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Bifunctional thiophosphinamide catalyzed highly enantioselective Michael addition of acetone to (*E*)-2-azido β-nitrostyrenes and the subsequent reductive cyclization

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ABSTRACT

We have proven that primary amine/thiophosphinamide incorporating (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine is an efficient catalyst for the asymmetric Michael addition of acetone to (*E*)-2-azido β-nitrostyrenes. Under the optimal reaction conditions, the corresponding Michael addition products were obtained in excellent yields with almost perfect stereocontrol. Upon treatment with $Et_3SiH/InCl_3$, the Michael addition products could be successfully converted to the related 2-methyltetrahydroquinolines in acceptable yields with moderate to excellent diastereoselectivity and without appreciable loss in optical purity. This process provides a highly enantioselective pathway for the synthesis of biologically important 2-methyltetrahydroquinoline derivatives.

1. Introduction

Among various nitrogen-containing heterocycles, the tetrahydroquinoline ring system is a fascinating and privileged structural motif and is found in various biologically active natural products and pharmacologically relevant therapeutic agents [1]. Particularly, their 2-methyl substituted analogues (2-methyltetrahydroquinolines, 2-MeTHQs) exhibit interesting biochemical activities (Fig. 1). For example, Helquinoline (**1**) is a new tetrahydroquinoline antibiotic from *Janibacter limosus* Hel 1 [2], compound **2**, a kind of CRTH2 antagonists, is beneficial for the treatment of allergic diseases [3], 1-benzenesulfonyl-2-MeTHQ (**3**) demonstrated interesting activity against *Trypanozoma cruzi* with low cytotoxicity [4], *N*-formyl-2-MeTHQ (**4**) functions as a potent EPAC inhibitor [5], I-BET726 (**5**) [6] and 1-acetyl-2-MeTHQ (**6**) [7] are selective BET bromodomain inhibitors. Moreover, as a key scaffold of a variety of phosphoramidite ligands, 2-MeTHQ also has wide application in asymmetric catalysis [8]. Due to the significance of these structural units in drug discovery, medicinal chemistry and asymmetric catalysis, the development of new methodologies for the synthesis of 2-MeTHQ derivatives will be of great importance and remains a challenging task. In contrast to the great progress made in the asymmetric synthesis of optically active THQ derivatives through either organo- or metal catalysis [9], the methodology for the asymmetric synthesis of 2-MeTHQs with high enantioselectivity has been rarely explored. Up to date, two strategies were developed for the organocatalytic asymmetric synthesis of enantiomerically enriched 2-MeTHQs, one is the chiral phosphoric acid catalyzed transfer hydrogenation of 2-methylquinolines [10], the other is an in situ generated chiral supramolecular assembly catalyst promoted asymmetric Michael addition of acetone to 2-azido nitroolefins followed by reductive cyclization [11]. However, the later protocol still suffers from some limitations in the Michael addition step, such as low catalytic activity (72 h is needed to ensure the full conversion), moderate yields (50–65%, only one example is over 90%) and unsatisfactory enantioselectivity (89–92% ee). Recently, we have proved that primary amine/thiophosphinamides are efficient catalysts to promote the Michael addition of acetone to simple [12] and *ortho*-hydroxyl nitroolefins [13] in a highly enantioselective manner. We envisioned that this type of catalyst may demonstrate great advantage over the aforementioned chiral supramolecular

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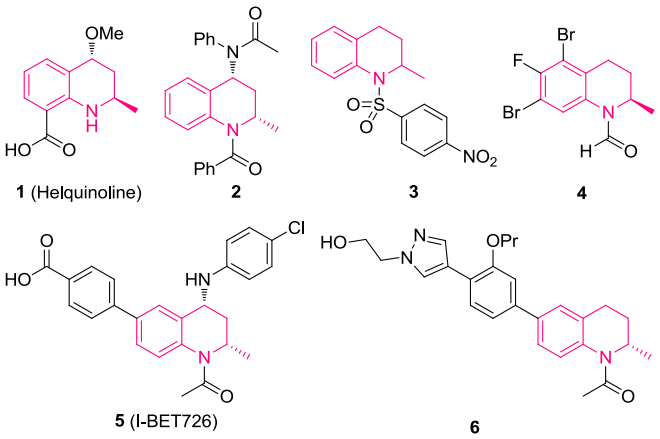


Fig. 1. 2-MeTHQ-based natural products and pharmaceuticals.

assembly catalyst in terms of both catalytic efficacy and enantioselectivity. Herein we report a stereoselective synthesis of 2-MeTHQs via primary amine/thiophosphinamide catalyzed asymmetric Michael addition of acetone to 2-azido nitroolefins and the subsequent reductive cyclization. The corresponding cyclization products were obtained in acceptable yields with good diastereoselectivities and excellent enantioselectivities (93—>99% ee).

2. Results and discussion

We started our investigation by examination of the catalytic activity and stereoselectivity of a series of bifunctional thiophosphoramide or thiophosphinamide-based primary amines **I**–**IV** (Fig. 2) in the model reaction of (*E*)-1-azido-2-(2-nitrovinyl)benzene (**7a**) and acetone in dichloromethane at 20 °C. The results are listed in Table 1.

