig. 6 Transition state geometries for the reaction of 3-methylbenzofuran-2(3*H*)-one (**1a**) and nitrostyrene (**2a**) (units: kcal mol^{-1}).

Among these transition states, TS2 shows the lowest energy (Fig. 6). We hypothesized that the hydrogen bonding interaction between the key proton abstracted from the developing enolate by the dimethylamino group of catalyst **4g** and the nitro group of **2a** (1.84 Å) contributed to the electrostatic stabilization of the TS2. Furthermore, the potential π–π interaction between the two aromatic rings of **1a** and **2a** in TS2 would also help drop the energy. This computed result means that the TS2's corresponding compound was the main product of our asymmetric catalytic reaction, which is consistent with the experimental results.

In order to understand the effects of the substitution's position on nitrostyrene on stereoselectivities in the current studied Michael strategy, transition states of the reaction of 3-methylbenzofuran-2(3*H*)-one (**1a**) and 2-chloro substituted nitrostyrene (**2h**) were also investigated. As shown in Fig. 7, the enantioselectivity's energy gap of the reaction between **1a** and **2h** is 2.0 kcal mol^{-1} (TS5 and TS6 in Fig. 7), which is 1.4 kcal mol^{-1} higher than the corresponding reaction between **1a** and **2a** (0.6 kcal mol^{-1}, TS2 and TS4 in Fig. 6). Based on the calculated results, it is obvious that the enantioselectivity of **3h** should be higher than **3a**, which is in good qualitative agreement with experimental results (86% ee for **3h** and 66% ee for **3a**, Table 3). It is worth noting that the observed possible lone pair–π interaction between the Cl atom and the aromatic ring of nitrostyrene may contribute to the stabilization of the TS5.[12]

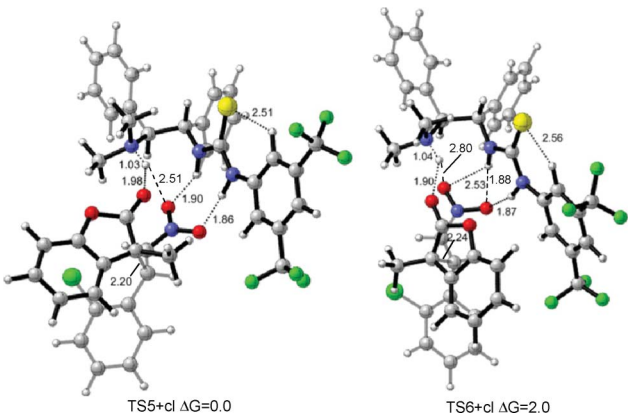


Fig. 7 Transition state geometries for the reaction of 3-methylbenzofuran-2(3*H*)-one (**1a**) and 2-chloro substituted nitrostyrene (**2h**) (units: kcal mol^{-1}).

Using the same transition state model, we also investigated the transition states of the reaction between **1a** and **2a** catalyzed by the Takemoto catalyst (See Fig. S2 in ESI†). From the results, we can see that only a 0.2 kcal mol^{-1} energy gap was found to be responsible for the enantioselectivity. This observation was also in agreement with our initial screening results of the bifunctional tertiary-amine catalysts (entry 3 in Table 1).

Conclusion

In summary, we have presented a highly enantioselective Michael addition reaction of 3-substituted benzofuran-2(3*H*)-ones to nitroolefins by a simple bifunctional tertiary-amine thiourea organocatalyst. The reaction scope is substantial and a number of aryl or alkyl substituted benzofuran-2(3*H*)-ones and nitroolefins could be successfully applied to give multifunctional chiral benzofuran-2(3*H*)-one compounds with an all carbon-substituted quaternary stereocenter and a tertiary stereocenter with moderate to very good enantioselectivities. Theoretical calculations with

the DFT method on the current Michael strategy was also conducted. More endeavors demonstrating the further derivations and reactions of the Michael products are in progress in our laboratory.

