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Enantioselective Synthesis of *trans*-Dihydrobenzofurans via Primary Amine-Thiourea Organocatalyzed Intramolecular Michael Addition

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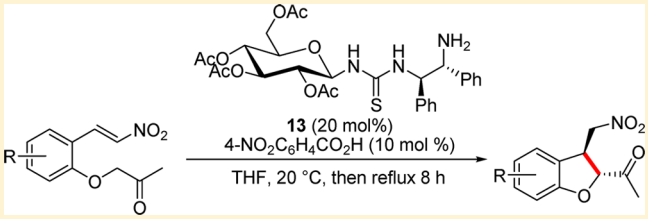
Supporting Information

ABSTRACT: A primary amine-thiourea organocatalyzed intramolecular Michael addition access was developed for the synthesis of *trans*-dihydrobenzofurans. Under the catalysis of an (*R*,*R*)-1,2-diphenylethylamine derived primary amine-thiourea bearing a glucosyl scaffold, the corresponding *trans*-dihydrobenzofurans were obtained in high yields with excellent level of enantioselectivities (94 to >99% ee). Moreover, an in situ isomerization occurring at high temperature gave good to excellent *trans*/*cis* ratios as well (*trans*/*cis*: 84/16−96/4).



1. INTRODUCTION

The dihydrobenzofurans (DHBs) belong to an important class of heterocycles, principally because this ring-system constitutes the core skeleton of an increasing number of biologically active natural products and pharmaceuticals (Figure 1).[1] For example,

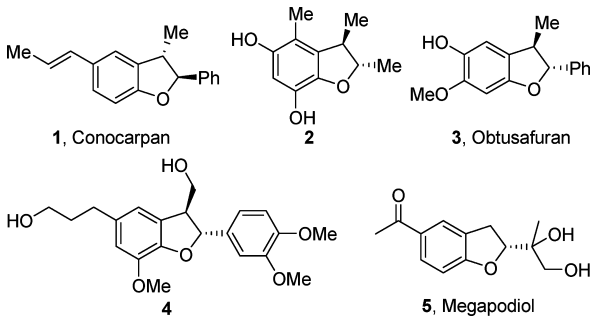


Figure 1. Natural products and pharmaceuticals that contain dihydrobenzofuran rings.

(+)-Conocarpan (**1**), which was first isolated from the wood of *Conocarpus erectus*,[2] exhibits a diverse array of biological activities, including insecticidal,[3] antifungal,[4] and antitrypanosomal properties.[5] 2,3,4-Trimethyl-5,7-dihydroxy-2,3-dihydrobenzofuran (**2**), isolated from a culture broth of *Penicillum citrinum F5*, exhibited antioxidant properties.[6] Obtusafuran (**3**), a simple dihydrobenzofuran isolated from several *Dalbergia* species, was shown to have potent induction of the anticarcinogenic marker enzyme, quinone reductase.[7] (2*R*,3*S*)-3′,4-Di-*O*-methylcedrusin (**4**), identified as one of the minor constituents of the red latex called "dragon blood" in traditional medicine, was found to act as an inhibitor of cell proliferation.[1c] Megapodiol (**5**) is an antileukemic agent.[8]

The remarkable significance of the 2,3-dihydrobenzofuran ring system in both natural products and synthetic pharmaceuticals has motivated chemists to develop various approaches for the construction of DHBs.[1a,b,9] However, methods for their preparation in a catalytic asymmetric fashion are limited and rely mainly on the application of transition metal catalysis. These include Pd,[10] Ir,[11] and Ru-catalyzed asymmetric hydrogenation of substituted benzofurans,[12] Pd-catalyzed Wacker-type cyclization of *o*-allylphenols,[13] Ti(IV)-promoted coupling of (*E*)-1,2-dimethoxy-4-(prop-1-enyl)-benzene and 2-methoxy-1,4-benzoquinone,[14] Rh-catalyzed C−H insertion of aryldiazoacetates,[15] and Ag-catalyzed Sakurai condensation of aromatic aldehydes and 2,3-dihydrobenzoxasilepines.[16] Regarding the organocatalyzed asymmetric synthesis of DHBs with high enantioselectivity, to date only three reports can be found: Through cinchona alkaloid enantioselective interrupted Feist−Bénary reaction and the subsequent transformations, Calter and co-worker realized the construction of the DHB core skeleton of (−)-variabilin and (−)-glycinol.[17] Jørgensen reported an anodic oxidation/organocatalytic protocol for the α-arylation of aldehydes with *N*-tosyl-4-aminophenol, giving access to DHBs in good yields and excellent enantiomeric excesses.[18] Recently, Jørgensen developed another elegant organocatalytic approach to optically active DHBs, under the catalysis of a L-prolinol silylether, three types of optically active *trans*-DHBs having three contiguous stereogenic centers can be efficiently accessed by one-pot reaction cascades.[19] Therefore, the development of alternative asymmetric reactions able to provide rapid access to optically active DHBs, especially *trans*-DHBs, will be of great importance and highly desirable. Recently, the organocatalyzed asymmetric intramolecular reactions including intramolecular Michael addition have been providing powerful and practical method for the highly stereocontrolled construction of carbo- or

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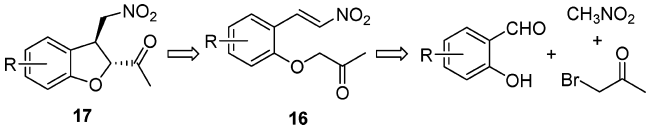
heterocyclic compounds.[20] However, to the best of our knowledge, the asymmetric intramolecular nitro-Michael addition has been so far unexplored. Herein we report an efficient, mild, and highly enantioselective method for the preparation of *trans*-DHBs by organocatalyzed intramolecular nitro-Michael addition.[21]

2. RESULTS AND DISCUSSION

Recently, we have demonstrated that primary amine-thiophosphoramides **6**,**7** are efficient organocatalysts for the Michael addition of acetone to nitroolefins.[22] Under the catalysis of **6**, adducts from the asymmetric Michael addition of acetone to both aromatic and aliphatic nitroolefins were obtained in high yields with excellent enantioselectivities under mild reaction conditions.[22b] Encouraged by the successful results mentioned above, we conceived that 2,3-dihydrobenzofuran derivatives **17** could be synthesized as well from the intramolecular Michael addition of keto-nitroolefins **16**, which might be generated from readily available salicylaldehydes, bromoacetone, and nitromethane (Scheme 1).