As shown in Table 1, both the chiral diamine skeleton and substituent on phosphorus atom have an important role on the outcome of the reaction. The use of (1*R*,2*R*)-cyclohexane-1,2-diamine derived thiophosphoramide **I** as the catalyst resulted in the formation of the corresponding adduct **8a** in a quite low yield (13%) with 84% ee (entry 1). However, both the yield (53%) and enantioselectivity (95% ee) were markedly improved by employing thiophosphoramide **II** incorporating a (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine skeleton as the catalyst (entry 2 vs. entry 1). A slightly improvement in both yield and ee value were obtained by replacing the phenoxy group with either ethoxy or phenyl group (entries 3,4 vs. entry 2). Thiophosphinamide **IIc** proved to be the most promising catalyst candidate for this transformation affording the product **3a** in 61% yield with ee value of 98% (entry 4). It is worth noting that increase the rigidity of the diamine skeleton is detrimental to the reaction. The use of thiophosphinamide **III** bearing a rigid (*R*,*R*)-9,10-dihydro-9,10-ethanonanthracene-11,12-diamine scaffold resulted in sharply decrease both in yield and enantioselectivity. Additionally, the nucleophilicity of the priamary amine

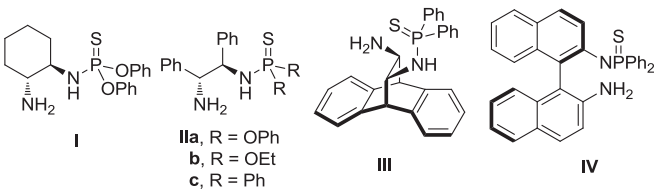
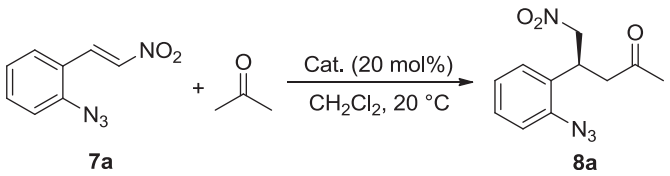


Fig. 2. Catalyst candidates.

Table 1
Catalyst evaluation.[a]



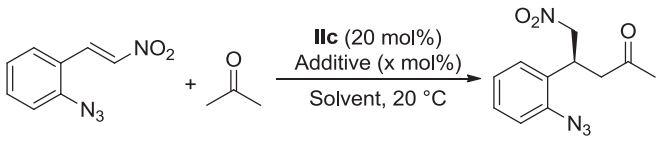
Entry	Catalyst	Time (day)	Yield (%)[b]	Ee (%)[c]
1	**I**	5	13	84
2	**IIa**	7	53	95
3	**IIb**	5.5	58	96
4	**IIc**	4	61	98
5	**III**	4	13	−12
6	**IV**	7	NR	/

[a] All of the reactions were carried out with **7a** (0.3 mmol), acetone (3.0 mmol) and the catalyst (20 mol%) in 1.5 mL of dichloromethane at 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determination by HPLC analysis with a chiral stationary phase.

also have an obvious influence on the catalytic activity. The less nucleophilic thiophosphinamide **IV** derived from (*R*)-1,1′-binaphthyl-2,2′-diamine was completely inactive in the model reaction and failed to afford product **8a**.

With the promising catalyst **IIc** in hand, other factors, such as acidic cocatalyst, solvent, catalyst loading, and reaction temperature, influencing the reaction were thoroughly investigated employing the reaction between (*E*)-1-azido-2-(2-nitrovinyl)benzene (**7a**) and acetone as the model. The results are summarized in Table 2.

Table 2
Optimization of reaction conditions.[a]



Entry	Additive (x mol%)	Solvent	Time (h)	Yield (%)[b]	Ee (%)[c]
1	–	CH_2Cl_2	96	61	98
2	PhOH (20)	CH_2Cl_2	96	40	99
3	$PhCO_2H$ (20)	CH_2Cl_2	10	95	98
4	4-$O_2NC_6H_4CO_2H$ (20)	CH_2Cl_2	72	68	98
5	4-$MeOC_6H_4CO_2H$ (20)	CH_2Cl_2	36	74	98
6	$PhCO_2H$ (5)	CH_2Cl_2	16	95	98
7	$PhCO_2H$ (1)	CH_2Cl_2	40	83	98
8[d]	$PhCO_2H$ (5)	CH_2Cl_2	16	95	98
9[e]	$PhCO_2H$ (5)	CH_2Cl_2	48	86	98
10[d]	$PhCO_2H$ (5)	THF	16	95	98
11[d]	$PhCO_2H$ (5)	Acetone	16	56	99
12[d]	$PhCO_2H$ (5)	CH_3CN	14	60	96
13[d]	$PhCO_2H$ (5)	Ether	16	37	95
14[d]	$PhCO_2H$ (5)	Hexane	20	82	99
15[d]	$PhCO_2H$ (5)	Toluene	16	95	99
16[d,f]	$PhCO_2H$ (5)	Toluene	50	83	98

[a] Unless otherwise specified, all of the reactions were carried out with **7a** (0.3 mmol), acetone (3.0 mmol) and catalyst **IIc** (20 mol%), acidic cocatalyst (x mmol %) in 1.5 mL of solvent at 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determination by HPLC analysis with a chiral stationary phase.
[d] The catalyst loading is 10 mol%.
[e] The amount of catalyst is 5 mol%.
[f] The reaction was performed at 0 °C.

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In an effort to further improve the yield of the model reaction, we first examined the influence of acidic cocatalyst on the reaction (entries 2–5). It was gratifying that unaltered enantioselectivity but dramatically improvement both in the reaction rate and yield was observed with the addition of 20 mol% of benzoic acid as the cocatalyst (entry 3 vs. entry 1). Comparable results were obtained by adjusting the amount of benzoic acid to 5 mol% (entry 6). Further lowering the loading of benzoic acid to 1 mol% led to a sluggish reaction accompanied with decreased yield albeit with maintained ee value (entry 7). Moreover, the amount of catalyst **IIc** could be successfully reduced to 10 mol% without any detrimental effect on the reaction (entry 8). Although the enantioselectivity remained unaltered, further reducing the catalyst loading to 5 mol % resulted in a somewhat sluggish reaction and an obviously decreased yield (entry 9). Additionally, solvent evaluation revealed that the reaction medium have limited influence on the stereocontrol of the reaction (entry 10–15, 95–99% ee). A slightly improved ee value of 99% with unaltered yield was observed by performing the reaction in toluene. No fruitful results were obtained by lowering the reaction temperature to 0 °C (entry 16).

