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Copper(II)-Catalyzed Asymmetric Henry Reaction of *o*-Alkynylbenzaldehydes Followed by Gold(I)-Mediated Cycloisomerization: An Enantioselective Route to Chiral 1*H*-Isochromenes and 1,3-Dihydroisobenzofurans

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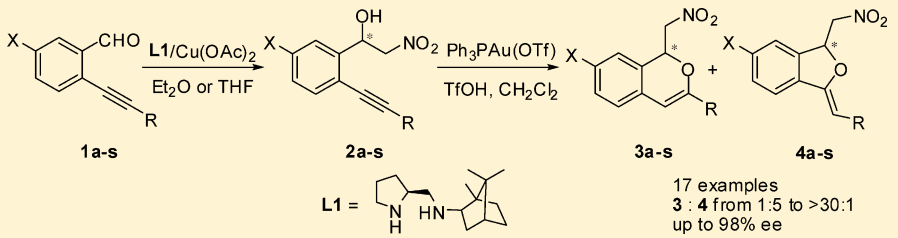
Supporting Information



ABSTRACT: By combining the copper(II)-catalyzed asymmetric Henry reaction of *o*-alkynylbenzaldehydes with subsequent gold(I)-catalyzed cycloisomerization, optically active 1*H*-isochromenes and 1,3-dihydroisobenzofurans were successfully synthesized in good overall yields with good to excellent enantioselectivities (up to 98%). Various substrates were investigated, and a correlation between the regioselectivity and electronic nature of the substrates was studied. The substrates with electron-donating groups at the alkynyl moiety preferred a 6-*endo*-*dig* manner to generated 1*H*-isochromenes **3** as main products (up to >30:1) while the ones with electron-withdrawing groups were inclined to undergo 5-*exo*-*dig* cyclization to form 1,3-dihydroisobenzofurans **4** (up to 1:5).

INTRODUCTION

1*H*-Isochromenes and 1,3-dihydroisobenzofurans are important classes of heterocyclic compounds because of their fascinating biological and pharmacological activities.[1] For example, isochromene carboxamides exhibit excellent activity against the human ovarian cancer cell line SKOV3,[2] and dihydroisobenzofuran derivative pestacin displays potent antioxidant activity and moderate antifungal properties.[3] Among the methods for constructing such types of oxygen-containing heterocycles, the cycloisomerization of *o*-alkynylaryl alcohols is one of the most reliable and atom-economic.[4,5] The alkynylaryl alcohols are usually prepared[4] or generated in situ[5,6] by nucleophilic additions of *o*-alkynylaryl aldehydes. Nucleophiles such as alcohols,[5c,f] phosphites,[5d] terminal alkynes,[5b] active methylene compounds[5c] and organometallic reagents[5e] have been successfully utilized on the basis of this strategy. The cycloisomerization step is usually mediated by bases[4a,b,5d] or transition-metal catalysts[4c−f,5a−c,g] under thermal conditions. Nevertheless, the enantioselective version of this reaction sequence has rarely been reported.[5e]

Since the seminal contribution of Shibasaki in 1992,[7] significant progress has been achieved in the implementation of asymmetric addition of nitroalkanes to carbonyl compounds (Henry reaction).[8,9] Recently, our group has developed a novel chiral diamine ligand for Cu(II)-catalyzed Henry reaction.[9e] Motivated by our previous work, we anticipated that nitromethane might be a potential nucleophile in the above-mentioned addition-cycloisomerizaiton sequence. We envisioned that the chiral *β*-nitro alcohols obtained in the addition step would undergo subsequent cycloisomerization without racemization to give chiral 1*H*-isochromenes and 1,3-dihydroisobenzofurans. From the outset of our investigation, we were reminded of the fact that *β*-nitro alcohols may suffer from dehydration, retro-Henry process, and racemization under thermal or basic conditions. Thus, we initiated our study to identify mild and base-free conditions to avoid side reactions and racemization during the cycloisomerization.

In recent decades, great progress has been made on the gold-catalyzed hydroalkoxylation of alkynes,[10] especially the intramolecular versions, which provide efficient accesses to oxygen-containing hetereocycles from alkynylacohols under mild conditions.[11] Therefore, gold catalysis might be an ideal choice for the cyclization of the Henry products of *o*-alkynylbenzaldehydes. Herein, we present our research results on constructing chiral 1*H*-isochromenes and 1,3-dihydroisobenzofurans by combining the asymmetric Henry reaction with gold-catalyzed cycloisomerization.

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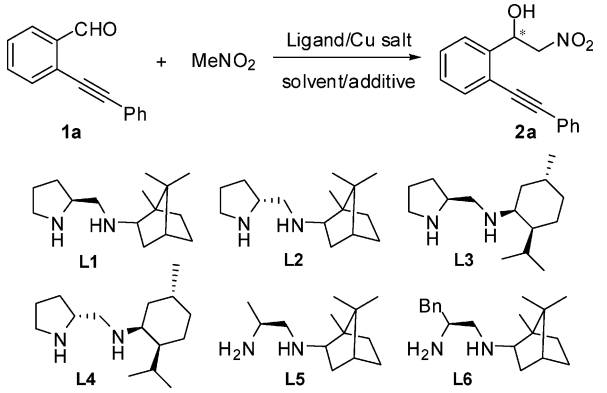
RESULTS AND DISCUSSION

At the very beginning, we examined chiral diamine−Cu(II) complex catalyzed Henry reaction between *o*-phenylethynylbenzaldehyde **1a** and nitromethane. A series of chiral diamine ligands **L1**−**L6** were first screened. The reaction was performed in nitromethane at 4 °C in the presence of 10 mol % of ligand and 10 mol % of $Cu(OAc)_2·H_2O$. The reaction proceeded readily, and **1a** was consumed after 24 h (Table 1). Among all the ligands tested, **L1** was identified to be the best one in terms of both the yield and enantioselectivity of the Henry adduct **2a** (Table 1, entry 1). When the ligand **L2** derived from D-proline was used instead, the configuration-inversed stereomer was obtained with much lower enantioselectivity (entry 2). The ligands **L3** and **L4** derived from (+)-(1*S*,2*S*,5*R*)-menthylamine showed a similar change in stereoselectivity but failed to offer better results (entries 3 and 4). **L5** and **L6**, prepared from camphor amine with L-alanine and L-phenylalanine, respectively, also showed inferior enantioselectivities (entries 5 and 6). These results are in agreement with our previous observations,[10] which revealed that the nitronate would attack the aldehyde from the *re* face when **L1** was used. Therefore, the absolute configuration of **2a** was tentatively assigned as *S*. Next, various bivalent copper salts were evaluated in combination with **L1** in nitromethane at 4 °C (entries 7−10). $Cu(OAc)_2·H_2O$ was chosen for further studies in consideration of both the yield and enantioselectivity.

Table 1. Ligand and Copper Salt Screening of Catalytic Asymmetric Henry Reaction[a]



entry	catalyst	time (h)	yield (%)	ee[b] (%)
1	**L1**/$Cu(OAc)_2·H_2O$	24	93	93
2	**L2**/$Cu(OAc)_2·H_2O$	24	92	−40
3	**L3**/$Cu(OAc)_2·H_2O$	24	90	81
4	**L4**/$Cu(OAc)_2·H_2O$	24	91	−67
5	**L5**/$Cu(OAc)_2·H_2O$	24	92	63
6	**L6**/$Cu(OAc)_2·H_2O$	24	93	72
7	**L1**/$CuCl_2·2H_2O$	36	60	94
8	**L1**/$CuBr_2$	36	54	91
9	**L1**/$CuSO_4·5H_2O$	24	96	80
10	**L1**/$Cu(OTf)_2$	24	74	86

[a]Unless otherwise stated, reactions were carried out on a 0.2 mmol scale of **1a** in 2.0 mL of nitromethane in the presence of 10 mol % of ligand−Cu(II) complex at 4 °C. [b]Determined by chiral HPLC analysis.

The reaction conditions were then optimized utilizing this catalyst system. The data is shown in Table 2. When the reaction was carried out at −20 °C, the starting material **1a** could still be consumed after an extended time; however, the ee value of the product was hardly improved (Table 2, entry 1). Reduction of the catalyst loading to 5 mol % did not erode the enantioselectivity but led to the incomplete reaction (entry 2). The reaction was accelerated significantly by addition of 50% mol of TEA as additive; in the meantime, a loss of enantioselectivity was observed (entry 3). Next, a variety of typical solvents were surveyed in the presence of 25 equiv of nitromethane. Fortunately, when THF was employed as the solvent, the ee value was enhanced to 96% and the yield remained excellent (entry 4). The reaction proceeded slower and less selectively in dichloromethane and chloroform (entries 5 and 6). Diethyl ether was also an ideal choice, providing excellent yield and enantioselectivity (97% ee) after 24 h (entry 7). The reactions in ethanol, toluene, DMF, or acetonitrile all underwent smoothly but provided **2a** with relatively lower enantioselectivity (entries 8−11). The ee value was further raised to 98% when the reaction was conducted at −40 °C after a slightly extended time (Table 2, entry 12).