Scheme 1. General Strategy for the Synthesis of Dihydrobenzofuran Derivatives



In an initial study, a series of bifunctional primary amine organocatalysts[23] including thiophosphoramides **6**−**8**, cinchona alkaloid derivative **9**, and bifunctional thioureas **10**−**15** bearing either different chiral diamine skeletons or different substituents on the nitrogen atom of the thiourea moiety were chosen as the catalyst candidates (Figure 2), and the intramolecular Michael addition of keto-nitroolefin **16a** was selected as a model reaction. The experimental results are summarized in Table 1.

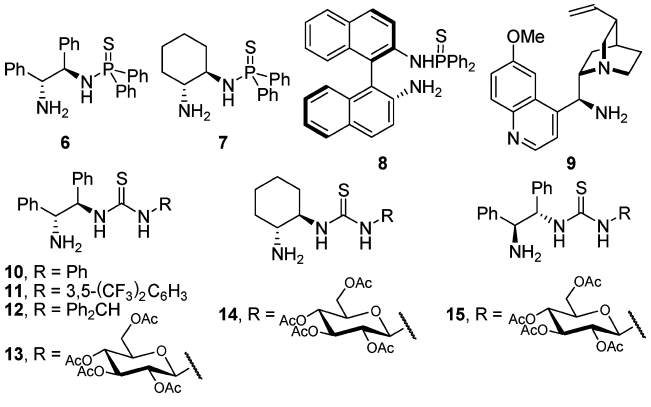
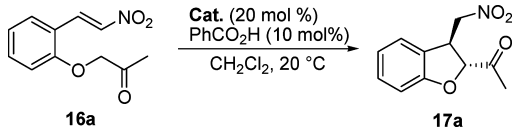


Figure 2. Catalyst candidates.

The results listed in Table 1 clearly indicated that the catalytic activity and enantioselectivity of the thiophosphoramide catalysts are highly dependent on their chiral diamine skeleton (Table 1, entries 1−3). Under the catalysis of thiophosphoramide **6** bearing (*R*,*R*)-1,2-diphenylethane-1,2-diamine skeleton, the intramolecular Michael addition of keto-nitroolefin **16a** proceeded smoothly to provide the desired dihydrobenzofuran product **17a** with good enantioselectivity

Table 1. Catalyst Screening[a]



entry	catalyst	time (h)	yield (%)[b]	dr (*trans*/*cis*)[c]	ee (%)[d]
1	**6**	96	47	61/39	87 (97)
2	**7**	96	55	94/6	52 (48)
3	**8**	120	NR[e]		
4	**9**	24	78	52/48	−23 (−95)
5	**10**	20	55	90/10	90 (98)
6	**11**	6	82	66/34	83 (82)
7	**12**	8	80	75/25	92 (67)
8	**13**	4	91	70/30	93 (94)
9	**14**	96	51	74/26	81 (96)
10	**15**	24	80	56/44	90 (−93)

[a]All reactions were carried out using keto-nitroolefin (0.25 mmol) in the presence of catalyst (20 mol %), cocatalyst $PhCO_2H$ (10 mol %) in CH_2Cl_2 (0.5 mL) at 20 °C. [b]Yield of the isolated product after chromatography on silica gel. [c]Determined by ^1H NMR and HPLC analysis. [d]Determined by chiral HPLC analysis. Values in the parentheses were ee value of the minor isomer. [e]NR means no reaction occurred.

(Table 1, entry 1, 87% ee for the major isomer). A sharp decrease in enantioselectivity was observed when thiophosphoramide **7** derived from (*R*,*R*)-cyclohexane-1,2-diamine was employed as the catalyst (Table 1, entry 2, 52% ee for the major isomer). Under identical conditions, thiophosphoramide **8** prepared from (*R*)-1,1′-binaphthyl-2,2′-diamine was completely inactive and failed to afford product **17a** (Table 1, entry 3). The readily available cinchona alkaloid derivative **9** exhibited much higher catalytic activity; the corresponding adduct was obtained with 78% yield in 24 h albeit with quite low stereocontrol (Table 1, entry 4, 52/48 dr, 23% ee). Since primary amine-thioureas have been proven to be efficient catalysts for the intermolecular nitro-Michael addition,[24] to further improve the enantioselectivity of the reaction, bifunctional primary amine-thioureas[25] **10**−**14** were screened for the model reaction. In general, bifunctional thioureas are promising catalysts for this transformation (Table 1, entries 5−9). However, the substituents on the nitrogen atom of the thiourea moiety and chiral diamine backbone of these thioureas play a crucial role on both the catalytic efficacy and chiral induction ability. Thioureas **10**−**13** bearing (*R*,*R*)-1,2-diphenylethane-1,2-diamine skeleton proved to be highly efficient for this reaction. The reaction was complete in 4−20 h, giving the corresponding product **17a** with enantioselectivities of 90, 83, 92, and 93% ee for the major diastereomer, respectively (Table 1, entries 5−8). In contrast, the use of thiourea **14** derived from (*R*,*R*)-cyclohexane-1,2-diamine resulted in a quite slower reaction and significant erosion in enantioselectivity (Table 1, entry 9, 81% ee for the major isomer). In terms of chemical yield and enantioselectivity of the major diastereomer, thiourea **13** derived from (*R*,*R*)-1,2-diphenylethane-1,2-diamine bearing a glucosyl scaffold[26] was the best choice for the model reaction. In addition, under otherwise identical conditions, thiourea **15** derived from (*S*,*S*)-1,2-diphenylethane-1,2-diamine bearing a glucosyl scaffold demonstrated much lower catalytic activity. Although almost the same enantioselectivity was observed, the addition product was obtained at a prolonged reaction time with marked decrease in diastereoselectivity (Table 1, entry 10