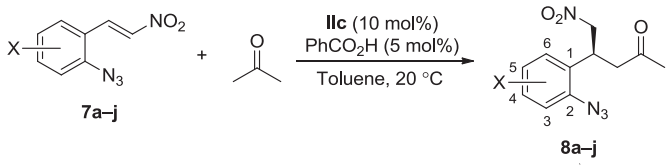
On the basis of the optimized conditions for (*E*)-1-azido-2-(2-nitrovinyl)benzene **7a**, the reaction was further extended to a series of functionalized 1-azido-2-(2-nitrovinyl)benzenes **1b**–**m** (Table 3). As shown in Table 3, the reaction of other 1-azido-2-(2-nitrovinyl)benzenes bearing either electron-withdrawing (entries 2–10) or electron-donating (entry 11) substituent on the benzene ring ran smoothly to give the corresponding Michael addition products in good to excellent yields (85–98%) with uniformly high levels of enantioselectivity (96–>99% ee). In addition, fused 1-azido-2-(2-nitrovinyl)benzene **7l** also worked well to afford the corresponding adduct **8l** in excellent yield with perfect stereocontrol (entry 12). Moreover, 1-azido-2-naphthaldehyde derived nitroolefin **7m** proven to be a suitable reaction partner, giving the desired product **8m** in 91% yield. Unfortunately, the ee value of this product cannot be determined since two enantiomers are inseparable on all the tested chiral stationary phases (entry 13). These results indicate that thiophosphinamide catalyst **IIc** is obviously outperformed Ramachary's supramolecular-organocatalyst, with which ee value ranging from 89% to 92% was obtained.

With these optically pure azido ketoes **8** in hand, the further transformation of them into medicinally significant 2-methyltetrahydroquinolines **9** was carried out through reductive amination using the Bencivenni–Nanni protocol (Table 4) [15]. Upon treatment with $InCl_3$–Et_3SiH in MeOH at 0–25 °C, azido ketoes **8** bearing electron-neutral (entry 1), electron-withdrawing (entries 2–7), electron-donating group (entry 8) on the benzene ring could be successfully to be converted into the corresponding *cis*-2-MeTHQs **9a**–**h** and **9k** in acceptable yields without appreciable loss in optical purity. With respect to diastereoselectivity, except for 5-chloro substituted 2-MeTHQ **9e**, which was obtained as a single diastereomer, all the other 2-MeTHQs were obtained with moderated diastereoselectivities (77/23–86/14 dr). Owing to the existence of an additional azido group, the reductive cyclization of Michael addition products **8i** and **8j** resulted in a complex reaction mixture and failed to give the desired 2-MeTHQ derivatives. Moreover, under the same conditions, the reaction of fused azido ketones **8l** and **8m** only provided the corresponding aromatization products **10** and **11** in moderate yield, which may be formed via the elimination of nitromethane of the in situ generated 4-nitromethyl-3,4-dihydroquinoline intermediates [14].

To determine the relative and absolute configuration of the obtained chiral 2-MeTHQs, a crystalline *N*-tosylated derivative **12** was obtained in moderate yield through the reaction of **8a** and tosyl chloride in refluxing pyridine under nitrogen atmosphere (Scheme 1). The relative and absolute configurations of product **12** were unequivocally determined to be *cis* and (2*R*,4*S*) by single-crystal X-ray diffraction analysis [16]. Since none of the bonds to the stereogenic carbon have been broken during the tosylation reaction, the original configuration of compound **8a** is retained.

The catalytic cycle of the Michael addition reaction was proposed based on experiment results (Scheme 2). The primary amine reacts first with acetone to form an enamine intermediate **A** with the aid of benzoic acid. Subsequently, the enamine nucleophilic attacks the nitro olefin from the *Si*-face to give the addition intermediate **B** via the given transition state formed through hydrogen-

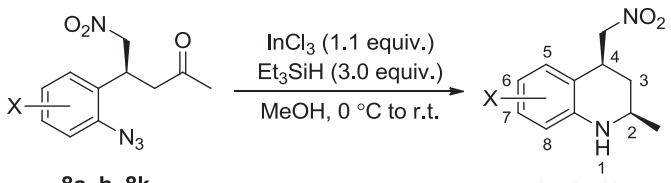
Table 3
Substrate scope of **IIc**-catalyzed asymmetric Michael addition of acetone to (*E*)-1-azido-2-(2-nitrovinyl)benzenes **7**.[a]



Entry	8 (X)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**8a** (H)	16	95	99
2	**8b** (4-F)	24	98	>99
3	**8c** (4-Cl)	16	87	99
4	**8d** (5-Cl)	16	88	>99
5	**8e** (6-Cl)	20	85	98
6	**8f** (4-Br)	16	91	>99
7	**8g** (5-Br)	16	89	96
8	**8h** (4-CN)	16	90	99
9	**8i** (4-N_3)	16	92	>99
10	**8j** (6-N_3)	16	90	>99
11	**8k** (4-Me)	16	92	>99
12	**8l** (4,5-OCH_2O)	16	93	>99
13	**8m** (3,4-CH=CH–CH=CH)	16	91	ND

[a] All of the reactions were carried out with **7** (0.3 mmol), acetone (3.0 mmol) and catalyst **IIc** (10 mol%), $PhCO_2H$ (5 mmol %) in 1.5 mL of toluene at 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determination by HPLC analysis with a chiral stationary phase.