Experimental section

General remarks

Commercial reagents were used as received, unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained using an electrospray ionization (ESI) mass spectrometer. Bifunctional tertiary-amine thiourea/urea catalysts were synthesized from the literature methods.[5] **3p** was a known compound.[5h]

General experimental procedure of Michael reaction

To a stirred solution of 3-substituted benzofuran-2(3*H*)-one (0.1 mmol) and nitroolefin (1.5 equiv.) in dry toluene (400 uL) was added thiourea-catalyst (0.1 equiv.) at –60 °C with 40 mg 4 Å molecular sieves. After the reaction completed, the reaction solution was concentrated *in vacuo* and the crude was purified by flash chromatography to afford the product.

3a: The Michael product was synthesized according to the general procedure as a white solid in 96% overall yield. $[\alpha]_D^{15}$ –42.6 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.31 (1H, t, *J* = 7.91 Hz), 7.26–7.15 (4H, m), 7.03–6.98 (2H, m), 6.91 (2H, d, *J* = 7.38 Hz), 5.01 (1H, d, *J* = 4.57 Hz), 4.95–4.89 (1H, t, *J* = 11.95 Hz), 4.00 (1H, d, *J* = 4.57 Hz), 1.58 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.7, 152.7, 133.9, 129.8, 129.0, 128.9, 128.8, 128.5, 124.5, 124.0, 111.2, 75.5, 50.3, 49.8, 21.6 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{15}NO_4 + Na]^+$ 320.0893, found 320.0896. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 10.5 min (major), 12.3 min (minor).

3b: The Michael product was synthesized according to the general procedure as a white solid in 92% overall yield. $[\alpha]_D^{15}$ –202.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (1H, t, *J* = 7.73 Hz), 7.21–7.17 (1H, t, *J* = 7.38 Hz), 7.06–7.00 (2H, m), 6.81 (2H, d, *J* = 8.00 Hz), 6.70 (2H, d, *J* = 8.00 Hz), 4.98 (1H, d, *J* = 4.31 Hz), 4.89–4.83 (1H, t, *J* = 11.87 Hz), 3.96 (1H, d, *J* = 4.04 Hz), 3.74 (3H, s), 1.58 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.7, 159.7, 152.7, 130.0, 129.8, 129.1, 125.6, 124.5, 123.9, 113.9, 111.2, 75.7, 55.2, 50.0, 49.7, 21.6 ppm; HRMS (ESI$^+$): calcd. for $[C_{18}H_{17}NO_5 + Na]^+$ 350.0999, found 350.1004. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 18.2 min (major), 15.8 min (minor).

3c: The Michael product was synthesized according to the general procedure as a white solid in 90% overall yield. $[\alpha]_D^{15}$ –135.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.34 (1H, t, *J* = 7.82 Hz), 7.23–7.20 (1H, t, *J* = 7.56 Hz), 7.09 (1H, d, *J* = 7.38 Hz), 7.02 (1H, d, *J* = 7.91 Hz), 6.88 (4H, d, *J* = 6.77 Hz), 4.97 (1H, d, *J* = 4.04 Hz), 4.89–4.83 (1H, t, *J* = 12.13 Hz), 4.02 (1H, d, *J* = 3.69 Hz), 1.59 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.5, 164.0, 161.6, 152.7, 130.6, 130.5, 130.1, 130.0, 129.6, 128.7, 124.6, 123.7, 115.7, 115.5, 111.4, 75.5, 49.9, 49.7, 21.7 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{14}FNO_4 + Na]^+$ 338.0799, found 338.0804. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 19), 1.0 mL min^{-1}; t_R = 20.8 min (major), 16.5 min (minor).