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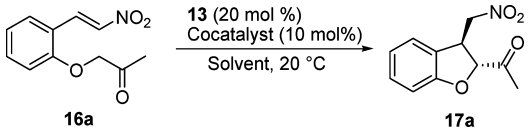
Table 2. Optimization of the Reaction Conditions[a]



16a 17a

entry	solvent	additive	time (h)	yield (%)[b]	*trans*/*cis*[c]	ee (%)[d]
1	CH_2Cl_2	$PhCO_2H$	4	91	70/30	93 (94)
2	$CHCl_3$	$PhCO_2H$	16	56	51/49	94 (95)
3	THF	$PhCO_2H$	24	99	72/28	95 (96)
4	Toluene	$PhCO_2H$	5	91	38/62	94 (95)
5	MeOH	$PhCO_2H$	84	49	8/92	83 (83)
6	THF	$4\text{-}NO_2C_6H_4CO_2H$	6	99	88/12	96 (98)
7	THF	CH_3CO_2H	168	95	76/24	92 (98)
8	THF	PhOH	168	trace		
9[e]	THF	$4\text{-}NO_2C_6H_4CO_2H$	4	91	70/30	96 (99)
10[f]	THF	$4\text{-}NO_2C_6H_4CO_2H$	19	91	59/41	96 (99)
11[g]	THF	$4\text{-}NO_2C_6H_4CO_2H$	72	75	78/22	94 (99)
12[h]	THF	$4\text{-}NO_2C_6H_4CO_2H$	6	95	96/4	96 (98)

[a]Reaction conditions: Keto-nitroolefin **16a** (0.25 mmol), cocatalyst (10 mol %) in 0.5 mL of solvent in the presence of 20 mol % of catalyst **13**. [b]Yield of the isolated product after chromatography on silica gel. [c]Determined by ^{1}H NMR and HPLC analysis. [d]Determined chiral HPLC analysis. Values in the parentheses were ee value of the minor isomer. [e]The reaction was performed at 30 °C . [f]The reaction was performed at 0 °C. [g]The reaction conducted in the presence of 10 mol % of catalyst. [h]After completion of the reaction, the reaction mixture was warmed to reflux for 8 h.

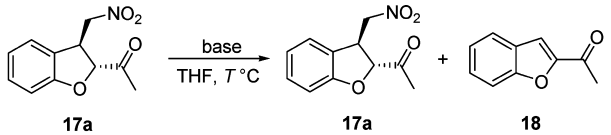
vs entry 8). This indicates that the (*R*,*R*)-configuration of 1,2-diphenylethane-1,2-diamine matched the chirality of glucosyl moiety to enhance the catalytic activity of the catalyst.

Having confirmed thiourea **13** as the optimum catalyst for the reaction, other factors, such as solvent, cocatalyst, catalyst loading, and reaction temperature, influencing the reaction were thoroughly investigated employing the intramolecular Michael addition of keto-nitroolefin **16a** as the model. The results are listed in Table 2.

With 20 mol % of **13** in combination of 10 mol % of $PhCO_2H$ as the catalyst at 20 °C, various solvents have been examined for this reaction (Table 2, entries 1−5). Except for methanol in which obvious erosion in enantioselectivity was observed, this asymmetric intramolecular Michael addition could be carried out smoothly in several conventional solvents with almost the same high level of enantioselectivity. The use of THF resulted in both the highest diastereo- (*trans*/*cis*: 72/28) and enantioselectivity (95% ee) (Table 2, entry 3). A survey of acidic cocatalysts revealed that the acid strength of the cocatalyst has an important influence on the reaction. The use of more acidic 4-nitrobenzoic acid instead of benzoic acid as the cocatalyst resulted in significant acceleration of the reaction and further improvement of the diastereo- and enantioselectivity to 88/12 (*trans*/*cis*) and 96% ee, respectively. The use of less acidic acetic acid or phenol as the cocatalyst led to a sluggish reaction, especially when phenol was employed; the resulting catalytic system was not active at all. Performing the reaction at higher or lower temperature both resulted in the decrease of diastereoselectivity albeit with the same high level of ee value for the major diastereomer (Table 2, entries 9 and 10). In addition, reducing the amount of **13** from 20 to 10 mol % resulted in a remarkable decrease both in the turnover frequency and the diastereoselectivity (Table 2, entry 11).

Up to now, under the optimized reaction conditions (20 mol % of thiourea **13** as the catalyst, 10 mol % 4-nitrobenzoic acid as the additive, in THF at 20 °C), excellent enantioselectivity (96% ee) has been obtained albeit with to some extent unsatisfactory diastereoselectivity (*trans*/*cis*: 88/12). We envisioned that the existence of an acidic proton adjacent to the acetyl group may offer an opportunity to transform the *cis*-isomer to the thermodynamically favorable *trans*-isomer via the base promoted enolization. When the reaction was complete, different base (1 equiv) was added, and the resulting mixture was stirred at room temperature or warmed to reflux for a period of time. As we expected, the *trans*/*cis* ratio was significantly improved, though unwanted formation of 2-acetobenzofuran (**18**), a side product arising via the retro-Michael addition, severely competed with the desired pathway (Scheme 2). We then sought to improve the *trans*/*cis* ratio

Scheme 2. Base-Promoted Isomerization of the Product 17a



17a (*trans*/*cis* = 88/12) **17a** **18**

Base	Temp.	Time (h)	**17a** (*trans*/*cis*)	**18** (%)
NaOH	rt	1	93/7	63
NaOMe	rt	8	94.5/5.5	12.6
NaOMe	reflux	1	92/8	34

efficiently while preventing side reactions. We noticed that this intramolecular Michael addition proceeded via an enamine mechanism. Since both the substrate **16** and the product **17** have a carbonyl group, the isomerization of product could also be engineered in the presence of the catalyst **13** under reflux to give the thermodynamically favorable *trans*-isomer through enamine intermediate.[27] To our delight, the diastereoselectivity of the reaction could be further sharply increased to 96/4 (*trans*/*cis*) by just simply refluxing the reaction mixture for 8 h after completion of the reaction (Table 2, entry 12).

To investigate the scope of the process, a wide range of keto-nitroolefins bearing different substituent on the benzene ring were subjected to the bifunctional thiourea-catalyzed intramolecular Michael addition reaction. The results are summarized in Table 3.