Table 4
Reductive cyclization of the Michael addition product **8**.[a]



Entry	9 (X)	Yield (%)[b]	Dr (*cis*/*trans*)[c]	Ee (*cis*/*trans*) (%)[d]
1	**9a** (H)	60	86/14	98/98
2	**9b** (7-F)	49	82/18	99/>99
3	**9c** (7-Cl)	58	81/19	99/98
4	**9d** (6-Cl)	62	79/21	97/98
5	**9e** (5-Cl)	51	>99/1	93
6	**9f** (7-Br)	61	82/18	>99/>99
7	**9g** (6-Br)	49	84/16	>99/>99
8	**9h** (7-CN)	55	84/16	>99/98
9	**9k** (7-Me)	52	77/23	99/99

[a] Reaction conditions: A mixture of **8** (0.2 mmol), Et_3SiH (0.3 mmol) and $InCl_3$ (0.3 mmol) in 2 mL of methanol was stirred at 0 °C for 2 h, and then reacted at room temperature for 12 h.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by ^1H NMR analysis.
[d] Determination by HPLC analysis with a chiral stationary phase.

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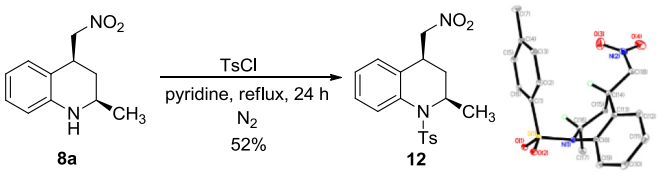
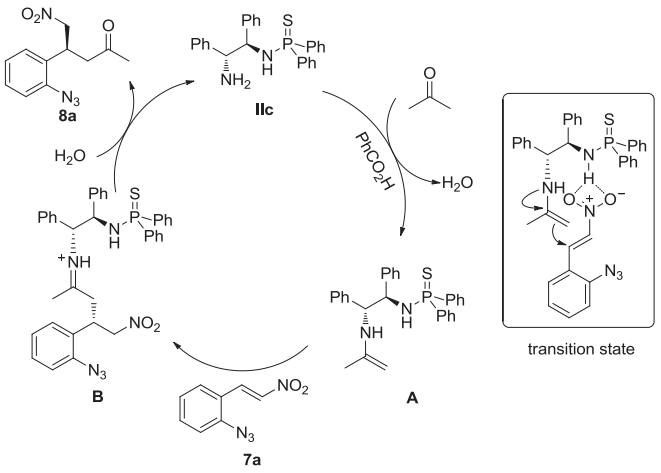


Scheme 1. Tosylation of tetrahydroquinoline **8a** and the X-ray crystal structure of the tosylated product (2*R*,4*S*)-**12**. Most of the hydrogen atoms have been omitted for clarity.



Scheme 2. Proposed catalytic cycle.

bonding interaction between the acidic hydrogen of thiophosphinamide moiety and the nitro group. Finally, hydrolysis of the resulting iminium ion intermediate **B** affords the product (*S*)-**8a** and regenerates catalyst **IIc**.

3. Conclusion

In conclusion, the primary amine/thiophosphinamide catalyzed Michael addition of acetone to (*E*)-1-azido-2-(2-nitrovinyl)benzenes and the subsequent reductive cyclization have been investigated. Under the catalysis of a chiral thiophosphinamide derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, the reaction of a wide range of (*E*)-1-azido-2-(2-nitrovinyl)benzenes ran smoothly to generate the corresponding Michael addition products in excellent yields with uniformly high levels of enantioselectivity (96–>99% ee). Moreover, the obtained δ-azido ketones were successfully converted into 2-methyltetrahydroquinoline derivatives upon treatment with $InCl_3$–Et_3SiH in MeOH in acceptable yields and moderate to excellent diastereoselectivities without any appreciable loss in the enantioselectivities. This method serves as a useful tool for the highly enantioselective synthesis of medicinally important 2-methyltetrahydroquinoline derivatives.

4. Experimental section

4.1. General procedure for the IIc catalyzed asymmetric Michael addition of acetone to (E)-1-azido-2-(2-nitrovinyl)benzenes **7**

A mixture the thiophosphinamide catalyst **IIc** (8.6 mg, 0.02 mmol), benzoic acid (1.2 mg, 0.01 mmol) and acetone (0.6 mmol, 3 equivalents) in toluene (0.5 mL) was stirred at room temperature to form a clear solution. Then, to the resulting solution was added (*E*)-2-azido β-nitrostyrene (0.2 mmol) at the same temperature. After the reaction is complete (monitored by TLC), the reaction mixture was concentrated under reduced pressure to afford the crude addition product **8** which were purified by column chromatography on silica gel (200–300 mesh, petroleum ether/ethyl acetate = 20/1). The title compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and specific rotation data. The enantiomeric excess of the pure products was determined by HPLC analysis using a chiral stationary phase.

*4.1.1. (S)-4-(2-Azidophenyl)-5-nitropentan-2-one (**8a**)*

Pale yellow oil, 71 mg, 95% yield, $[\alpha]_D^{20}$ +20.2 (c 0.87, $CHCl_3$), 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (t, *J* = 7.6 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 4.74 (dd, *J* = 12.4, 7.2 Hz, 1 H), 4.71 (dd, *J* = 12.4, 6.8 Hz, 1 H), 4.21 (quintet, *J* = 6.8 Hz, 1 H), 3.04 (dd, *J* = 18.0, 7.6 Hz, 1 H), 2.95 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.4, 137.8, 129.5, 129.4, 129.1, 125.2, 118.7, 44.6, 35.0, 30.2. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 33.50 (major) and 36.47 min (minor).