3d: The Michael product was synthesized according to the general procedure as a white solid in 90% overall yield. $[\alpha]_D^{15}$ –207.8 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (2H, d, *J* = 7.65 Hz), 7.43–7.39 (4H, t, *J* = 7.73 Hz), 7.36–7.31 (2H, m), 7.21–7.18 (1H, t, *J* = 7.38 Hz), 7.08 (1H, d, *J* = 7.65 Hz), 7.03–6.97 (3H, m), 5.02 (1H, d, *J* = 3.34 Hz), 4.97–4.91 (1H, t, *J* = 11.87 Hz), 4.06 (1H, d, *J* = 4.04 Hz), 1.61 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.7, 152.7, 141.5, 140.1, 132.8, 129.9, 129.3, 129.0, 128.8, 127.6, 127.2, 127.0, 124.6, 123.9, 111.3, 75.5, 50.0, 49.9, 21.7 ppm; HRMS (ESI$^+$): calcd. for $[C_{23}H_{19}NO_4 + Na]^+$ 396.1206, found 396.1207. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 29.9 min (major), 18.4 min (minor).

3e: The Michael product was synthesized according to the general procedure as a white solid in 87% overall yield. $[\alpha]_D^{15}$ –369.1 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (1H, t, *J* = 7.73 Hz), 7.24–7.09 (4H, m), 7.03 (1H, d, *J* = 7.91 Hz), 6.97–6.92 (1H, m), 6.85 (1H, d, *J* = 8.26 Hz), 5.07–4.96 (1H, m), 4.90–4.84 (1H, t, *J* = 11.95 Hz), 4.03–3.97 (1H, m), 1.59 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.5, 177.4, 152.7, 152.1, 134.9, 134.5, 132.7, 132.3, 130.2, 130.1, 129.7, 129.6, 129.5, 128.8, 128.6, 124.7, 124.6, 123.7, 123.6, 111.4, 111.1, 75.3, 75.0, 50.0, 49.8, 22.9, 21.8 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{14}ClNO_4 + Na]^+$ 354.0504, found 354.0510. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 19), 1.0 mL min^{-1}; t_R = 25.0 min (major), 18.2 min (minor).

3f: The Michael product was synthesized according to the general procedure as a white solid in 87% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.38 (1H, t, *J* = 7.63 Hz), 7.28–7.24 (2H, m), 7.14 (1H, d, *J* = 7.39 Hz), 7.07 (1H, d, *J* = 8.13 Hz), 6.98 (1H, s), 6.80 (1H, d, *J* = 8.13 Hz), 4.99–4.92 (1H, m), 4.85–4.79 (1H, t, *J* = 11.94 Hz), 3.98–3.95 (1H, m), 1.59 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.1, 152.7, 134.1, 133.3, 132.8, 130.8, 130.6, 130.3, 129.9, 128.2, 124.9, 123.6, 111.6, 75.2, 49.7, 49.6, 21.9 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{13}Cl_2NO_4 + Na]^+$ 388.0114, found 388.0120. The ee was not determined because the two enantiomers could not be separated on the Daicel chiralpak columns.

3g: The Michael product was synthesized according to the general procedure as a white solid in 91% overall yield. $[\alpha]_D^{15}$ –114.3 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 7.94 Hz), 7.84 (1H, s), 7.44–7.38 (2H, m), 7.31–7.16 (3H, m), 7.02 (1H, d, *J* = 8.13 Hz), 5.21–5.07 (1H, m), 5.02–4.90 (1H, m), 4.17–4.13 (1H, m), 1.68 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.9, 177.0, 152.6, 152.0, 148.0, 147.9, 136.6, 136.1, 135.4, 133.5, 130.5, 129.9, 129.8, 129.7, 128.0, 125.1, 124.9, 124.0, 123.8, 123.6, 123.5, 123.4, 111.6, 111.2, 75.1, 74.6, 50.3, 50.1, 49.7, 22.7, 22.0 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{14}N_2O_6 + Na]^+$ 365.0744, found

365.0735. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 4), 1.0 mL min^{-1}; t_R = 13.5 min (major), 16.8 min (minor).

3h: The Michael product was synthesized according to the general procedure as a white solid in 95% overall yield. $[\alpha]_D^{15}$ −179.1 (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, d, *J* = 7.51 Hz), 7.25–7.23 (1H, m), 7.20–7.15 (3H, m), 7.11–7.06 (2H, m), 6.89 (1H, d, *J* = 7.88 Hz), 5.07 (1H, d, *J* = 4.37 Hz), 5.02–4.97 (1H, t, *J* = 12.12 Hz), 4.92 (1H, d, *J* = 4.37 Hz), 1.69 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.8, 151.9, 135.2, 133.3, 130.2, 129.5, 129.2, 127.4, 126.5, 124.2, 110.6, 75.6, 50.4, 44.9, 23.2 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{14}ClNO_4 + Na]^+$ 354.0504, found 354.0500. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 19), 1.0 mL min^{-1}; t_R = 12.2 min (major), 11.1 min (minor).