Indeed, this transformation has a broad substrate generality. Both electron-rich and electron-deficient salicylaldehydes with

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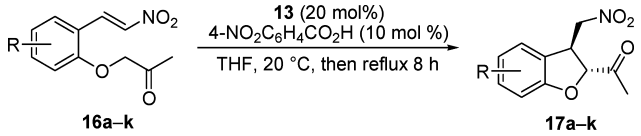
Table 3. Substrate Scope of the Asymmetric Intramolecular Michael Addition Catalyzed by 13[a]



entry	R	time (h)	yield (%)[b,c]	*trans*/*cis*[c,d]	ee (%)[c,e]
1	H (**a**)	6	95	96/4	96
2[f]	H (**a**)	8	91	98/2	>99
3	5-F (**b**)	8	>99 (82)	90/10 (>99/1)	97 (>99)
4	5-Cl (**c**)	10	99	94/6	97
5	5-Br (**d**)	12	97	94/6	97
6	5-NO_2 (**e**)	18	>99 (93)	95/5 (98.5/1.5)	94 (97)
7	7-MeO (**f**)	10	99 (87)	92/8 (96.5/3.5)	97 (>99)
8	5-MeO (**g**)	11	97 (81)	88/12 (>99/1)	98 (>99)
9	7-Me (**h**)	10	95 (78)	84/16 (99/1)	97 (>99)
10	6-Me (**i**)	10	92	96/4	98
11	5-Me (**j**)	10	97 (80)	87/13 (>99/1)	97 (99)
12	4,5-CH=CH—CH=CH (**k**)	14	96	96/4	95

[a]Reaction conditions: Keto-nitroolefins **16** (0.25 mmol), 4-nitrobenzoic acid (10 mol %), and catalyst **13** (20 mol %) in THF (0.5 mL) at 20 °C, then reflux for 8 h. [b]Isolated yield. [c]Values in the parentheses were the data after a single recrystallization. [d]Determined by ^{1}H NMR and HPLC analysis. [e]Determined by chiral HPLC analysis. [f]The reaction was carried out on 10 mmol scale.

various substitution patterns derived keto-nitroolefins participate in the intramolecular Michael addition to give DHBs in excellent yields with excellent diastereo- (*trans*/*cis*: 84/16−96/4) and enantioselectivities (94 to >99% ee) (Table 3, entries 1−12). Moreover, it is worth noting that the reaction can also be carried out in gram scale giving the isolated product without any erosion in diastereo- and enantioselectivity, which demonstrates the potential application of this method for preparative purposes. For example, the reactions of keto-nitroolefin **16a** on 10 mmol scale resulted in the formation of dihydrobenzofuran **17a** in excellent yield and stereocontrol along (*trans*/*cis*: 98/2, >99% ee) (Table 3, entry 2). Since all of the products **17** were solid, in some cases, the unsatisfactory *trans*/*cis* ratios could be markedly improved via a single recrystallization (Table 3, entries 3, 6−9 and 11).

The relative and absolute configuration of the product **17i** is unequivocally established by X-ray analysis (see the Supporting Information), and the remaining configurations are assumed by analogy.

3. CONCLUSION

In summary, we have described a convenient and scalable procedure for the preparation of *trans*-dihydrobenzofurans in high yields with excellent diastereo- and enantioselectivities via a primary amine-thiourea organocatalyzed intramolecular Michael addition from readily available starting materials.

4. EXPERIMENTAL SECTION

All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were acquired on either a 300 or 400 MHz instrumental. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and 77.0 ($CDCl_3$) or 2.50 and 39.43 (DMSO-d_6). Enantiomeric excesses were determined on a HPLC instrument (chiral column; mobile phase: hexane/*i*-PrOH). All temperatures were uncorrected. Thiophosphoramides **6**,[22b] **7**,[22a] **8**[22b] and thioureas **10**,[26d] **11**,[28] **13**,[26e] **14**,[26a] **15**[26e] were synthesized according to the literature procedure.

4.1. Synthesis of Thiourea 12. To a solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (0.86 g, 4.04 mmol) in methylene chloride (10 mL) was slowly added a solution of isothiocyanatodiphenylmethane (1.02 g, 4 mmol) in methylene chloride (15 mL) at 0 °C during 1 h. The resulting mixture was then stirred overnight at room temperature. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford the desired product **12** as a white solid: 1.28 g, 73% yield, mp 76−78 °C, $[\alpha]_D^{20}$ +10.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (br. s, 2 H), 4.29 (s, 1 H), 5.27 (br. s, 1 H), 6.09 (br. s, 1 H), 6.64 (s, 1 H), 7.06 (s, 2 H), 7.19−7.24 (m, 5 H), 7.28−7.32 (m, 14 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 59.8, 62.5, 64.0, 126.5, 127.2, 127.6, 127.7, 128.0, 128.5, 128.8, 128.9, 139.7, 141.5, 180.9; HRMS (ESI) *m*/*z* calc'd for $C_{28}H_{28}N_3S$ $[M + H]^+$ 438.1998, found 438.1994.

4.2. Synthesis of Ketone-Nitroolefins 16. To a suspension of K_2CO_3 (2.21 g, 16 mmol) in acetone (50 mL) was added 1-bromopropan-2-one (1 mL, 1.5 equiv) and the corresponding nitroolefins (8 mmol). The resulting mixture was stirred at 0 °C until complete consumption of the starting material was observed by TLC. The solvent was removed under reduced pressure. The crude product was purified either by recrystallization from methanol or by column chromatography to furnish the corresponding keto-nitroolefin.

1-(2-((*E*)-2-Nitrovinyl)phenoxy)propan-2-one (**16a**): Yellow solid, 67% yield, 1.19 g, mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 4.74 (s, 2 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 8.06 (d, *J* = 13.6 Hz, 1 H), 8.19 (d, *J* = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.5, 73.0, 112.0, 119.7, 122.2, 132.4, 133.3, 134.7, 139.0, 157.3, 202.9; HRMS (ESI) *m*/*z* calc'd for $C_{11}H_{11}NO_4Na$ $[M + Na]^+$ 244.0586, found 244.0578.