Table 2. Optimization of Catalytic Asymmetric Henry Reaction[a]

enrty	solvent	additive	time (h)	yield (%)	ee[b] (%)
1[c]	$MeNO_2$	none	48	91	94
2	$MeNO_2$	none	60	63	93
3	$MeNO_2$	TEA[d]	24	95	85
4	THF	TEA	24	95	96
5	CH_2Cl_2	TEA	36	92	79
6	$CHCl_3$	TEA	36	91	66
7	Et_2O	TEA	24	95	97
8	EtOH	TEA	24	95	86
9	$PhCH_3$	TEA	24	93	90
10	DMF	TEA	24	91	86
11	MeCN	TEA	24	91	87
12[e]	Et_2O	TEA	30	95	98

[a]Unless otherwise stated, reactions were performed with 0.2 mmol of **1a**, 5 mol % of **L1**-$Cu(OAc)_2·H_2O$ complex, additive, and 25 equiv of nitromethane in 2 mL of indicated solvent at −20 °C. [b]Determined by chiral HPLC analysis. [c]10 mol % of Cu(II)−**L1** complex was used. [d]TEA 50 mol %. [e]Reaction conducted at −40 °C.

Next, we turned to investigate the subsequent cycloisomerization of the alkynol **2a**. The cyclization reaction of **2a** was initially performed in dichloromethane at 4 °C utilizing 5 mol % of the metal catalysts listed in Table 3. To our delight, gold complex showed high efficiency in this intramolecular hydroalkoxylation. The reaction mediated by $Ph_3PAu(OTf)$ achieved completion in 1 h, furnishing the 6-*endo*-*dig* product **3a** and 5-*exo*-*dig* product **4a** in comparable yields (Table 3, entry 1). The reaction mediated by palladium(II) chloride proceeded much slower and afforded **3a** and **4a** in moderate yields with poor regioselectivity after 10 h (entry 2). Cyclization products were not detected when palladium(II) acetate, bis(triphenylphosphine)palladium(II) chloride, silver triflate, or copper acetate served as catalyst after 12 h under the same conditions (entries 3−6). Further study of the gold(I)-catalyzed reaction revealed that addition of 5 mol % of triflic acid accelerated the process remarkably, indicating that the presence of triflic acid could promote protondeauration step (entry 7). During the reaction, we noticed that the 5-*exo*-*dig* product **4a** was not stable enough and inclined to decompose slowly under the reaction conditions. Fortunately, when the reaction was performed at −20 °C with 2 mol % of the catalyst, the isolated yield of 5-*exo*-*dig* product **4a** increased to 44%,

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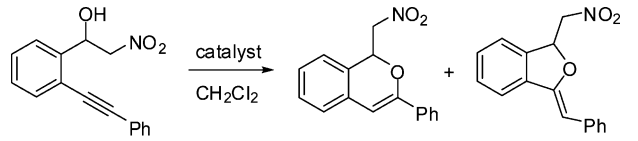
Table 3. Catalysts Screening of the Cycloisomerization Step.[a]



2a 3a 4a

entry	catalyst	time (h)	yield of **3a** (%)	yield of **4a** (%)
1	$Ph_3PAu(OTf)$[b]	1	44	41
2	$PdCl_2$	10	41	36
3	$Pd(OAc)_2$	12	not observed	not observed
4	$PdCl_2(PPh_3)_2$	12	not observed	not observed
5	AgOTf	12	not observed	not observed
6	$Cu(OAc)_2{\cdot}H_2O$	12	not observed	not observed
7	$Ph_3PAu(OTf)$/TfOH	0.3	45	39
8[c,d]	$Ph_3PAu(OTf)$/TfOH	1	45	44
9[d]	TfOH	12	not observed	not observed

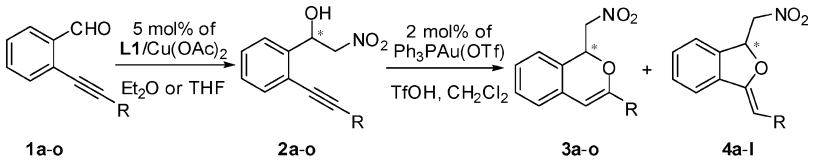
[a]Unless otherwise stated, reactions were performed with 0.2 mmol of **2a** in the presence of 5 mol % of indicated catalyst at 4 °C. [b]Generated in situ by Ph_3PAuCl and AgOTf. [c]2 mol % of catalysts were used. [d]Reaction conducted at −20 °C.

while the yield of 6-*endo-dig* counterpart **3a** remained 45% (entry 8). The control experiment revealed that triflic acid alone could not catalyze the cycloisomerization (entry 9). The addition of base such as DBU or TBAF led to the decomposition of **2a** into the *o*-phenylethynylbenzaldehyde **1a** via the retro-Henry process, and no cyclization products were detected.

With the optimized conditions in hand, we started to examine the substrate scope of this reaction sequence. The Henry reactions of **1a**−**o** were performed following the general procedure under the established conditions. After simple treatment,[12] the crude products **2a**−**o** were directly subjected to the Au(I)-catalyzyed cycloisomerization reactions. The results are summarized in Table 4.

Gratifyingly, the stereochemistry of intermediate **2a** was well preserved during cyclization through both 6-*endo-dig* and 5-*exo-dig* ways under the reaction conditions, providing almost equal amounts of 1*H*-isochromene **3a** and 1,3-dihydroisobenzofurans **4a** with excellent enantiopurity (98% ee, Table 4, entry 1). Another interesting result related to the regioselectivity was observed during investigation of the cyclization of other intermediates **2b**−**o**. The regioselectivity between 6-*endo-dig* and 5-*exo-dig* was very poor for **2a**, while in the case of 4-Me-Ph-substituted **2b**, the ratio of **3b** to **4b** was raised to 3:1 (entry 2). 3-Me-Ph and 2-Me-Ph substrates **2c** and **2d** were also examined, forming 1*H*-isochromenes **3c** and **3d** as main products versus **4c** and **4d**, respectively (entries 3 and 4). For **2e**, which bears a mesityl group on the alkynyl, the 6-*endo-dig* product **3e** was generated exclusively in high yield (entry 5). From these preliminary results, we realized that a direct dependence on the electronic nature of the alkynyl substituent may exist in the cycloisomerization step. Thus, further investigation of alkynylbenzaldehydes with electro-richer

Table 4. Scope of the Asymmetric Henry Reaction/Gold-Catalyzed Cycloisomerization Sequences[a]



1a-o 2a-o 3a-o 4a-l

1a (R=Ph) **1b** (R=4-Me-Ph) **1c** (R=3-Me-Ph) **1d** (R=2-Me-Ph) **1e** (R=Mes) **1f** (R=4-MeO-Ph) **1g** (R=3,4-diMeO-Ph) **1h** (R=4-F-Ph) **1i** (R=4-Cl-Ph) **1j** (R=3-Cl-Ph) **1k** (R=2-Cl-Ph) **1l** (R=4-Ac-Ph) **1m** (R=*n*-Bu) **1n** (R=*t*-Bu) **1o** (R=Pent)

entry	substrate	*T* (°C), time (h)[b]	ratio of **3**/**4**[c]	yield of **3**/**4** (%)	ee of **3**/**4**[d] (%)
1	**1a**	−40, 30	1:1	43/42	98/98
2	**1b**	−40, 48	3:1	64/21	97/92
3	**1c**	−40, 36	2:1	58/28	97/94
4	**1d**	−40, 36	6:1	72/11	91/nd[e]
5[f]	**1e**	−20, 40	>30:1[g]	92/nd	97/nd
6[f]	**1f**	−20, 72	9:1	77/nd	93/nd
7[f]	**1g**	−20, 36	9:1	85/nd	92/nd
8[f]	**1h**	−40, 30	1:1	46/44	97/97
9[f]	**1i**	−20, 48	1:1.5	38/55	96/94
10	**1j**	−20, 24	1:4	16/68	95/92
11	**1k**	−20, 24	1:3	20/61	95/75
12[f]	**1l**	−40, 60	1:5	15/76	nd/90
13	**1m**	−40, 24	24:1	82/nd	98/nd
14	**1n**	−40, 24	>30:1[g]	87/nd	98/nd
15	**1o**	−40, 24	25:1	80/nd	98/nd
16[h]	**1a**	−40, 36	1:1	45/43	98/96

[a]Unless otherwise stated, reactions were performed with 0.2 mmol of **1** and 25 equiv of nitromethane in the presence of 5 mol % of **L1**−Cu(II) complex and 50 mol % of TEA in 2 mL of diethyl ether at the indicated temperature. [b]Parameters of the Henry reaction. [c]Determined by ^{1}H NMR of the crude product. [d]Determined by chiral HPLC analysis. [e]Not determined. [f]Henry reaction carried out in Et_2O/THF (1:1). [g]The other isomer was not observed on ^{1}H NMR spectrum. [h]Reaction carried out on 2 mmol scale.