*4.1.2. (S)-4-(2-Azido-4-fluorophenyl)-5-nitropentan-2-one (**8b**)*

Pale yellow oil, 78 mg, 98% yield, $[\alpha]_D^{20}$ +13.6 (c 0.60, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (d, *J* = 8.4 Hz, 1 H), 6.79 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.76 (s, 1 H), 4.72 (dd, *J* = 12.4, 7.6 Hz, 1 H), 4.68 (dd, *J* = 12.4, 6.8 Hz, 1 H), 4.16 (quintet, *J* = 6.8 Hz, 1 H), 3.02 (dd, *J* = 18.0, 7.6 Hz, 1 H), 2.93 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.2, 162.6 (d, *J* = 249.7 Hz), 139.5 (d, *J* = 8.3 Hz), 130.9 (d, *J* = 9.2 Hz), 125.3 (d, *J* = 3.0 Hz), 112.3 (d, *J* = 21.2 Hz), 106.2 (d, *J* = 24.9 Hz), 77.6, 44.5, 34.5, 30.2. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 60.50 (major) and 70.23 min (minor).

*4.1.3. (S)-4-(2-Azido-4-chlorophenyl)-5-nitropentan-2-one (**8c**)*

Pale yellow oil, 74 mg, 87% yield, $[\alpha]_D^{20}$ +29.8 (c 0.95, $CHCl_3$), 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (d, *J* = 2.0 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 7.07 (dd, *J* = 8.4, 2.0 Hz, 1 H), 4.72 (dd, *J* = 12.4, 7.2 Hz, 1 H), 4.68 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.17 (quintet, *J* = 6.8 Hz, 1 H), 3.0 (dd, *J* = 18.0, 7.6 Hz, 1 H), 2.92 (dd, *J* = 18.4, 6.4 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.3, 141.1, 139.4, 130.8, 126.0, 115.5, 109.3, 77.6, 44.4, 34.6, 30.2. HRMS (ESI) *m/z* calcd for $C_{11}H_{11}ClN_4NaO_3$ $[M+Na]^+$: 305.0412, found 305.0415. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 12.94 (major) and 14.99 min (minor).

*4.1.4. (S)-4-(2-Azido-5-chlorophenyl)-5-nitropentan-2-one **(8d)***

Pale yellow oil, 75 mg, 88% yield, $[\alpha]_D^{20}$ +18.4 (c 1.05, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.17 (d, *J* = 2.0 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 1 H), 4.72 (dd, *J* = 13.2, 5.2 Hz, 1 H), 4.69 (dd, *J* = 12.8, 6.8 Hz, 1 H), 4.17 (quintet, *J* = 6.8 Hz, 1 H), 3.02 (dd, *J* = 18.4, 7.6 Hz, 1 H), 2.92 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.17 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 204.9, 136.5, 131.3, 130.5, 129.5, 129.1, 119.9, 77.3, 44.3, 34.7, 30.1. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 44.14 (major) and 47.84 min (minor).

*4.1.5. (S)-4-(2-Azido-6-chlorophenyl)-5-nitropentan-2-one (**8e**)*

Pale yellow oil, 77 mg, 85% yield, $[\alpha]_D^{20}$ +14.9 (c 0.95, $CHCl_3$), 98% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, *J* = 8.0 Hz, 1 H), 7.20 (s, 1 H), 7.07 (d, *J* = 8.8 Hz, 1 H), 4.80–4.93 (m, 3 H), 3.11–3.17 (m, 1 H), 2.99–3.04 (m, 1 H), 2.16 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz):

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δ 205.2, 139.8, 136.6, 129.4, 127.6, 126.8, 117.5, 76.4, 44.1, 29.9, 29.7. HRMS (ESI) *m/z* calcd for $C_{11}H_{11}ClN_4NaO_3$ $[M+Na]^+$: 305.0412, found 305.0415. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 43.71 (major) and 47.30 min (minor).

*4.1.6. (S)-4-(2-Azido-4-bromophenyl)-5-nitropentan-2-one (**8f**)*

Pale yellow oil, 89 mg, 91% yield, $[\alpha]_D^{20}$ +18.6 (c 1.2, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (d, *J* = 1.6 Hz, 1 H), 7.23 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 4.72 (dd, *J* = 12.4, 7.2 Hz, 1 H), 4.68 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.16 (quintet, *J* = 6.8 Hz, 1 H), 3.01 (dd, *J* = 18.4, 7.6 Hz, 1 H), 2.92 (dd, *J* = 18.4, 6.4 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.0, 136.5, 131.2, 130.4, 129.5, 129.1, 119.8, 77.3, 44.2, 34.6, 30.1. HRMS (ESI) *m/z* calcd for $C_{11}H_{11}BrN_4NaO_3$ $[M+Na]^+$: 348.9907, found 348.9910. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 48.84 (major) and 53.68 min (minor).

*4.1.7. (S)-4-(2-Azido-5-bromophenyl)-5-nitropentan-2-one (**8g**)*

Pale yellow oil, 87 mg, 89% yield, $[\alpha]_D^{20}$ +11.8 (c 1.7, $CHCl_3$), 96% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 (d, *J* = 8.4 Hz, 1 H), 7.00 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 4.73 (dd, *J* = 12.4, 7.2 Hz, 1 H), 4.69 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.17 (quintet, *J* = 6.8 Hz, 1 H), 3.02 (dd, *J* = 18.4, 7.6 Hz, 1 H), 2.93 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.16 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.0, 137.1, 134.4, 131.3, 120.3, 120.0, 119.5, 77.4, 44.3, 35.1, 30.2. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 99:1, flow rate = 0.8 mL/min, wavelength = 254 nm): t_R = 54.43 (major) and 59.50 min (minor).