1-(4-Fluoro-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16b**): Yellow solid, 66% yield, 1.32 g, mp 106−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 4.73 (s, 2 H), 6.75 (dd, *J* = 8.8 and 4.0 Hz, 1 H), 7.11−7.16 (m, 1 H), 7.21 (dd, *J* = 8.4 and 2.8 Hz, 1 H), 8.01 (d, *J* = 13.6 Hz, 1 H), 8.13 (d, *J* = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 73.5, 113.3 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 23.7 Hz), 119.5 (d, *J* = 23.4 Hz), 120.7 (d, *J* = 7.9 Hz), 133.4, 139.8, 153.5, 157.1 (d, *J* = 241.8 Hz), 202.5; HRMS (ESI) *m*/*z* calc'd for $C_{11}H_{10}FNO_4Na$ $[M + Na]^+$ 262.0492, found 262.0484.

1-(4-Chloro-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16c**): Yellow solid, 56% yield, 1.15 g, mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 4.74 (s, 2 H), 6.73 (d, *J* = 8.8 Hz, 1 H), 7.37 (dd, *J* = 8.8 and 2.4 Hz, 1 H), 7.47 (d, *J* = 2.4 Hz, 1 H), 8.02 (d, *J* = 13.6 Hz, 1 H), 8.10 (d, *J* = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 73.2, 113.3, 121.1, 127.2, 131.5, 132.6, 133.2, 139.8, 155.7, 202.1; HRMS (ESI) *m*/*z* calc'd for $C_{11}H_{10}ClNO_4Na$ $[M + Na]^+$ 278.0191, found 278.0193.

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1-(4-Bromo-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16d**): Yellow solid, 50% yield, 1.20 g, mp 130−133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 4.74 (s, 2 H), 6.68 (d, J = 8.8 Hz, 1 H), 7.51 (dd, J = 8.8 and 2.4 Hz, 1 H), 7.61 (d, J = 2.4 Hz, 1 H), 8.02 (d, J = 13.6 Hz, 1 H), 8.10 (d, J = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 73.1, 113.8, 114.3, 121.6, 133.1 134.4, 135.5, 139.8, 156.2, 202.0; HRMS (ESI) m/z calc'd for $C_{11}H_{10}BrNO_4Na$ $[M + Na]^+$ 321.9685, found 321.9679.

1-(4-Nitro-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16e**): Pale yellow solid, 72% yield, 1.53 g, mp 164−166 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.20 (s, 3 H), 5.27 (s, 2 H), 7.29 (d, J = 9.2 Hz, 1 H), 8.28 (d, J = 13.6 Hz, 1 H), 8.33 (d, J = 9.2 Hz, 1 H), 8.52 (d, J = 13.6 Hz, 1 H), 8.78 (s, 1 H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) 26.0, 73.4, 113.7, 119.4, 128.1, 128.3, 133.0, 140.8, 141.2, 161.9, 201.8; HRMS (ESI) m/z calc'd for $C_{11}H_{10}N_2O_6Na$ $[M + Na]^+$ 289.0431, found 289.0426.

1-(2-Methoxy-6-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16f**): Yellow solid, 70% yield, 1.41 g, mp 90−91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 3.85 (s, 3 H), 4.69 (s, 2 H), 7.02−7.04 (m, 1 H), 7.10−7.15 (m, 2 H), 7.79 (d, J = 13.6 Hz, 1 H), 8.33 (d, J = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.2, 55.9, 77.4, 115.8, 121.3, 123.9, 124.5, 134.5, 138.7, 147.4, 151.9, 204.7; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_5Na$ $[M + Na]^+$ 274.0686, found 274.0685.

1-(4-Methoxy-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16g**): Yellow solid, 56% yield, 1.13 g, mp 118−119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3 H), 3.79 (s, 3 H), 4.68 (s, 2 H), 6.73 (d, J = 8.8 Hz, 1 H), 6.95−6.99 (m, 2 H), 8.09 (d, J = 13.6 Hz, 1 H), 8.15 (d, J = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 55.8, 73.5, 113.3, 116.3, 118.8, 120.1, 134.5, 139.1, 151.7, 154.2, 203.4; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_5Na$ $[M + Na]^+$ 274.0686, found 274.0682.

1-(2-Methyl-6-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16h**): Yellow solid, 55% yield, 1.04 g, mp 97−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 6 H), 4.44 (s, 2 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 7.70 (d, J = 13.6 Hz, 1 H), 8.26 (d, J = 14.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 16.2, 26.4, 77.7, 123.7, 125.7, 127.2, 132.0, 134.2, 135.5, 138.3, 156.6, 203.0; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0737, found 258.0730.

1-(5-Methyl-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16i**): Yellow solid, 68% yield, 1.28 g, mp 91−93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 2.38 (s, 3 H), 4.72 (s, 2 H), 6.59 (s, 1 H), 6.88 (d, J = 7.6 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 8.03 (d, J = 13.6 Hz, 1 H), 8.15 (d, J = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 22.0, 26.4, 72.9, 112.8, 116.9, 123.0, 132.4, 134.9, 138.1, 144.8, 157.3, 203.1; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0737, found 258.0733.

1-(4-Methyl-2-((*E*)-2-nitrovinyl)phenoxy)propan-2-one (**16j**): Yellow solid, 80% yield, 1.51 g, mp 130−133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3 H), 2.31 (s, 3 H), 4.69 (s, 2 H), 6.68 (d, J = 8.4 Hz, 1 H), 7.22 (d, J = 8.4 Hz, 1 H), 7.29 (s, 1 H), 8.01 (d, J = 13.6 Hz, 1 H), 8.16 (d, J = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 20.2, 26.4, 73.1, 112.0, 119.3, 131.6, 132.6, 133.9, 134.8, 138.7, 155.4, 203.3; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0737, found 258.0743.