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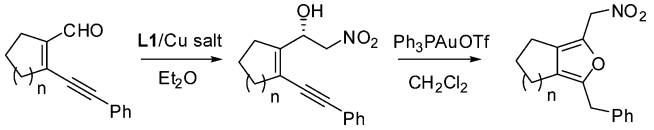
groups such as 4-MeO-Ph (**1f**)[13] and 3,4-diMeO-Ph (**1g**) seemed to be necessary. As expected, the products **3f** and **3g** with six-membered ring were predominantly generated (9:1) (entries 6 and 7). In addition, other functional groups with different induction ability were also taken into consideration. The 4-F-Ph-substituted **2h** exhibited similar selectivity with **2a** (entry 8), while intermediate **2i** with a 4-Cl-Ph preferred 5-*exo-dig* cyclization to give product **3i** and **4i** in the ratio of 1:1.5 (entry 9). When the substituents were changed to *m*- or *o*-chlorophenyl (**1j** and **1k**), the selectivity between the 6-*endo-dig* and 5-*exo-dig* pathways was further improved to 1:4 and 1:3, respectively (entries 10 and 11). The reaction of **2l** with a more electron-deficient acetyl group furnished the 1,3-dihydroisobenzofuran **4l** preferentially (entry 12). In some cases, a slight lose of enantiopurity was observed for 5-*exo-dig* products **4**, which might be ascribed to the subsequent side reaction of 1,3-dihydroisobenzofuran.[14]

Moreover, alkylethynylbenzaldehydes **1m−o** were also examined. The isomerization of intermediates **2m−o** generated by Henry reaction underwent smoothly under the reaction conditions, and almost only the 6-*endo-dig* products **3m−o** were afforded in good yields with excellent enantioselectivities (entries 13−15). The reaction sequence of **1a** can be enlarged to 2 mmol scale without notable lose of yield and enantioselectivity (entry 16). The structures of **3m** and **3o** were easily determined by ^{1}H NMR spectroscopy since the proton on the olefin was not split by the methylene of R group. Besides, the structures of **3a** and **4l** were confirmed unambiguously by X-ray diffraction.[15] Thus, the structural assignment of other analogues was given by comparison of their NMR spectra.

Besides *o*-alkynyl benzaldehydes **1a−o**, 2-alkynylcycloalkene aldehydes were also prepared and tested under the optimized conditions to expand the scope of this reaction sequence. The intermediates **2p** and **2q** were smoothly produced by the Henry reaction. However, during the gold(I)-catalyzed cycloisomerization, achiral tetrasubstituted furans **5p** or **5q**, rather that the expected chiral cyclized products, were produced as the major products, possibly due to the rapid 1,5-hydride shift driven by the formation of aromatic system (Scheme 1).

Scheme 1. Reactions of 2-Alkynylcycloalkene Aldehydes



1p, n=1
1q, n=2

2p-2q

5p, 60 % yield
5q, 56 % yield

From the results obtained with **1a−o**, it is evident that the regioselectivity of cycloisomerization is dependent on the electronic property of alkyne. The alkyne substrate with an electron-donating group (EDG) has a tendency to react in a 6-*endo-dig* way to form 1-*H*-isochromene, while that bearing an electron-withdrawing (EWG) favors the 5-*exo-dig* manner to offer 1,3-dihydroisobenzofuran. These observations are in accordance with some previous reports about the cycloisomerizaiton of alkynols[16] or alkynylimines.[17] As depicted in Figure 1, the EDGs would push the electron atmosphere of the triple bond toward Cα and decrease the electronic density around Cβ, which favors Cβ toward a nucleophilic attack to

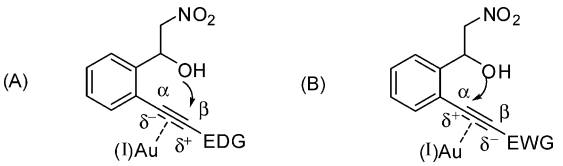


Figure 1. Influence of the substituent at Cβ on triple bond polarization.

yield 6-*endo-dig* product (A). Similarly, the EWGs would decrease the electron density around Cα, leading to the formation of a 5-*exo-dig* propensity (B).

To gain further insight of our assumption, we analyzed the chemical shifts of the alkyne carbon of Henry products **2a,b,f,h−i,l−o**.[18] To avoid the influence of steric or anisotropic effect, the phenyl groups with *ortho* or *meta* substituents were excluded. The alkyne carbon chemical shifts were assigned by two-dimensional HMBC experiments, and the ^{13}C NMR curves are drawn in Figure 2. As compared to **2a** (R = Ph), the EDG caused a downfield shift of Cβ and an upfield shift of Cα, indicating nucleophilic attack at Cβ is favored in the hydroalkoxylation, and this speculation is in accordance with our experimental results (Table 4). On the other hand, when Cβ was substituted by EWG such as chloride and acetyl, the shift of Cα and Cβ changed conversely and as a consequence the attack at Cα is favored.

Additionally, the influence of the substituent on the phenyl at Cα-end was also surveyed by performing the reaction of substrates **2r** and **2s** (Scheme 2). The cycloisomerization of **2r** with a 5-methoxyl group on the phenyl at Cα-end gave **3r** and **4r** with poor regioselectivity. This reaction was performed with 5 mol % of catalyst but without triflic acid because of the instability of the 5-*exo-dig* product **4r** under the reaction conditions. The cycloisomerization of **2s** with a 5-nitro group happened under the standard conditions to furnish an inseperable mixtue of **3s** and **4s** at a ratio of 4:1 as determined by ^{1}H NMR.

The chemical shifts of the alkyne carbon of **2r** and **2s** were also studied and compared with that of **2a** (Figure 3). The Cβ of **2r** is slightly upfield shifted after introducing a methoxyl group and the 5-*exo-dig* manner would be favored. However, only a small amount of **4r** was isolated by column chromatography, which may be ascribed to the decomposition of **4r** during isolation. On the other hand, the ^{13}C NMR spectrum of **2s** reveals a downfield shift of Cβ and upfield shift of Cα, favoring the nucleophilic attack at Cβ to afford the 6-*endo-dig* product **3s** as the major isomer. From these results, we can speculate that the influence of substituents on the phenyl at Cα-end is not as significant as those on the phenyl of Cβ-end.

In conclusion, we have developed a novel asymmetric Henry reaction/gold catalyzed cycloisomerization sequence for the synthesis of chiral 1*H*-isochromenes and 1,3-dihydroisobenzofurans frameworks under mild conditions. The chirality was introduced by the C_1-symmetric chiral diamine-Cu(II) complex catalyzed Henry reaction and preserved in the Au(I) catalyzed cycloisomerization. A pronounced electronic effect on the regioselectivity of cycloisomerization was observed. By tuning the electronic property of the substituents, many substrates could be selectively transformed to one major product. Further study on the methodology for constructing chiral heterocycles is ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Solvents were purified according to the standard procedures and distilled before use. Reagents and starting