3i: The Michael product was synthesized according to the general procedure as a white solid in 98% overall yield. $[\alpha]_D^{15}$ −181.5 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.37 (2H, m), 7.23–7.17 (3H, m), 7.11–7.07 (1H, t, *J* = 7.51 Hz), 7.02–6.98 (1H, t, *J* = 7.26 Hz), 6.90 (1H, d, *J* = 8.00 Hz), 5.11–5.07 (1H, m), 4.00–4.88 (2H, m), 1.70 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.8, 151.9, 135.0, 133.7, 129.8, 129.6, 129.2, 128.1, 126.6, 126.4, 124.5, 124.2, 110.6, 75.8, 50.4, 47.7, 23.4 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{14}BrNO_4 + Na]^+$ 397.9998, found 397.9995. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 19), 1.0 mL min^{-1}; t_R = 12.8 min (major), 11.8 min (minor).

3j: The Michael product was synthesized according to the general procedure as a white solid in 85% overall yield. $[\alpha]_D^{15}$ −30.5 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–6.96 (6H, m), 6.82–6.78 (1H, m), 5.26 (1H, d, *J* = 3.69 Hz), 5.14–5.08 (1H, t, *J* = 11.33 Hz), 4.92 (1H, d, *J* = 3.20 Hz), 1.78 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.7, 162.6, 160.2, 152.2, 136.3, 136.2, 130.6, 130.3, 130.1, 129.8, 129.6, 129.4, 126.3, 126.0, 124.4, 124.2, 124.0, 123.6, 122.6, 122.4, 115.6, 115.4, 115.0, 114.9, 114.7, 111.0, 110.8, 110.7, 74.7, 74.6, 73.5, 73.4, 73.2, 48.5, 45.3, 25.4 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{13}ClFNO_4 + Na]^+$ 372.0209, found 372.0402. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 15.0 min (major), 18.4 min (minor).

3k: The Michael product was synthesized according to the general procedure as a white solid in 87% overall yield. $[\alpha]_D^{15}$ −205.7 (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.18 (1H, m), 7.10–7.06 (1H, t, *J* = 7.88 Hz), 6.99–6.89 (4H, m), 6.83–6.80 (1H, t, *J* = 7.39 Hz), 5.53–5.34 (2H, m), 5.22–5.19 (1H, m), 1.75 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.5, 152.2, 137.6, 134.7, 132.5, 129.7, 129.2, 128.8, 124.1, 123.6, 110.9, 73.8, 48.0, 46.9, 28.4 ppm; HRMS (ESI$^+$): calcd. for $[C_{17}H_{13}Cl_2NO_4 + Na]^+$ 388.0114, found 388.0118. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 12.6 min (major), 17.9 min (minor).

3l: The Michael product was synthesized according to the general procedure as a white solid in 85% overall yield. $[\alpha]_D^{15}$ +216.5 (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (1H, d, *J* = 8.74 Hz), 7.81–7.70 (2H, m), 7.58–7.55 (1H, t, *J* = 7.14 Hz), 7.46–7.43 (1H, m), 7.41–7.36 (1H, m), 7.31–7.25 (1H, m), 7.11–6.97 (2H, m), 6.89 (1H, d, *J* = 7.88 Hz), 6.78 (1H, d, *J* = 7.75 Hz), 5.22–5.16 (1H, m), 5.11–4.96 (2H, m), 1.60 (1H, s), 1.56 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 179.3, 177.7, 152.7, 152.1, 133.9, 132.6, 132.5, 131.5, 130.6, 129.7, 129.4, 129.2, 129.1, 128.9, 126.7, 126.6, 125.9, 124.8, 124.5, 124.4, 124.3, 124.1, 124.0, 123.9, 123.0, 122.8, 111.1, 110.8, 76.3, 76.2, 50.6, 49.4, 43.0, 42.3, 23.6, 21.3 ppm; HRMS (ESI$^+$): calcd. for $[C_{21}H_{17}NO_4 + Na]^+$ 370.1050, found 370.1043. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 9.9 min (major), 10.8 min (minor).