1-(1-((*E*)-2-Nitrovinyl)naphthalen-2-yloxy)propan-2-one (**16k**): Orange solid, 90% yield, 1.95 g, mp 165−167 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3 H), 4.91 (s, 2 H), 7.09 (d, J = 9.0 Hz, 1 H), 7.44−7.49 (m, 1 H), 7.60−7.66 (m, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.94 (d, J = 9.0 Hz, 1 H), 8.17 (d, J = 8.4 Hz, 1 H), 8.39 (d, J = 13.5 Hz, 1 H), 8.82 (d, J = 13.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 73.4, 112.5, 124.9, 128.7, 129.0, 129.3, 130.4, 133.2, 134.1, 141.3, 156.4, 202.3; HRMS (ESI) m/z calc'd for $C_{15}H_{13}NO_4Na$ $[M + Na]^+$ 294.0737, found 294.0736.

4.3. General Procedure for the Catalytic Asymmetric Intramolecular Michael Addition. Keto-nitroolefin **16** (0.25 mmol), 4-nitrobenzoic acid (0.025 mmol), and primary amine/thiourea catalyst (0.05 mmol) were dissolved in THF (0.5 mL). The resulting solution was stirred at 20 °C until complete consumption of keto-nitroolefin (TLC monitoring). Then, the reaction mixture was refluxed for an additional 8 h. After cooling to room temperature, the mixture was directly purified by column chromatography on silica gel (100−200 mesh, PE/EtOAc = 15/1) to afford the desired product **17**. The enantiomeric excess of the pure product was determined by chiral HPLC analysis.

1-((2*R*,3*S*)-2,3-Dihydro-3-(nitromethyl)benzofuran-2-yl)ethanone (**17a**): White solid, 95% yield, 53 mg, mp 78−80 °C, $[\alpha]_D^{20}$ −52.3 (*c* 1.0, $CHCl_3$), 96/4 *trans*/*cis*, 96% ee for *trans* isomer, 98% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 4.32 (dt, J = 4.4 and 6.8 Hz, 1 H), 4.62 (d, J = 6.8 Hz, 2 H), 4.91 (d, J = 4.4 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 7.15 (d, J = 7.2 Hz, 1 H), 7.23 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 43.2, 77.4, 87.8, 110.4, 122.0, 123.5, 124.7, 130.3, 158.6, 206.4; HRMS (ESI) m/z calc'd for $C_{11}H_{11}NO_4Na$ $[M + Na]^+$ 244.0580, found 244.0587; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 12.49 (minor, *cis* isomer), 13.03 (major, *cis* isomer), 15.28 (major, *trans* isomer) and 17.25 min (minor, *trans* isomer).

1-((2*R*,3*S*)-5-Fluoro-2,3-dihydro-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17b**): White solid, >99% yield, 60 mg, mp 70−72 °C, $[\alpha]_D^{20}$ −53.0 (*c* 1.0, $CHCl_3$), 90/10 *trans*/*cis*, 97% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 2.70 H, *trans* isomer), 2.40 (s, 0.30 H, *cis* isomer), 4.34 (dt, J = 4.8 and 7.6 Hz, 1 H), 4.64 (d, J = 7.6 Hz, 2 H), 4.92 (d, J = 4.8 Hz, 0.90 H, *trans* isomer), 5.16 (d, J = 10.0 Hz, 0.10 H, *cis* isomer), 6.86−6.96 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 27.7, 42.1, 43.1, 73.3, 77.0, 86.0, 88.3, 110.8 (d, J = 8.3 Hz), 112.0 (d, J = 25.6 Hz), 116.8 (d, J = 24.3 Hz), 124.8 (d, J = 8.6 Hz), 154.6, 158.0 (d, J = 240.3 Hz), 206.2; HRMS (ESI) m/z calc'd for $C_{11}H_{10}FNO_4Na$ $[M + Na]^+$ 262.0486, found 262.0487; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 97:3, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 23.13 (major, *cis* isomer), 25.61 (major, *trans* isomer) and 33.88 min (minor, *trans* isomer).

1-((2*R*,3*S*)-5-Chloro-2,3-dihydro-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17c**): White solid, 99% yield, 63 mg, mp 60−62 °C, $[\alpha]_D^{20}$ −31.8 (*c* 1.0, $CHCl_3$), 94/6 *trans*/*cis*, 97% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 2.82 H, *trans* isomer), 2.40 (s, 0.18 H, *cis* isomer), 4.33 (dt, J = 4.8 and 6.8 Hz, 1 H), 4.63 (d, J = 6.8 Hz, 2 H), 4.94 (d, J = 4.8 Hz, 0.94 H, *trans* isomer), 5.16 (d, J = 10.0 Hz, 0.06 H, *cis* isomer), 6.86 (d, J = 8.8 Hz, 1 H), 7.10 (s, 0.06 H, *cis* isomer), 7.15 (s, 0.94 H, *trans* isomer), 7.21 (dd, J = 8.8 and 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 42.9, 77.0, 88.3, 111.5, 124.9, 125.4, 126.9, 130.3, 157.3, 205.7; HRMS (ESI) m/z calc'd for $C_{11}H_{10}ClNO_4Na$ $[M + Na]^+$ 278.0191, found 278.0192; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 97:3, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 23.13 (major, *cis* isomer), 25.61 (major, *trans* isomer) and 33.88 min (minor, *trans* isomer).

1-((2*R*,3*S*)-5-Bromo-2,3-dihydro-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17d**): White solid, 97% yield, 73 mg, mp 70−72 °C, $[\alpha]_D^{20}$ −21.7 (*c* 1.0, $CHCl_3$), 94/6 *trans*/*cis*, 97% ee for *trans* isomer, 99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 2.82 H, *trans* isomer), 2.39 (s, 0.18 H, *cis* isomer), 4.33 (dt, J = 4.8 and 6.8 Hz, 1 H), 4.63 (d, J = 6.8 Hz, 2 H), 4.94 (d, J = 4.8 Hz, 0.94 H, *trans* isomer), 5.15 (d, J = 10.0 Hz, 0.06 H, *cis* isomer), 6.82 (d, J = 8.4 Hz, 1 H), 7.24 (s, 0.06 H, *cis* isomer), 7.29 (s, 0.94 H, *trans* isomer), 7.35 (dd, J = 8.4 and 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 42.8, 77.0, 88.2, 112.0, 113.9, 125.9, 127.8, 133.2, 157.8, 205.6; HRMS (ESI) m/z calc'd for $C_{11}H_{10}BrNO_4Na$ $[M + Na]^+$ 321.9685, found 321.9688; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 97:3, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 21.42 (minor, *cis* isomer), 25.19 (major, *cis* isomer), 26.82 (major, *trans* isomer) and 37.69 min (minor, *trans* isomer).