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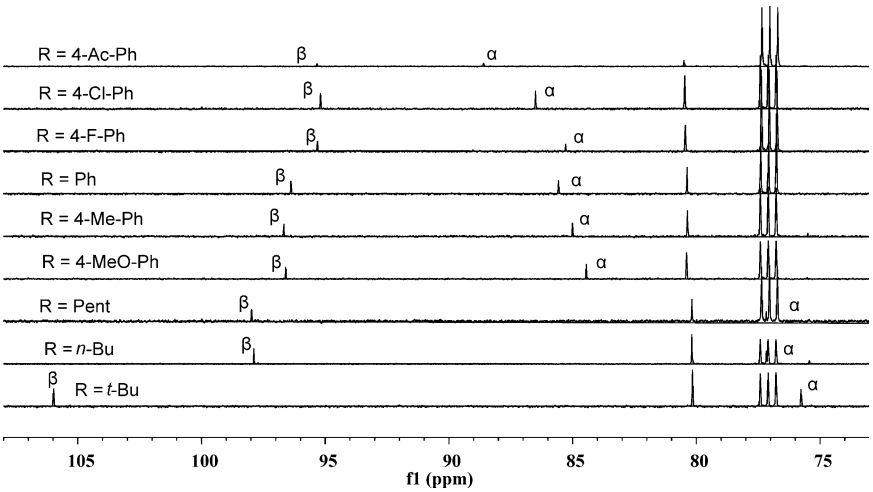
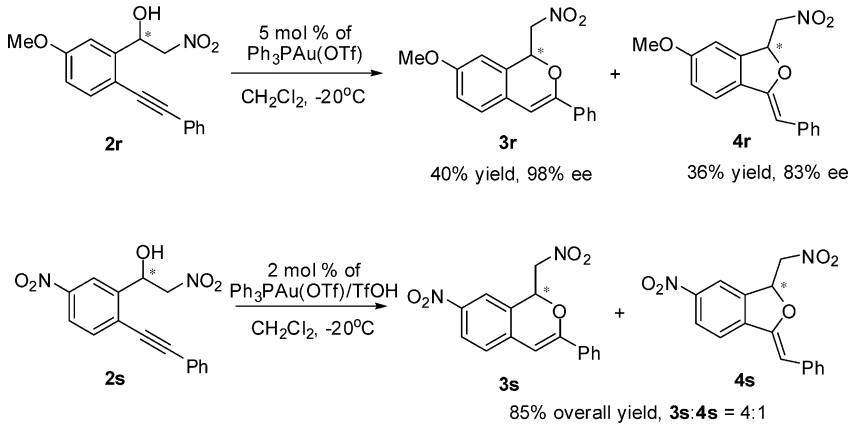


Figure 2. Experimental ^{13}C NMR spectra of the Henry products.

Scheme 2. Reactions of nitroalcohols 2r and 2s



materials purchased from commercial suppliers were used without further purification unless otherwise stated. For thin-layer chromatography (TLC), silica gel plates GF254 were used, and compounds were visualized by irradiation with UV light, I_2, or by treatment with basic $KMnO_4$. NMR spectra were measured on a 400 MHz spectrometer. ^1H NMR chemical shifts were reported in ppm with tetramethylsilane (TMS, δ 0 ppm) as the internal standard. Data for ^1H NMR are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Data for ^{13}C NMR are reported as ppm. High resolution mass spectral analyses (HRMS) were measured using APCI ionization. High performance liquid chromatography (HPLC) analysis was performed on chiral columns. Optical rotations were measured in the solvent indicated. Flash chromatography was carried out on silica gel 200−300 mesh.

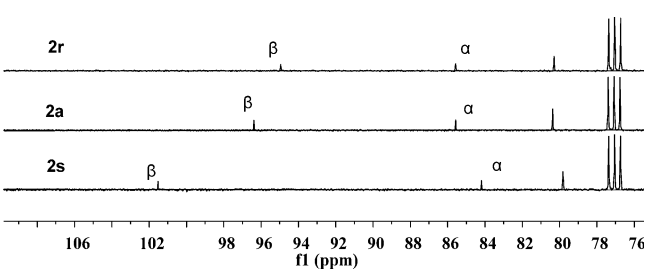


Figure 3. Experimental ^{13}C NMR spectra of the Henry products **2r** and **2s**.

Preparation of Substrates 1a−s. The 2-alkynylbezaldehydes **1a−o,r−s** were prepared by Pd/Cu catalyzed Sonogashira coulping between the corresponding 2-bromobenzaldehyde and terminal acetylenes or between 2-ethynylbenzaldehyde and corresponding iodobenzene according to refs 17 and 19, and the ^1H and ^{13}C NMR of the products are in agree with published data. 2-Alkynylcycloalkene aldehydes **1p** and **1q** were also prepared according to the literature.[20]

Typical Procedure for the Asymmetric Henry Reaction and Gold-Catalyzed Cycloisomerization Sequence. Ligand **L1** (2.4 mg, 0.01 mmol, 5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2 mg, 0.01 mmol, 5 mol %) were added to 2 mL of indicated solvent, and the mixture was stirred for 2 h at room temperature to afford a blue solution. To the mixture the *o*-phenylethynylbenzylaldehyde **1a** (41 mg, 0.2 mmol) was added, and the solution was then cooled to −40 °C, stirred, and followed by the addition of nitromethane (270 μL, 5 mmol) and TEA (14 μL, 0.1 mmol). The stirring was continued until the aldehyde was fully consumed as indicated by TLC, and then 200 μL of 2 M HCl and 2 mL of water were added to quench the reaction. The mixture was extracted with ether for three times, and the combined organic layer was dried over anhydrous Na_2SO_4. After concentrated under vacuo, the crude product was dissolved in 3 mL of dichloromethane and cooled to −20 °C. To the solution, 2 mol % of TfOH, Ph_3PAuCl, and AgOTf was added successively and the mixture was stirred for additional 0.5−2 h until **2a** was completely consumed as indicated by TLC.[21] At this point, saturated brine (1 mL) was added under stirring. After the organic layer was separated, the aqueous phase was extracted with ether. The combined organic phase was dried over anhydrous $MgSO_4$, concentrated and purified by flash chromatography to afford the cycloisomerization products **3a** and **4a**.

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Preparation of Racemic Products. All the racemic compounds were prepared by the cycloisomerization of the corresponding racemic nitrolalcohols **2a**−**s** which were obtained by the Henry reaction catalyzed by 30 mol % of triethylamine with 20 equiv of nitromethane in dichloromethane at room temperature.

2-Nitro-1-(2-(phenylethynyl)phenyl)ethanol (2a): $[\alpha]^{25}_{D}$ = +28.64 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.58−7.51 (m, 3H), 7.44−7.29 (m, 5H), 6.00 (d, *J* = 9.4 Hz, 1H), 4.80 (dd, *J* = 13.1, 2.4 Hz, 1H), 4.52 (dd, *J* = 13.1, 9.8 Hz, 1H), 3.00 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 132.3, 131.6, 129.1, 129.0, 128.6, 128.5, 125.7, 122.3, 120.6, 96.4, 85.6, 80.4, 69.6; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 28.2, t_{minor} = 31.2, 98% ee.

1-(Nitromethyl)-3-phenyl-1*H*-isochromene (3a): $[\alpha]^{25}_{D}$ = −191.91 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.61 (m, 2H), 7.44−7.29 (m, 4H), 7.24 (td, *J* = 7.5, 1.2 Hz, 1H), 7.20−7.08 (m, 2H), 6.50 (s, 1H), 6.15 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.96 (dd, *J* = 12.4, 10.3 Hz, 1H), 4.37 (dd, *J* = 12.4, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 133.4, 130.8, 129.6, 129.4, 128.5, 127.3, 125.3, 125.2, 124.7, 124.4, 100.2, 76.6, 74.9; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{14}NO_3$ (M + H^+) 268.0968, found 268.0967; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 17.2, t_{minor} = 22.0, 98% ee.

(*Z*)-1-Benzylidene-3-(nitromethyl)-1,3-dihydroisobenzofuran (4a): $[\alpha]^{25}_{D}$ = −101.35 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.41−7.27 (m, 4H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.31 (dd, *J* = 8.3, 3.7 Hz, 1H), 6.00 (s, 1H), 4.74 (dd, *J* = 13.3, 3.8 Hz, 1H), 4.65 (dd, *J* = 13.2, 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 136.6, 135.3, 135.2, 129.8, 129.2, 128.5, 128.2, 126.1, 121.5, 120.4, 98.6, 81.3, 78.5; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{14}NO_3$ (M + H^+) 268.0968, found 268.0964; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 18.6, t_{minor} = 22.7, 98% ee.

2-Nitro-1-(2-(*p*-tolylethynyl)phenyl)ethanol (2b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H), 7.28 (td, *J* = 7.5, 1.2 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.94 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.74 (dd, *J* = 13.1, 2.4 Hz, 1H), 4.45 (dd, *J* = 13.1, 9.9 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 139.3, 132.2, 131.5, 129.4, 128.9, 128.5, 125.6, 120.8, 119.2, 96.7, 85.0, 80.4, 69.7, 21.6.

1-(Nitromethyl)-3-*p*-tolyl-1*H*-isochromene (3b): $[\alpha]^{25}_{D}$ = −191.90 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.27−7.04 (m, 5H), 6.45 (s, 1H), 6.13 (dd, *J* = 10.2, 2.7 Hz, 1H), 4.95 (dd, *J* = 12.3, 7.2 Hz, 1H), 4.36 (dd, *J* = 12.3, 3.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 139.6, 130.9, 130.6, 129.6, 129.2, 127.0, 125.2, 124.6, 124.4, 99.5, 76.5, 74.9, 21.4; HRMS (APCI, *m*/*z*): calcd for $C_{17}H_{16}NO_3$ (M + H^+), 282.1125, found 282.1135; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 21.0, t_{minor} = 22.5, 97% ee.