*4.1.8. (S)-3-Azido-4-(1-nitro-4-oxopentan-2-yl)benzonitrile (**8h**)*

Pale yellow oil, 74 mg, 90% yield, $[\alpha]_D^{20}$ +21.3 (c 0.66, $CHCl_3$), 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, *J* = 1.2 Hz, 1 H), 7.40 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 4.77 (dd, *J* = 12.8, 7.2 Hz, 1 H), 4.72 (dd, *J* = 12.8, 6.0 Hz, 1 H), 4.24 (quintet, *J* = 6.8 Hz, 1 H), 3.05 (dd, *J* = 18.4, 7.6 Hz, 1 H), 2.96 (dd, *J* = 18.4, 6.4 Hz, 1 H), 2.17 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 204.6, 139.4, 134.8, 130.6, 128.5, 121.7, 117.4, 113.2, 77.2, 44.0, 35.0, 30.2. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 23.82 (major) and 28.36 min (minor).

*4.1.9. (S)-4-(2,4-Diazidophenyl)-5-nitropentan-2-one (**8i**)*

Pale yellow oil, 80 mg, 92% yield, $[\alpha]_D^{20}$ +11.4 (c 0.63, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (d, *J* = 8.4 Hz, 1 H), 6.79 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.76 (d, *J* = 2.0 Hz, 1 H), 4.72 (dd, *J* = 12.4, 7.2 Hz, 1 H), 4.68 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.16 (quintet, *J* = 6.8 Hz, 1 H), 3.02 (dd, *J* = 18.0, 7.2 Hz, 1 H), 2.92 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.3, 141.1, 139.4, 130.8, 126.0, 115.5, 109.3, 77.6, 44.4, 34.7, 30.2. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 19.53 (major) and 22.97 min (minor).

*4.1.10. (S)-4-(2,6-Diazidophenyl)-5-nitropentan-2-one (**8j**)*

Red oil, 78 mg, 90% yield, $[\alpha]_D^{20}$ +21.3 (c 0.72, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (t, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 4.82 (dd, *J* = 12.4, 8.8 Hz, 1 H), 4.76 (dd, *J* = 12.4, 6.8 Hz, 1 H), 4.59–4.67 (m, 1 H), 3.07 (dd, *J* = 18.0, 8.0 Hz, 1 H), 2.95 (dd, *J* = 18.0, 6.0 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.4, 140.3, 129.6, 121.0, 115.0, 76.8, 44.3, 31.1, 29.9. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 99:1, flow rate = 0.5 mL/min, wavelength = 254 nm): t_R = 61.82 min (major).

*4.1.11. (S)-4-(2-Azido-4-methylphenyl)-5-nitropentan-2-one (**8k**)*

Pale yellow oil, 72 mg, 92% yield, $[\alpha]_D^{20}$ +11.8 (c 1.0, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05 (d, *J* = 7.6 Hz, 1 H), 6.96 (s, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 4.71 (dd, *J* = 12.4, 7.6 Hz, 1 H), 4.68 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.16 (quintet, *J* = 6.8 Hz, 1 H), 3.01 (dd, *J* = 18.0, 7.2 Hz, 1 H), 2.92 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.34 (s, 3 H), 2.14 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.6, 139.4, 137.5, 129.2, 126.4, 126.1, 119.2, 77.9, 44.7, 34.7, 30.2, 21.0. HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_4NaO_3$ $[M+Na]^+$: 285.0958, found 285.0960. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 25.80 (major) and 27.84 min (minor).

*4.1.12. (S)-4-(6-Azidobenzo[d][1,3]dioxol-5-yl)-5-nitropentan-2-one (**8l**)*

Red oil, 82 mg, 93% yield, $[\alpha]_D^{20}$ +22.6 (c 0.77, $CHCl_3$), >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.66 (s, 1 H), 6.64 (s, 1 H), 5.97 (s, 2 H), 4.68 (dd, *J* = 12.4, 7.6 Hz, 1 H), 4.64 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.13 (quintet, *J* = 6.8 Hz, 1 H), 2.98 (dd, *J* = 18.0, 7.2 Hz, 1 H), 2.89 (dd, *J* = 18.0, 6.4 Hz, 1 H), 2.15 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.5, 148.1, 145.2, 131.0, 122.2, 108.8, 101.9, 99.6, 77.9, 44.7, 34.7, 30.2. HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_4NaO_5$ $[M+Na]^+$: 315.0700, found 315.0672. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 17.56 (major) and 19.82 min (minor).

*4.1.13. (S)-4-(1-Azidonaphthalen-2-yl)-5-nitropentan-2-one (**8m**)*

Pale yellow oil, 81 mg, 91% yield, $[\alpha]_D^{20}$ +28.4 (c 0.86, $CHCl_3$), the two enantiomers of this compound are inseparable in all the tested chiral stationary phase. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 1 H), 7.63 (t, *J* = 8.0 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 4.83 (dd, *J* = 12.4, 6.8 Hz, 1 H), 4.78 (dd, *J* = 12.4, 4.8 Hz, 1 H), 4.68 (quintet, *J* = 6.8 Hz, 1 H), 3.07 (dd, *J* = 18.0, 7.2 Hz, 1 H), 3.01 (dd, *J* = 18.0, 6.8 Hz, 1 H), 2.16 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.1, 133.8, 129.2, 128.8, 128.5, 127.4, 127.4, 126.8, 124.6, 121.9, 78.3, 45.4, 35.0, 30.2.

*4.2. General procedure for the reductive cyclization of Michael products **8***

To a stirring mixture of anhydrous $InCl_3$ (66 mg, 0.3 mmol), triethylsilane (70 mg, 0.6 mmol) in 2.0 mL of methanal was added a solution of the Michael addition product **8** (0.2 mmol) in 2.0 mL of methanol at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with the addition of 10 mL of water. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), the combined organic layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude tetrahydroquinoline **9**, which was further purified by column chromatography on silica gel (200–300 mesh, petroleum ether/ethyl acetate = 15/1). The title compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and specific rotation data. The enantiomeric excess of the pure tetrahydroquinolines was determined by HPLC analysis using a chiral stationary phase.