1-((2*R*,3*S*)-2,3-Dihydro-5-nitro-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17e**): Pale yellow solid, >99% yield, 67 mg, mp 96−100 °C, $[\alpha]_D^{20}$ −29.2 (*c* 1.0, $CHCl_3$), 95/5 *trans*/*cis*, 94% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 2.85 H, *trans* isomer), 2.45 (s, 0.15 H, *cis* isomer), 4.44 (dt, J = 5.2 and 6.4 Hz, 1 H), 4.74 (d, J = 6.4 Hz, 2 H), 5.18 (d, J = 5.2 Hz, 0.95 H, *trans* isomer), 5.33 (d, J = 10.4 Hz, 0.05 H, *cis* isomer), 7.02 (d, J = 8.8 Hz, 1 H), 8.06 (d, J = 1.6 Hz, 0.05 H, *cis* isomer), 8.11 (d, J = 1.6 Hz, 0.95 H,

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trans isomer), 8.20 (dd, J = 8.8 and 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.6, 41.9, 76.5, 89.4, 110.5, 121.3, 125.2, 127.4, 142.9, 163.6, 204.1; HRMS (ESI) m/z calc'd for $C_{11}H_{10}N_2O_6Na$ $[M + Na]^+$ 289.0431, found 289.0434; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 61.89 (major, *cis* isomer), 69.95 (major, *trans* isomer) and 110.73 min (minor, *trans* isomer).

1-((2*R*,3*S*)-2,3-dihydro-7-methoxy-3-(nitromethyl)benzofuran-2-yl)ethanone (**17f**): White solid, 99% yield, 62 mg, 75−77 °C, $[\alpha]_D^{20}$ −11.5 (*c* 1.0, $CHCl_3$), 92/8 *trans*/*cis*, 97% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 2.76 H, *trans* isomer), 2.44 (s, 0.24 H, *cis* isomer), 3.90 (s, 3 H), 4.37 (dt, J = 4.8 and 7.6 Hz, 1 H), 4.62 (d, J = 7.6 Hz, 2 H), 4.95 (d, J = 4.8 Hz, 0.92 H, *trans* isomer), 5.19 (d, J = 10.0 Hz, 0.08 H, *cis* isomer), 6.72 (d, J = 7.2 Hz, 0.08 H, *cis* isomer), 6.76 (d, J = 7.2 Hz, 0.92 H, *trans* isomer), 6.85 (d, J = 7.6 Hz, 1 H), 6.91 (t, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 43.7, 56.0, 77.3, 88.3, 113.0, 116.4, 122.9, 124.7, 144.9, 147.0, 206.3; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_5Na$ $[M + Na]^+$ 274.0686, found 274.0685; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 49.34 (major, *cis* isomer), 76.17 (major, *trans* isomer) and 85.15 min (minor, *trans* isomer).

1-((2*R*,3*S*)-2,3-Dihydro-5-methoxy-3-(nitromethyl)benzofuran-2-yl)ethanone (**17g**): Yellow solid, 97% yield, 61 mg, mp 34−36 °C, $[\alpha]_D^{20}$ −25.8 (*c* 1.0, $CHCl_3$), 88/12 *trans*/*cis*, 98% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 2.64 H, *trans* isomer), 2.36 (s, 0.36 H, *cis* isomer), 3.73 (s, 3 H), 4.30 (dt, J = 4.4 and 6.8 Hz, 1 H), 4.62 (d, J = 6.8 Hz, 2 H), 4.86 (d, J = 4.4 Hz, 0.88 H, *trans* isomer), 5.11 (d, J = 9.6 Hz, 0.12 H, *cis* isomer), 6.67 (d, J = 2.0 Hz, 0.12 H, *cis* isomer), 6.72 (d, J = 2.0 Hz, 0.88 H, *trans* isomer), 6.78 (dd, J = 2.4 and 8.8 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4 (*trans* isomer), 27.7 (*cis* isomer), 42.3 (*cis* isomer), 43.8 (*trans* isomer), 56.0, 73.6 (*cis* isomer), 77.3 (*trans* isomer), 86.5 (*cis* isomer), 88.1 (*trans* isomer), 110.4, 110.6, 115.6, 124.4, 152.5, 155.1, 206.8; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_5Na$ $[M + Na]^+$ 274.0686, found 274.0686; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 97:3, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 25.01 (major, *cis* isomer), 33.45 (major, *trans* isomer) and 36.04 min (minor, *trans* isomer).

1-((2*R*,3*S*)-2,3-Dihydro-7-methyl-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17h**): White solid, 95% yield, 56 mg, mp 54−56 °C, $[\alpha]_D^{20}$ −29.0 (*c* 1.0, $CHCl_3$), 84/16 *trans*/*cis*, 97% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3 H), 2.31 (s, 2.52 H, *trans* isomer), 2.41 (s, 0.48 H, *cis* isomer), 4.33 (dt, J = 4.4 and 6.8 Hz, 1 H), 4.62 (d, J = 6.8 Hz, 2 H), 4.90 (d, J = 4.4 Hz, 0.84 H, *trans* isomer), 5.14 (d, J = 9.6 Hz, 0.16 H, *cis* isomer), 6.84−6.88 (m, 1 H), 6.99 (d, J = 7.2 Hz, 0.84 H, *trans* isomer), 7.04−7.08 (m, 1.16 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 13.7 (*cis* isomer), 15.0 (*trans* isomer), 26.3 (*trans* isomer), 28.4 (*cis* isomer), 42.4 (*cis* isomer), 43.6 (*trans* isomer), 73.8 (*cis* isomer), 77.6 (*trans* isomer), 85.9 (*cis* isomer), 87.6 (*trans* isomer), 120.8 (*trans* isomer), 121.6 (*cis* isomer), 121.9 (*cis* isomer), 122.0 (*trans* isomer), 122.8 (*trans* isomer), 125.5 (*cis* isomer), 127.2 (*cis* isomer), 128.8 (*trans* isomer), 130.9 (*cis* isomer), 131.4 (*trans* isomer), 157.0, 206.8; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0737, found 258.0740; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol = 97:3, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 25.20 (major, *cis* isomer), 27.96 (major, *trans* isomer) and 35.70 min (minor, *trans* isomer).