(*Z*)-1-(4-Methylbenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4b): $[\alpha]^{25}_{D}$ = −77.05 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.54 (m, 3H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 6.32 (dd, *J* = 8.3, 3.4 Hz, 1H), 5.99 (s, 1H), 4.75 (dd, *J* = 13.2, 3.7 Hz, 1H), 4.66 (dd, *J* = 13.1, 8.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 136.5, 135.9, 135.3, 132.4, 129.7, 129.2, 129.0, 128.2, 121.4, 120.3, 98.6, 81.2, 78.6, 21.3; HRMS (APCI, *m*/*z*): calcd for $C_{17}H_{16}NO_3$ (M + H^+), 282.1125, found 282.1133; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 28.4, t_{minor} = 26.0, 92% ee.

2-Nitro-1-(2-(*m*-tolylethynyl)phenyl)ethanol (2c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.45−7.28 (m, 4H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 5.98 (dd, *J* = 9.6, 1.6 Hz, 1H), 4.79 (dd, *J* = 13.1, 2.4 Hz, 1H), 4.51 (dd, *J* = 13.1, 9.8 Hz, 1H), 3.01 (br, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 138.3, 132.3, 132.2, 129.9, 129.0, 128.7, 128.5, 128.4, 125.7, 122.1, 120.7, 96.6, 85.3, 80.4, 69.7, 21.2.

1-(Nitromethyl)-3-*m*-tolyl-1*H*-isochromene (3c): $[\alpha]^{25}_{D}$ = −142.79 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.42 (m, 2H), 7.32 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.22 (td, *J* = 7.5, 1.3 Hz, 1H), 7.19−7.09 (m, 3H), 6.47 (s, 1H), 6.13 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.95 (dd, *J* = 12.4, 10.2 Hz, 1H), 4.35 (dd, *J* = 12.4, 3.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 138.1, 133.3, 130.8, 130.3, 129.6, 128.4, 127.2, 125.9, 125.3, 124.7, 124.4, 122.5, 100.2, 76.5, 74.9, 21.5; HRMS (APCI, *m*/*z*) calcd for $C_{17}H_{16}NO_3$ (M + H^+), 282.1125, found 282.1131; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 26.5, t_{minor} = 23.0, 97% ee.

(*Z*)-1-(3-Methylbenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4c): $[\alpha]^{25}_{D}$ = −69.00 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.53−7.42 (m, 3H), 7.39 (td, *J* = 7.4, 0.9 Hz, 1H), 7.34−7.28 (m, 1H), 7.28−7.20 (m, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.33 (dd, *J* = 8.4, 3.8 Hz, 1H), 5.99 (s, 1H), 4.76 (dd, *J* = 13.2, 3.9 Hz, 1H), 4.67 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 137.9, 136.5, 135.2, 135.1, 129.8, 129.2, 129.0, 128.4, 127.0, 125.4, 121.5, 120.4, 98.7, 81.3, 78.6, 21.6; HRMS (APCI, *m*/*z*) calcd for $C_{17}H_{16}NO_3$ (M + H^+), 282.1125, found 282.1119; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 24.7, t_{minor} = 23.5, 94% ee.

2-Nitro-1-(2-(*o*-tolylethynyl)phenyl)ethanol (2d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.60−7.49 (m, 2H), 7.41 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 7.30−7.15 (m, 3H), 6.01 (dd, *J* = 9.7, 1.7 Hz, 1H), 4.79 (dd, *J* = 13.4, 2.5 Hz, 1H), 4.53 (dd, *J* = 13.3, 9.8 Hz, 1H), 3.01 (br, 1H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 139.2, 132.6, 132.2, 129.7, 129.1, 129.0, 128.5, 125.9, 125.8, 122.2, 121.0, 95.1, 89.4, 80.2, 69.4, 20.8.

1-(Nitromethyl)-3-*o*-tolyl-1*H*-isochromene (3d): $[\alpha]^{25}_{D}$ = −56.62 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.39 (m, 1H), 7.32 (td, *J* = 7.5, 1.3 Hz, 1H), 7.29−7.17 (m, 4H), 7.10 (ddd, *J* = 10.3, 7.6, 0.7 Hz, 2H), 6.14 (dd, *J* = 9.8, 3.4 Hz, 1H), 6.04 (s, 1H), 5.06 (dd, *J* = 12.7, 9.8 Hz, 1H), 4.51 (dd, *J* = 12.7, 3.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 136.5, 134.1, 130.9, 130.8, 129.5, 129.1, 129.0, 127.3, 125.9, 124.7, 124.5, 124.1, 104.5, 76.8, 74.8, 20.9; HRMS (APCI, *m*/*z*) calcd for $C_{17}H_{16}NO_3$ (M + H^+), 282.1125, found 282.1129; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 95:5, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 18.0, t_{minor} = 20.4, 91% ee.

(*Z*)-1-(2-Methylbenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4d). Compound **4d** was generated as a minor product, typical peaks: ^{1}H NMR (101 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.16 (s, 1H), 4.76 (dd, *J* = 13.2, 4.1 Hz, 1H), 4.69 (dd, *J* = 13.2, 8.1 Hz, 1H).

1-(2-(Mesitylethynyl)phenyl)-2-nitroethanol (2e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.3 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33 (td, *J* = 7.5, 1.3 Hz, 1H), 6.89 (s, 2H), 5.99 (d, *J* = 9.9 Hz, 1H), 4.74 (dd, *J* = 13.6, 2.5 Hz, 1H), 4.51 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.46 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 138.7, 132.7, 128.8, 128.5, 128.0, 127.9, 125.8, 121.5, 119.2, 94.0, 93.4, 80.0, 69.2, 21.4, 21.1.

3-Mesityl-1-(nitromethyl)-1*H*-isochromene (3e): $[\alpha]^{25}_{D}$ = 42.72 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 6.8 Hz, 2H), 6.87 (s, 2H), 6.13 (dd, *J* = 9.6, 3.1 Hz, 1H), 5.79 (s, 1H), 5.06 (dd, *J* = 12.6, 9.9 Hz, 1H), 4.54 (dd, *J* = 12.8, 3.3 Hz, 1H), 2.31 (s, 6H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 138.6, 137.1, 131.6, 130.7, 129.5, 128.3, 127.1, 124.4, 124.2, 124.1, 104.7, 77.4, 74.7, 21.1, 19.9; HRMS (APCI, *m*/*z*) calcd for $C_{19}H_{20}NO_3$ (M + H^+), 310.1443, found 310.1448; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90: 10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 12.5, t_{minor} = 14.6, 97% ee.

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)-2-nitroethanol (2f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.55−7.44 (m, 3H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (td, *J* = 7.5, 1.3 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.98 (dd, *J* = 9.8, 1.8 Hz, 1H), 4.79 (dd, *J* = 13.0, 2.4 Hz, 1H), 4.50 (dd, *J* = 13.0, 9.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 139.3, 133.2, 132.0, 128.7, 128.4, 125.6, 121.0, 114.4, 114.3, 96.6, 84.4, 80.4, 69.7, 55.4.

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3-(4-Methoxyphenyl)-1-(nitromethyl)-1*H*-isochromene (3f): $[\alpha]^{25}_{D}$ = −138.11 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.55 (m, 2H), 7.31 (td, *J* = 7.5, 1.1 Hz, 1H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1H), 7.12 (dd, *J* = 11.4, 7.6 Hz, 2H), 6.93−6.86 (m, 2H), 6.37 (s, 1H), 6.11 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.95 (dd, *J* = 12.3, 10.3 Hz, 1H), 4.35 (dd, *J* = 12.3, 3.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 150.3, 131.1, 129.6, 126.9, 126.8, 126.0, 125.0, 124.4, 124.3, 113.9, 98.6, 76.50, 74.9, 55.4; HRMS (APCI, *m*/*z*) calcd for $C_{17}H_{16}NO_4$ (M + H$^+$), 298.1074, found 298.1056; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 70:30, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 37.4, t_{minor} = 30.3, 93% ee.

(*Z*)-1-(4-Methoxybenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4f). Compound **4f** was generated as a minor product, typical peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 8.5, 3.3 Hz, 1H), 5.95 (s, 1H), 4.73 (dd, *J* = 13.2, 3.5 Hz, 1H), 4.60 (dd, *J* = 13.2, 8.6 Hz, 1H).