3m: The Michael product was synthesized according to the general procedure as a white solid in 90% overall yield. $[\alpha]_D^{15}$ −114.0 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (1H, m), 7.26 (2H, d, *J* = 6.89 Hz), 7.21–7.13 (4H, m), 7.10 (2H, d, *J* = 7.63 Hz), 4.52 (1H, d, *J* = 5.29 Hz), 4.37 (1H, d, *J* = 6.53 Hz), 2.93 (1H, d, *J* = 5.42 Hz), 2.69–2.52 (2H, m), 1.91–1.83 (1H, m), 1.62–1.55 (1H, m), 1.53 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.3, 152.6, 140.3, 129.7, 129.5, 128.6, 128.3, 126.4, 124.8, 123.5, 111.4, 76.0, 49.4, 43.9, 33.7, 31.1, 22.6 ppm; HRMS (ESI$^+$): calcd. for $[C_{19}H_{19}NO_4 + Na]^+$ 348.1206, found 348.1206. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 11.6 min (major), 10.0 min (minor).

3n: The Michael product was synthesized according to the general procedure as a white solid in 88% overall yield. $[\alpha]_D^{15}$ +323.0 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.34 (1H, t, *J* = 7.63 Hz), 7.24–7.15 (3H, m), 4.50 (1H, d, *J* = 6.28 Hz), 4.31 (1H, d, *J* = 5.54 Hz), 3.01–2.94 (1H, m), 1.54 (3H, s), 1.25–1.08 (2H, m), 0.91 (3H, d, *J* = 6.53 Hz), 0.86 (3H, d, *J* = 6.53 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.4, 152.6, 129.6, 124.7, 123.5, 111.3, 76.3, 49.7, 42.3, 38.2, 25.7, 23.4, 22.4, 21.3 ppm; HRMS (ESI$^+$): calcd. for $[C_{15}H_{19}NO_4 + Na]^+$ 300.1206, found 300.1205. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 19), 1.0 mL min^{-1}; t_R = 7.5 min (major), 6.9 min (minor).

3o: The Michael product was synthesized according to the general procedure as a white solid in 91% overall yield. $[\alpha]_D^{15}$ −37.1 (*c* 0.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–6.66 (14H, m), 5.06–4.96 (2H, m), 4.27–4.17 (1H, m), 3.44–3.05 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.9, 176.1, 153.1, 152.7, 134.2, 133.9, 133.7, 133.6, 130.0, 129.9, 129.5, 129.3, 128.8, 128.7, 128.6, 128.5, 128.2, 127.3, 127.1, 126.8, 126.6, 125.1, 124.4, 124.3, 123.9, 111.0, 110.7, 75.9, 75.5, 56.8, 56.7, 50.6, 50.1, 47.3, 42.6, 41.7 pm; HRMS (ESI$^+$): calcd. for $[C_{23}H_{19}NO_4 + Na]^+$ 396.1206, found 396.1201. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 38.3 min (major), 42.2 min (minor) and t_R = 74.2 min (major), 81.1 min (minor).