1-((2*R*,3*S*)-2,3-Dihydro-6-methyl-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17i**): White solid, 92% yield, 54 mg, mp 133−135 °C, $[\alpha]_D^{20}$ −23.0 (*c* 1.0, $CHCl_3$), 96/4 *trans*/*cis*, 98% ee for *trans* isomer, 64% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 2.33 (s, 2.88 H, *trans* isomer), 2.40 (s, 0.12 H, *cis* isomer), 4.28 (dt, J = 4.4 and 6.8 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 2 H), 4.89 (d, J = 4.4 Hz, 0.96 H, *trans* isomer), 5.13 (d, J = 10.0 Hz, 0.04 H, *cis* isomer), 6.76 (d, J = 8.0 Hz, 1 H), 6.77 (s, 1 H), 7.03 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 21.5, 26.4, 43.1, 77.6, 88.1, 111.1, 120.5, 122.9, 124.3, 140.9, 158.9, 206.7; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0737, found 258.0740; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 0.8 mL/min, wavelength = 220 nm) t_R = 18.92 (minor, *cis* isomer), 19.83 (major, *cis* isomer), 24.08 (major, *trans* isomer) and 28.77 min (minor, *trans* isomer).

1-((2*R*,3*S*)-2,3-Dihydro-5-methyl-3-(nitromethyl)benzofuran-2-yl)-ethanone (**17j**): White solid, 97% yield, 57 mg, mp 78−79 °C, $[\alpha]_D^{20}$ −31.8 (*c* 1.0, $CHCl_3$), 87/13 *trans*/*cis*, 97% ee for *trans* isomer, 99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3 H), 2.30 (s, 2.61 H, *trans* isomer), 2.39 (s, 0.39 H, *cis* isomer), 4.29 (dt, J = 4.8 and 7.2 Hz, 1 H), 4.61 (d, J = 7.2 Hz, 2 H), 4.87 (d, J = 4.8 Hz, 0.87 H, *trans* isomer), 5.12 (d, J = 9.6 Hz, 0.13 H, *cis* isomer), 6.83 (d, J = 8.8 Hz, 1 H), 6.91 (s, 0.13 H, *cis* isomer), 6.96 (s, 0.87 H, *trans* isomer), 7.05 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 19.1 (*cis* isomer), 20.7 (*trans* isomer), 26.4 (*trans* isomer), 28.4 (*cis* isomer), 42.0 (*cis* isomer), 43.3 (*trans* isomer), 73.8 (*cis* isomer), 77.5 (*trans* isomer), 86.3 (*cis* isomer), 87.9 (*trans* isomer), 110.0, 123.5, 125.1, 130.7, 131.6, 156.6, 206.7; HRMS (ESI) m/z calc'd for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0737, found 258.0743; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 220 nm) t_R = 13.76 (minor, *cis* isomer), 16.90 (major, *cis* isomer), 19.80 (major, *trans* isomer) and 28.21 min (minor, *trans* isomer).

1-((1*S*,2*R*)-1,2-Dihydro-1-(nitromethyl)naphtho[2,1-b]furan-2-yl)-ethanone (**17k**): Pale yellow solid, 96% yield, 65 mg, mp 110−111 °C, $[\alpha]_D^{20}$ −35.0 (*c* 1.0, $CHCl_3$), 96/4 *trans*/*cis*, 95% ee for *trans* isomer, >99% ee for *cis* isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3 H), 4.44 (dd, J = 10.0 and 12.4 Hz, 1 H), 4.68 (d, J = 10.0 Hz, 1 H), 4.80 (dd, J = 2.8 and 12.8 Hz, 1 H), 5.12 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 8.8 Hz, 1 H), 7.29 (t, J = 7.6 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.57 (d, J = 8.4 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.2, 43.2, 76.0, 89.0, 112.1, 114.3, 121.3, 124.0, 128.0, 129.3, 129.6, 129.9, 131.8, 156.8, 206.2; HRMS (ESI) m/z calc'd for $C_{15}H_{13}NO_4Na$ $[M + Na]^+$ 294.0737, found 294.0735; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 0.7 mL/min, wavelength = 220 nm) t_R = 47.59 (major, *cis* isomer), 49.69 (major, *trans* isomer) and 59.32 min (minor, *trans* isomer).

4.4. Base-Promoted Isomerization of Product 17a. When **13** catalyzed intramolecular Michael addition of keto-nitroolefin **16a** was complete, different base (1 equiv) was added, and the resulting mixture was stirred at room temperature or warmed to reflux for a period of time indicated in Scheme 2. The *trans*/*cis* ratio of product **17a** and the amount of the side product **18** was determined by GC analysis. The structure of the side product **18** was determined by NMR analysis after being purified by column chromatograph on silica gel.

2-Acetobenzofuran (**18**): Yellow solid, mp 58−60 °C (lit.,[29] mp 69−71 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.69 (s, 3 H), 7.30 (t, J = 7.6 Hz, 1 H), 7.47 (t, J = 8.0 Hz, 1 H), 7.49 (s, 1 H), 7.57 (d, J = 8.4 Hz, 1 H), 7.70 (d, J = 8.0 Hz, 1 H) (lit.,[30] 2.60 (s, 3 H), 7.29−7.33 (m, 1 H), 7.45−7.50 (m, 2 H), 7.57 (d, 1 H), 7.70 (d, 1 H)); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 26.4, 112.4, 113.0, 123.2, 123.8, 127.0, 128.2, 152.5, 155.6, 188.6 (lit.,[30] 26.8, 112.8, 113.4, 123.7, 124.3, 127.5, 128.7, 153.1, 156.1, 189.0).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra, HPLC analysis, and the complete data for the reported crystal structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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