1-(2-((3,4-Dimethoxyphenyl)ethynyl)phenyl)-2-nitroethanol (2g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.44−7.37 (m, 1H), 7.37−7.31 (m, 1H), 7.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 4.84 (dd, *J* = 13.0, 2.3 Hz, 1H), 4.54 (dd, *J* = 13.0, 10.0 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 148.9, 139.4, 131.9, 128.8, 128.5, 125.6, 125.0, 120.9, 114.5, 114.2, 111.2, 96.8, 84.3, 80.5, 69.8, 56.0, 55.9.

3-(3,4-Dimethoxyphenyl)-1-(nitromethyl)-1*H*-isochromene (3g): $[\alpha]^{25}_{D}$ = −154.88 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 7.29−7.10 (m, 5H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.38 (s, 1H), 6.13 (dd, *J* = 10.4, 3.0 Hz, 1H), 4.98 (dd, *J* = 12.2, 10.4 Hz, 1H), 4.37 (dd, *J* = 12.3, 3.1 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 150.2, 148.9, 131.0, 129.6, 126.9, 126.3, 125.1, 124.5, 124.4, 118.4, 110.9, 108.6, 99.0, 76.6, 75.1, 56.0, 55.9. HRMS (APCI, *m*/*z*) calcd for $C_{18}H_{18}NO_5$ (M + H$^+$), 328.1179, found 328.1198; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 70: 30, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 30.6, t_{minor} = 24.1, 92% ee.

(*Z*)-1-(3,4-Dimethoxybenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4g). Compound **4g** was generated as a minor product, typical peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 9.3, 3.0 Hz, 1H), 5.98 (s, 1H), 4.79 (dd, *J* = 13.0, 3.1 Hz, 1H), 4.60 (dd, *J* = 13.0, 9.4 Hz, 1H).

1-(2-((4-Fluorophenyl)ethynyl)phenyl)-2-nitroethanol (2h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.59−7.49 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.11−7.02 (m, 2H), 6.00 (d, *J* = 9.6 Hz, 1H), 4.79 (dd, *J* = 13.1, 2.3 Hz, 1H), 4.52 (dd, *J* = 13.1, 9.9 Hz, 1H), 2.94 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.9 (d, $^1J_{C,F}$ = 250.7 Hz), 139.5, 133.6 (d, $^3J_{C,F}$ = 8.5 Hz), 132.3, 129.2, 128.5, 125.7, 120.5, 118.4 (d, $^4J_{C,F}$ = 3.5 Hz), 116.0 (d, $^2J_{C,F}$ = 22.2 Hz), 95.3, 85.3, 80.5, 69.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.38.

3-(4-Fluorophenyl)-1-(nitromethyl)-1*H*-isochromene (3h): $[\alpha]^{25}_{D}$ = −197.13 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.59 (m, 2H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 7.24 (td, *J* = 7.5, 1.2 Hz, 1H), 7.19−7.11 (m, 2H), 7.11−7.03 (m, 2H), 6.42 (s, 1H), 6.14 (dd, *J* = 10.3, 3.1 Hz, 1H), 4.95 (dd, *J* = 12.3, 10.4 Hz, 1H), 4.38 (dd, *J* = 12.3, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ163.5 (d, $^1J_{C,F}$ = 249.6), 149.5, 130.6, 129.7, 129.5 (d, $^4J_{C,F}$ = 3.2), 127.3 (d, $^3J_{C,F}$ = 4.2), 127.2, 125.1, 124.7, 124.4, 115.6 (d, $^2J_{C,F}$ = 21.9), 100.0 (d, $^6J_{C,F}$ = 1.7), 76.5, 75.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.34; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{13}FNO_3$ (M + H$^+$), 286.0874, found 286.0858; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 95:5, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 27.8, t_{minor} = 26.5, 97% ee.

(*Z*)-1-(4-Fluorobenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4h): $[\alpha]^{25}_{D}$ = −82.84 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.60 (m, 2H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.42−7.36 (m, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.07−6.97 (m, 2H), 6.31 (dd, *J* = 8.6, 3.5 Hz, 1H), 5.97 (s, 1H), 4.77 (dd, *J* = 13.2, 3.6 Hz, 1H), 4.64 (dd, *J* = 13.2, 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, $^1J_{C,F}$ = 246.2), 153.14 (d, $^6J_{C,F}$ = 2.5 Hz), 136.4, 135.0, 131.5 (d, $^4J_{C,F}$ = 3.3), 129.8 (d, $^3J_{C,F}$ = 4.8), 129.7, 129.3, 121.5, 120.3, 115.4 (d, $^2J_{C,F}$ = 21.4), 97.5, 81.3, 78.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.56; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{13}FNO_3$ (M + H$^+$), 286.0874, found 286.0885; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 21.5, t_{minor} = 23.5, 97% ee.

1-(2-((4-Chlorophenyl)ethynyl)phenyl)-2-nitroethanol (2i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.50−7.44 (m, 2H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.37−7.29 (m, 3H), 5.97 (d, *J* = 9.8 Hz, 1H), 4.76 (dd, *J* = 13.0, 2.3 Hz, 1H), 4.50 (dd, *J* = 13.0, 9.9 Hz, 1H), 3.06 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 135.1, 132.8, 132.3, 129.4, 129.0, 128.5, 125.7, 120.8, 120.3, 95.2, 86.5, 80.5, 69.7.

3-(4-Chlorophenyl)-1-(nitromethyl)-1*H*-isochromene (3i): $[\alpha]^{25}_{D}$ = −93.39 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.6 Hz, 2H), 7.38−7.30 (m, 3H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 13.6, 7.5 Hz, 2H), 6.47 (s, 1H), 6.13 (dd, *J* = 10.3, 3.1 Hz, 1H), 4.93 (dd, *J* = 12.2, 10.5 Hz, 1H), 4.37 (dd, *J* = 12.3, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 135.3, 131.8, 130.4, 129.7, 128.7, 127.5, 126.5, 125.2, 124.9, 124.4, 100.6, 76.5, 75.0; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{13}ClNO_3$ (M + H$^+$), 302.0578, found 302.0572; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 24.2, t_{minor} = 21.0, 96% ee.

(*Z*)-1-(4-Chlorobenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4i): $[\alpha]^{25}_{D}$ = −99.84 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.56 (m, 3H), 7.49−7.38 (m, 2H), 7.34−7.25 (m, 3H), 6.32 (dd, *J* = 8.5, 3.6 Hz, 1H), 5.96 (s, 1H), 4.77 (dd, *J* = 13.2, 3.6 Hz, 1H), 4.65 (dd, *J* = 13.2, 8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 136.6, 134.9, 133.8, 131.4, 129.9, 129.5, 129.4, 128.6, 121.5, 120.5, 97.5, 81.5, 78.4; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{13}ClNO_3$ (M + H$^+$), 302.0578, found 302.0589; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 23.3, t_{minor} = 25.1, 93% ee.

1-(2-((3-Chlorophenyl)ethynyl)phenyl)-2-nitroethanol (2j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.58−7.51 (m, 2H), 7.47−7.39 (m, 2H), 7.38−7.27 (m, 3H), 5.99 (dd, *J* = 9.8, 2.0 Hz, 1H), 4.77 (dd, *J* = 13.0, 2.4 Hz, 1H), 4.52 (dd, *J* = 13.0, 9.8 Hz, 1H), 3.04 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 134.4, 132.4, 131.4, 129.9, 129.8, 129.5, 129.2, 128.6, 125.7, 124.0, 120.1, 94.7, 86.6, 80.4, 69.6.

3-(3-Chlorophenyl)-1-(nitromethyl)-1*H*-isochromene (3j): $[\alpha]^{25}_{D}$ = −110.29 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.56−7.51 (m, 1H), 7.39−7.28 (m, 3H), 7.28−7.24 (m, 1H), 7.17 (dd, *J* = 14.3, 7.5 Hz, 2H), 6.51 (s, 1H), 6.15 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.95 (dd, *J* = 12.3, 10.3 Hz, 1H), 4.39 (dd, *J* = 12.4, 3.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 135.2, 134.6, 130.2, 129.8, 129.7, 129.3, 127.7, 125.3, 125.2, 125.0, 124.4, 123.3, 101.2, 76.5, 75.0.; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{13}ClNO_3$ (M + H$^+$), 302.0578, found 302.0573; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 19.3, t_{minor} = 23.0, 95% ee.