*4.2.1. (2R,4S)-2-Methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9a**)*

Yellow solid, m.p. 49–50 °C, 25 mg, 60% yield, $[\alpha]_D^{20}$ = +30.4 (c 0.52, $CHCl_3$), *cis*/*trans* = 86/14, 98% ee for *cis* isomer, 98% ee for *trans* isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 7.04 (t, *J* = 7.6 Hz, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.67 (t, *J* = 7.6 Hz, 1 H), 4.93 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.38 (dd, *J* = 11.6, 10.4 Hz, 1 H), 3.74–3.82 (m, 2 H), 3.41–3.48 (m, 1 H), 2.03–2.08 (m, 1 H), 1.48–1.56 (m, 1 H), 1.23 (d, *J* = 6.0 Hz, 3 H); δ (*trans*-isomer, incomplete data) 4.56 (d, *J* = 8.0 Hz, 2 H), 3.63–3.69 (m, 1 H), 1.26 (d, *J* = 6.0 Hz, 3 H).^{13}C NMR

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($CDCl_3$, 100.6 MHz): δ (*cis*-isomer), 145.5, 128.1, 126.3, 118.7, 117.8, 115.1, 80.6, 46.6, 35.6, 35.0, 22.4; δ (*trans*-isomer, incomplete data), 144.6, 129.4, 128.5, 118.6, 117.4, 114.5, 80.8, 42.2, 31.8, 22.5. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 9.79 (major of *trans*-isomer), 12.96 (minor of *trans*-isomer), 14.52 (major of *cis*-isomer) and 22.31 min (minor of *cis*-isomer).

4.2.2. (2R,4S)-7-Fluoro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9b**)

Yellow solid, m.p. 85–87 °C, 22 mg, 49% yield, $[\alpha]_D^{20}$ = +18.7 (c 0.42, $CHCl_3$), *cis*/*trans* = 82/18, 99% ee for *cis*-isomer, >99% ee for *trans*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 6.88 (dd, *J* = 8.0, 6.8 Hz, 1 H), 6.35 (dt, *J* = 8.4, 2.4 Hz), 6.55 (dd, *J* = 10.4, 2.4 Hz, 1 H), 4.89 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.38 (dd, *J* = 12.0, 9.6 Hz, 1 H), 3.85 (br. s, 1 H), 3.68–3.75 (m, 1 H), 3.41–3.49 (m, 1 H), 2.02–2.07 (m, 1 H), 1.43–1.80 (m, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H); δ (*trans*-isomer, incomplete data) 6.95 (dd, *J* = 8.0, 6.0 Hz, 1 H), 6.19 (dd, *J* = 9.6, 2.4 Hz, 1 H), 4.52 (d, *J* = 0.8 Hz, 1 H), 4.50 (s, 1 H), 3.95 (br. s, 1 H), 3.61–3.65 (m, 1 H), 1.86 (d, *J* = 14.4 Hz, 2 H), 1.25 (d, *J* = 5.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer) 162.6 (d, *J* = 243.9 Hz), 146.8 (d, *J* = 10.8 Hz), 127.5 (d, *J* = 10.1 Hz), 114.3 (d, *J* = 2.6 Hz), 104.3 (d, *J* = 22.0 Hz), 101.1 (d, *J* = 24.3 Hz), 80.3, 46.5, 35.2, 34.5, 22.2; δ (*trans*-isomer, incomplete data) 145.9 (d, *J* = 10.9 Hz), 130.7 (d, *J* = 10.3 Hz), 113.0 (d, *J* = 2.4 Hz), 104.2 (d, *J* = 22.1 Hz), 100.5 (d, *J* = 24.7 Hz), 80.6, 42.1, 35.0, 31.6, 22.3 HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 26.75 (major of *trans*-isomer), 35.81 (minor of *trans*-isomer), 41.52 (major of *cis*-isomer) and 68.78 min (minor of *cis*-isomer).

4.2.3. (2R,4S)-7-Chloro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9c**)

Yellow solid, m.p.: 77–80 °C, 28 mg, 58% yield, $[\alpha]_D^{20}$ = +32.8 (c 0.32, $CHCl_3$), *cis*/*trans* = 81/19, 99% ee for *cis*-isomer, 98% ee for *trans*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 6.86 (d, *J* = 8.4 Hz, 1 H), 6.61 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.51 (d, *J* = 2.0 Hz, 1 H), 4.88 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.38 (dd, *J* = 12.0, 9.6 Hz, 1 H), 3.83 (br. s, 1 H), 3.64–3.74 (m, 1 H), 3.40–3.48 (m, 1 H), 2.04 (ddd, *J* = 12.8, 6.0, 2.4 Hz, 1 H), 1.45–1.53 (m, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H); δ (*trans*-isomer, incomplete data) 6.92 (d, *J* = 8.0 Hz, 1 H), 6.59 (dd, *J* = 7.2, 2.0 Hz, 1 H), 4.50–4.52 (m, 2 H), 3.93 (br. s, 1 H), 1.25 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer), 144.0, 128.0, 126.2, 122.2, 120.0, 116.1, 80.1, 46.5, 35.0, 34.8, 22.2; δ (*trans*-isomer, incomplete data), 143.2, 128.9, 128.5, 115.6, 80.1, 42.2, 35.3, 31.4, 22.3. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}ClN_2O_2$ $[M+H]^+$: 241.0738, found 241.0742. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 36.84 (major of *trans*-isomer), 49.33 (minor of *trans*-isomer), 53.52 (major of *cis*-isomer) and 87.75 min (minor of *cis*-isomer).