3q: The Michael product was synthesized according to the general procedure as a white solid in 91% overall yield. $[\alpha]_D^{23}$ +21.0 (*c* 1.0, $CHCl_3$); ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.72 (2H, d, *J* = 8.05 Hz), 7.51–7.43 (3H, m), 7.29 (1H, s), 7.22 (2H, d, *J* = 5.58 Hz), 7.14 (3H, t, *J* = 7.22 Hz), 6.89 (3H, t, *J* = 9.25 Hz), 4.99 (1H, d, *J* = 12.26 Hz), 4.86 (1H, d, *J* = 11.75 Hz), 4.76 (1H, s, *J* = 12.70 Hz), 2.85 (2H, q, *J* = 7.62 Hz, 7.47 Hz), 1.40 (3H, t, *J* = 7.70 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.4, 151.7, 140.7, 134.8, 133.0, 129.8, 129.5, 129.0, 128.8, 128.5, 127.5, 125.5, 111.4, 75.7, 59.2, 51.4, 28.8, 16.3 ppm; HRMS (ESI$^+$): calcd. for $[C_{24}H_{21}NO_4 + Na]^+$ 410.1363, found 410.1357. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 2 : 98), 1.0 mL min^{-1}; t_R = 12.5 min (major), 15.3 min (minor).

3r: The Michael product was synthesized according to the general procedure as a white solid in 87% overall yield. $[\alpha]_D^{23}$ +42.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (2H, d, J = 7.15 Hz), 7.53–7.44(5H, m), 7.29–7.23 (1H, m), 7.20–7.17 (2H, m), 6.93 (3H, t, J = 8.72 Hz), 4.98 (1H, t, J = 12.33 Hz), 4.88 (1H, d, J = 11.81 Hz), 4.73 (1H, d, J = 12.50 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.5, 152.0, 133.9, 132.5, 130.6, 129.7, 129.3, 129.0, 128.9, 128.7, 127.3, 126.3, 112.9, 75.2, 59.5, 51.3 ppm; HRMS (ESI^+): calcd. for $[C_{22}H_{16}ClNO_4 + Na]^+$ 416.0660, found 416.0658. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 2 : 98), 1.0 mL min^{-1}; t_R = 16.5 min (minor), 17.4 min (major).

3s: The Michael product was synthesized according to the general procedure as a white solid in 98% overall yield. $[\alpha]_D^{23}$ −11.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (2H, d, J = 8.32 Hz), 7.56 (2H, d, J = 7.21 Hz), 7.49–7.42 (3H, m), 7.21 (1H, d, J = 7.21 Hz), 7.15 (2H, t, J = 7.21 Hz), 6.89–6.84 (3H, m), 4.93 (1H, t, J = 12.20 Hz), 4.84 (1H, d, J = 12.20 Hz), 4.96 (1H, d, J = 12.20 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.3, 152.5, 133.9, 133.5, 132.5, 129.7, 129.4, 129.1, 129.0, 128.9, 128.7, 127.9, 127.3, 116.9, 113.3, 75.2, 59.4, 51.3 ppm; HRMS (ESI^+): calcd. for $[C_{22}H_{16}BrNO_4 + Na]^+$ 460.0155, found 460.0157. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 2 : 98), 1.0 mL min^{-1}; t_R = 21.2 min (major), 26.7 min (minor).

3t: The Michael product was synthesized according to the general procedure as a white solid in 90% overall yield. $[\alpha]_D^{23}$ −24.7 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (2H, d, J = 7.20 Hz), 7.47–7.37 (5H, m), 7.23 (1H, s), 7.15 (2H, s), 7.01 (1H, d, J = 6.40 Hz), 6.86 (2H, d, J = 6.40 Hz), 4.98 (1H, t, J = 11.82 Hz), 4.79 (1H, d, J = 11.60 Hz), 4.70 (1H, d, J = 12.40 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.7, 153.7, 135.4, 133.2, 132.6, 130.7, 129.7, 128.9, 128.5, 126.1, 124.5, 111.9, 75.4, 58.7, 51.6 ppm; HRMS (ESI^+): calcd. for $[C_{22}H_{16}ClNO_4 + Na]^+$ 416.0660, found 416.0656. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 2 : 98), 1.0 mL min^{-1}; t_R = 31.2 min (major), 33.0 min (minor).

Computation details

All calculations were performed at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level by means of the Gaussian 03 suite of program package.[13] This level of theory was demonstrated to be appropriate for studying the thiourea-based chiral bifunctional organocatalyst promoted asymmetric addition reactions.[10] All the bond lengths are in angstroms (Å), and energies in kcal mol^{-1}. Structures were generated using CYLview.[14]

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