(*Z*)-1-(3-Chlorobenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4j): $[\alpha]^{25}_{D}$ = −122.80 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (t, *J* = 1.8 Hz, 1H), 7.58 (dd, *J* = 13.9, 7.6 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.42 (td, *J* = 7.4, 1.0 Hz, 1H), 7.36−7.30 (m, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.14 (ddd, *J* = 8.0, 1.9, 0.9 Hz, 1H), 6.32 (dd, *J* = 8.2, 3.9 Hz, 1H), 5.94 (s, 1H), 4.78 (dd, *J* = 13.3, 3.9 Hz, 1H), 4.68 (dd, *J* = 13.3, 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 137.1, 136.8, 134.7, 134.2, 129.9, 129.6, 127.9, 126.2, 125.9, 121.5, 120.6, 97.3, 81.5, 78.3; HRMS (APCI, *m*/*z*) calcd for $C_{16}H_{13}ClNO_3$ (M + H$^+$), 302.0578, found 302.0587; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 25.7, t_{minor} = 30.1, 92% ee.

1-(2-((2-Chlorophenyl)ethynyl)phenyl)-2-nitroethanol (2k): ^{1}H NMR (400 MHz, CDCl3) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.61−7.55 (m, 2H), 7.46−7.39 (m, 2H), 7.34 (td, *J* = 7.5, 1.0 Hz, 1H), 7.32−7.23 (m, 2H), 6.03 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.83 (dd, *J* = 13.6, 2.5 Hz, 1H), 4.54 (dd, *J* = 13.6, 9.7 Hz, 1H), 3.25 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 135.8, 133.4, 132.7, 129.9, 129.6, 129.4, 128.5, 126.7, 125.9, 122.4, 120.2, 92.6, 90.7, 80.1, 69.1.

3-(2-Chlorophenyl)-1-(nitromethyl)-1*H*-isochromene (3k): $[\alpha]^{25}_{D}$ = −67.99 (*c*, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ;

^{1}H NMR (101 MHz, $CDCl_3$) δ 7.53 (dd, J = 5.9, 3.5 Hz, 1H), 7.43 (dd, J = 5.8, 3.5 Hz, 1H), 7.34 (dt, J = 7.5, 3.8 Hz, 1H), 7.30 (dd, J = 6.0, 3.5 Hz, 2H), 7.28−7.26 (m, 1H), 7.14 (dd, J = 17.0, 7.5 Hz, 2H), 6.42 (s, 1H), 6.18 (dd, J = 9.7, 3.5 Hz, 1H), 5.12 (dd, J = 12.8, 9.7 Hz, 1H), 4.49 (dd, J = 12.9, 3.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 132.9, 132.7, 130.5, 130.4, 130.2, 130.1, 129.6, 127.8, 126.9, 125.0, 124.9, 124.3, 106.2, 77.2, 75.0; HRMS (APCI, m/z) calcd for $C_{16}H_{13}ClNO_3$ (M + H^+), 302.0578, found 302.0584; HPLC (Chiralpak AD-H, hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 16.9, t_{minor} = 18.6, 95% ee.

(*Z*)-1-(2-Chlorobenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4k). $[\alpha]^{25}_D$ = −64.21 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 8.0, 1.5 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.45−7.39 (m, 1H), 7.39−7.29 (m, 2H), 7.28−7.22 (m, 1H), 7.09 (td, J = 7.9, 1.6 Hz, 1H), 6.47 (s, 1H), 6.32 (dd, J = 8.5, 3.6 Hz, 1H), 4.78 (dd, J = 13.3, 3.6 Hz, 1H), 4.65 (dd, J = 13.3, 8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 136.6, 135.0, 132.9, 132.1, 129.9, 129.7, 129.6, 129.3, 127.0, 126.9, 121.4, 120.9, 93.9, 81.5, 78.4; HRMS (APCI, m/z) calcd for $C_{16}H_{13}ClNO_3$ (M + H^+), 302.0578, found 302.0583; HPLC (Chiralpak AS-H, hexane/i-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 32.7, t_{minor} = 28.6, 75% ee.

1-(4-((2-(1-Hydroxy-2-nitroethyl)phenyl)ethynyl)phenyl)-ethanone (2l): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 6.04 (d, J = 9.7 Hz, 1H), 4.80 (dd, J = 13.1, 2.2 Hz, 1H), 4.55 (dd, J = 13.1, 9.9 Hz, 1H), 3.05 (br, 1H), 2.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 139.9, 136.7, 132.5, 131.8, 129.7, 128.6, 128.5, 127.1, 125.8, 120.0, 95.3, 88.6, 80.5, 69.6, 26.7.

1-(4-(1-(Nitromethyl)-1*H*-isochromen-3-yl)phenyl)ethanone (3l). Compound **3l** was generated as a minor product, typical peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.18 (dd, J = 10.4, 3.2 Hz, 1H), 4.96 (dd, J = 12.3, 10.4 Hz, 1H), 4.41 (dd, J = 12.4, 3.2 Hz, 1H).

(*Z*)-1-(4-Acetylbenzylidene)-3-(nitromethyl)-1,3-dihydroisobenzofuran (4l): $[\alpha]^{25}_D$ = −129.42 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 7.3 Hz, 1H), 7.51−7.40 (m, 2H), 7.35 (d, J = 7.5 Hz, 1H), 6.34 (dd, J = 8.6, 3.5 Hz, 1H), 6.04 (s, 1H), 4.82 (dd, J = 13.3, 3.6 Hz, 1H), 4.66 (dd, J = 13.3, 8.6 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 155.8, 140.4, 136.9, 134.6, 134.3, 130.0, 128.7, 128.0, 121.6, 120.8, 97.7, 81.8, 78.3, 26.5. HRMS (APCI, m/z) calcd for $C_{18}H_{16}NO_4$ (M + H^+), 310.1074, found 310.1103; HPLC (Chiralpak AS-H, hexane/i-PrOH = 60:40, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 52.9, t_{minor} = 29.6, 90% ee.

1-(2-(Hex-1-ynyl)phenyl)-2-nitroethanol (2m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.40 (dd, J = 7.6, 1.1 Hz, 1H), 7.33 (td, J = 7.6, 1.3 Hz, 1H), 7.26 (td, J = 7.6, 1.2 Hz, 1H), 5.89−5.78 (m, 1H), 4.71 (dd, J = 13.2, 2.4 Hz, 1H), 4.46 (dd, J = 13.2, 9.8 Hz, 1H), 3.17 (d, J = 4.4 Hz, 1H), 2.46 (t, J = 7.1 Hz, 2H), 1.67−1.56 (m, 2H), 1.54−1.40 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 132.3, 128.3, 128.2, 125.5, 121.4, 97.9, 80.2, 77.2, 69.5, 30.7, 22.1, 19.2, 13.6.

3-Butyl-1-(nitromethyl)-1*H*-isochromene (3m): $[\alpha]^{25}_D$ = −29.20 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dt, J = 7.5, 3.8 Hz, 1H), 7.20−7.12 (m, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 5.95 (dd, J = 10.3, 3.3 Hz, 1H), 5.69 (s, 1H), 4.88 (dd, J = 12.2, 10.3 Hz, 1H), 4.26 (dd, J = 12.3, 3.3 Hz, 1H), 2.25−2.11 (m, 2H), 1.60−1.45 (m, 2H), 1.44−1.28 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 130.8, 129.4, 126.5, 124.4, 124.3, 123.6, 100.3, 76.7, 74.5, 33.3, 28.5, 22.3, 13.8; HRMS (APCI, m/z) calcd for $C_{14}H_{18}NO_3$ (M + H^+), 248.1281, found 248.1292; HPLC (Chiralpak AS-H, hexane/i-PrOH = 95:5, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 15.5, t_{minor} = 17.4, 98% ee.

1-(2-(3,3-Dimethylbut-1-ynyl)phenyl)-2-nitroethanol (2n): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.39 (dd, J = 7.5, 1.2 Hz, 1H), 7.33 (td, J = 7.6, 1.3 Hz, 1H), 7.29−7.22 (m, 1H), 5.82 (ddd, J = 9.8, 4.2, 2.4 Hz, 1H), 4.71 (dd, J = 13.1, 2.4 Hz, 1H), 4.45 (dd, J = 13.1, 9.9 Hz, 1H), 3.12 (br, 1H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 132.2, 128.4, 128.2, 125.5, 121.2, 106.0, 80.2, 75.8, 69.6, 30.9, 28.3.

3-*tert*-Butyl-1-(nitromethyl)-1*H*-isochromene (3n): $[\alpha]^{25}_D$ = −23.86 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 7.3 Hz, 2H), 6.02 (dd, J = 10.0, 3.2 Hz, 1H), 5.73 (s, 1H), 4.88 (dd, J = 13.0, 10.0 Hz, 1H), 4.26 (dd, J = 13.0, 3.3 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 131.0, 129.4, 126.6, 124.4, 124.2, 124.1, 97.1, 76.4, 74.3, 35.1, 27.7; HRMS (APCI, m/z) calcd for $C_{14}H_{18}NO_3$ (M + H^+), 248.1281, found 248.1298; HPLC (Chiralpak AD-H, hexane/i-PrOH = 95:5, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 14.1, t_{minor} = 16.5, 98% ee.

1-(2-(Hept-1-ynyl)phenyl)-2-nitroethanol (2o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.30−7.26 (m, 1H), 5.85 (dd, J = 9.7, 2.1 Hz, 1H), 4.73 (dd, J = 13.2, 2.4 Hz, 1H), 4.48 (dd, J = 13.2, 9.8 Hz, 1H), 3.03 (br, 1H), 2.46 (t, J = 7.1 Hz, 2H), 1.75−1.56 (m, 2H), 1.50−1.30 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 132.4, 128.3, 128.2, 125.5, 121.4, 98.0, 80.2, 77.2, 69.6, 31.2, 28.3, 22.2, 19.5, 13.9.

1-(Nitromethyl)-3-pentyl-1*H*-isochromene (3o): $[\alpha]^{25}_D$ = −22.84 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (td, J = 7.5, 1.2 Hz, 1H), 7.15 (td, J = 7.5, 1.1 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 5.94 (dd, J = 10.2, 3.3 Hz, 1H), 5.68 (s, 1H), 4.88 (dd, J = 12.3, 10.3 Hz, 1H), 4.26 (dd, J = 12.3, 3.3 Hz, 1H), 2.24−2.10 (m, 2H), 1.62−1.41 (m, 2H), 1.41−1.20 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 130.8, 129.4, 126.5, 124.4, 123.6, 100.3, 76.7, 74.5, 33.6, 31.4, 26.1, 22.4, 14.0; HRMS (APCI, m/z) calcd for $C_{15}H_{20}NO_3$ (M + H^+), 262.1438, found 262.1454; HPLC (Chiralpak AD-H, hexane/i-PrOH = 95:5, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 13.1, t_{minor} = 11.5, 98% ee.

2-Nitro-1-(2-(phenylethynyl)cyclopent-1-enyl)ethanol (2p): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 6.5, 2.9 Hz, 2H), 7.39−7.28 (m, 3H), 5.52−5.39 (m, 1H), 4.61 (dd, J = 12.9, 9.3 Hz, 1H), 4.52 (dd, J = 12.9, 3.3 Hz, 1H), 2.83 (d, J = 3.8 Hz, 1H), 2.71−2.53 (m, 3H), 2.53−2.35 (m, 1H), 1.96 (p, J = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 131.5, 128.7, 128.5, 122.7, 122.6, 96.8, 83.8, 78.6, 67.6, 37.0, 32.0, 22.4.

1-Benzyl-3-(nitromethyl)-5,6-dihydro-4*H*-cyclopenta[*c*]furan (5p): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.2 Hz, 2H), 7.26−7.17 (m, 3H), 5.31 (s, 2H), 3.90 (s, 2H), 2.57 (dd, J = 9.3, 4.8 Hz, 2H), 2.37−2.18 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 137.5, 137.4, 131.7, 130.3, 128.9, 128.5, 126.6, 71.3, 34.0, 31.9, 23.5, 23.4.

2-Nitro-1-(2-(phenylethynyl)cyclohex-1-enyl)ethanol (2q): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.41 (m, 2H), 7.38−7.29 (m, 3H), 5.71−5.58 (m, 1H), 4.62−4.45 (m, 2H), 2.56 (d, J = 4.4 Hz, 1H), 2.47−2.24 (m, 3H), 2.03 (d, J = 18.4 Hz, 1H), 1.75−1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 131.4, 128.5, 128.4, 122.8, 119.1, 95.6, 87.0, 78.8, 70.9, 30.0, 24.0, 22.0, 21.9.

1-Benzyl-3-(nitromethyl)-4,5,6,7-tetrahydroisobenzofuran (5q): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.24−7.14 (m, 3H), 5.31 (s, 2H), 3.89 (s, 2H), 2.57−2.47 (m, 2H), 2.44−2.33 (m, 2H), 1.76−1.62 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 137.9, 135.7, 128.6, 128.5, 126.5, 126.1, 118.5, 70.5, 32.8, 22.9, 22.7, 20.2, 20.1.

2-Nitro-1-(5-nitro-2-(phenylethynyl)phenyl)ethanol (2s): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.5, 2.4 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.61−7.55 (m, 2H), 7.47−7.37 (m, 3H), 6.07 (d, J = 9.7 Hz, 1H), 4.86 (dd, J = 13.3, 2.2 Hz, 1H), 4.53 (dd, J = 13.3, 9.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 141.5, 133.0, 132.0, 130.0, 128.8, 127.1, 123.4, 121.4, 121.2, 101.5, 84.2, 79.8, 68.9.

1*H*-Isochromene **3r** and 1,3-dihydroisobenzofurans **4r** were generated as a mixture which could not be separated by chromatography on silica gel, and the typical peaks are described below.

7-Nitro-1-(nitromethyl)-3-phenyl-1*H*-isochromene (3s): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.28 (dd, J = 10.2, 3.2 Hz, 1H), 5.03 (dd, J = 12.7, 10.2 Hz, 1H), 4.51 (dd, J = 12.7, 3.3 Hz, 1H).

(*Z*)-1-Benzylidene-5-nitro-3-(nitromethyl)-1,3-dihydroisobenzofuran (4s): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, J = 7.7, 3.8 Hz, 1H), 6.20 (s, 1H), 4.87 (dd, J = 13.5, 3.9 Hz, 1H), 4.77 (dd, J = 13.5, 7.9 Hz, 1H).

2-Nitro-1-(5-methoxyl-2-(phenylethynyl)phenyl)ethanol (2r): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.49 (m, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.39−7.31 (m, 3H), 7.20 (d, J = 2.6 Hz, 1H), 6.86 (dd, J = 8.5, 2.7 Hz, 1H), 5.97 (d, J = 9.8 Hz, 1H), 4.82 (dd, J = 13.1, 2.3 Hz, 1H), 4.50 (dd, J = 13.1, 9.9 Hz, 1H), 3.84 (s, 3H), 3.04 (br, J = 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 141.5, 133.8, 131.4, 128.6, 128.5, 122.7, 114.3, 112.5, 111.2, 95.0, 85.6, 80.3, 69.6, 55.5.

7-Methoxy-1-(nitromethyl)-3-phenyl-1*H*-isochromene (3r): $[\alpha]^{25}_D$ = −119.11 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.58 (m, 2H), 7.42−7.29 (m, 3H), 7.11 (d, J = 8.4 Hz, 1H), 6.88 (dd, J = 8.4, 2.5 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 6.46 (s, 1H), 6.09 (dd, J = 10.2, 3.2 Hz, 1H), 4.94 (dd, J = 12.4, 10.3 Hz, 1H), 4.37 (dd, J = 12.4, 3.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 148.2, 133.5, 129.0, 128.5, 126.9, 126.1, 124.9, 123.5, 114.9, 110.3, 100.0, 74.9, 55.5; HRMS (APCI, m/z) calcd for $C_{17}H_{16}NO_4$ (M + H^+) 298.1074, found 298.1065; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90: 10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 27.4, t_{minor} = 30.0, 98% ee.

(*Z*)-1-Benzylidene-5-methoxy-3-(nitromethyl)-1,3-dihydroisobenzofuran (4r): $[\alpha]^{25}_D$ = −53.45 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.35 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.02 (dd, J = 8.5, 2.1 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.29 (dd, J = 8.3, 3.9 Hz, 1H), 5.89 (s, 1H), 4.77 (dd, J = 13.2, 3.9 Hz, 1H), 4.69 (dd, J = 13.2, 8.3 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 153.6, 138.4, 135.6, 128.4, 127.9, 127.6, 125.7, 121.6, 116.7, 106.1, 96.8, 80.9, 78.5, 55.8; HRMS (APCI, m/z) $C_{17}H_{16}NO_4$ (M + H^+) 298.1074, found 298.1080; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 254 nm), t_{major} = 31.9, t_{minor} = 40.9, 83% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray structural data (CIF), NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Experimental Section for the details.
(13) Substrate **1f** could not be completely consumed even after an extended period. Thus, the Henry product **2f** was isolated by flash chromatography and then subjected to the cyclization step.
(14) The decreasing of the ee values of 1,3-dihydroisobenzofurans seemed to have a relationship with the rate of cyclization step. The nitro alcohols **2k** and **2r** endured a slower cycloisomerization and the 1,3-dihydroisobenzofurans **4k** and **4r** suffered significant racemization.
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(21) The cyclization of substrates with an *ortho*-substituent such as **2d**, **2e**, and **2k** underwent more slowly than others and required a longer reaction time.