4.2.4. (2R,4S)-6-Chloro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9d**)

Yellow solid, m.p. 64–66 °C, 30 mg, 62% yield, $[\alpha]_D^{20}$ = +30.3 (c 0.62, $CHCl_3$), *cis*/*trans* = 79/21, *cis*/*trans* = 79/21, 97% ee for *cis*-isomer, 98% ee for *trans*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 6.98 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.93 (s, 1 H), 6.46 (d, *J* = 8.8 Hz, 1 H), 4.89 (dd, *J* = 12.4, 4.8 Hz, 1 H), 4.38 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.79 (br. s, 1 H), 3.72 (quintet, *J* = 5.2 Hz, 1 H), 3.37–3.48 (m, 1 H), 2.05 (ddd, *J* = 12.4, 5.6, 2.4 Hz, 1 H), 1.45–1.54 (m, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H); δ (*trans*-isomer, incomplete data) 6.44 (d, *J* = 8.8 Hz, 1 H), 4.53 (d, *J* = 8.0 Hz, 2 H), 3.89 (br. s, 1 H), 3.61–3.66 (m, 1 H), 1.83–1.87 (m, 1 H), 1.61–1.69 (m, 1 H), 1.25 (d, *J* = 6.0 Hz, 3 H) ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer) 144.0, 128.0, 126.2, 122.1, 120.0, 116.1, 80.1, 46.5, 35.0, 34.8, 22.2; δ (*trans*-isomer), 143.2, 128.9, 128.5, 121.6, 120.00, 118.7, 115.6, 80.4, 42.2, 35.3, 34.77, 31.4, 22.3. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 25.14 (major of *trans*-isomer), 31.88 (minor of *trans*-isomer), 33.43 (major of *cis*-isomer) and 51.27 min (minor of *cis*-isomer).

4.2.5. (2R,4S)-5-Chloro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9e**)

Yellow solid, m.p. 62–65 °C, 25 mg, 51% yield, $[\alpha]_D^{20}$ = +19.6 (c 0.23, $CHCl_3$), *cis*/*trans* >19/1, 93% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97 (t, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 4.77 (dd, *J* = 12.4, 4.0 Hz, 1 H), 4.42 (dd, *J* = 12.4, 11.6 Hz, 1 H), 3.98–4.01 (m, 2 H), 3.49–3.57 (m, 1 H), 1.91 (d, *J* = 18.0 Hz, 1 H), 1.60 (dd, *J* = 12.8, 4.4 Hz, 1 H), 1.27 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 146.1, 134.8, 129.1, 117.8, 114.3, 112.8, 77.3, 41.9, 33.5, 31.0, 22.3. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 25.14 (major of *trans*-isomer), 31.88 (minor of *trans*-isomer), 33.43 (major of *cis*-isomer) and 51.27 min (minor of *cis*-isomer).

4.2.6. (2R,4S)-7-Bromo-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9f**)

Yellow solid, m.p. 79–81 °C, 35 mg, 61% yield, $[\alpha]_D^{20}$ = +28.0 (c 0.76, $CHCl_3$), *cis*/*trans* = 82/18, >99% ee for *cis*-isomer, >99% ee for *trans*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 6.80 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.67 (s, 1 H), 4.88 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.38 (dd, *J* = 11.2, 6.4 Hz, 1 H), 3.82 (br. s, 1 H), 3.65–3.73 (m, 1 H), 3.40–3.46 (m, 1 H), 2.02–2.07 (m, 1 H), 1.45–1.54 (m, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H); δ (*trans*-isomer, incomplete data) 6.87 (d, *J* = 8.0 Hz, 1 H), 6.66 (s, 1 H), 4.51 (d, *J* = 8.0 Hz, 2 H), 3.91 (br. s, 1 H), 1.25 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer) 146.6, 127.6, 121.6, 120.3, 117.5, 117.3, 80.0, 46.5, 35.0, 34.6, 22.2; δ (*trans*-isomer, incomplete data), 130.7, 120.0, 116.8, 80.3, 42.1, 31.4, 22.3. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}BrN_2O_2$ $[M+H]^+$: 285.0233, found 285.0236. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 29.16 (major of *trans*-isomer), 39.68 (minor of *trans*-isomer), 48.67 (major of *cis*-isomer) and 74.50 min (minor of *cis*-isomer).

4.2.7. (2R,4S)-6-Bromo-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9g**)

Yellow solid m.p. 54–55 °C, 28 mg, 49% yield, $[\alpha]_D^{20}$ +29.8 (c 0.22, $CHCl_3$), *cis*/*trans* = 84/16, >99% ee for *cis*-isomer, >99% ee for *trans*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 7.11 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.06 (s, 1 H), 6.41 (dd, *J* = 8.4, 2.0 Hz, 1 H), 4.89 (dd, *J* = 12.0, 4.8 Hz, 1 H), 4.38 (dd, *J* = 11.2, 10.0 Hz, 1 H), 3.80 (br. s, 1 H), 3.69–3.74 (m, 1 H), 3.37–3.45 (m, 1 H), 2.02–2.07 (m, 1 H), 1.44–1.53 (m, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H); δ (*trans*-isomer, incomplete data) 7.13 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.39 (d, *J* = 8.0 Hz, 1 H), 4.52–4.24 (m, 2 H), 3.91 (s, 1 H), 3.06–3.15 (m, 1 H), 1.2 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer) 144.4, 130.9, 129.0, 120.6, 116.5, 109.1, 80.1, 46.5, 35.0, 34.8, 22.2; δ (*trans*-isomer, incomplete data), 143.6, 131.8, 131.3, 119.3, 116.0, 108.5, 80.4, 42.2, 35.2, 31.3, 22.3. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 14.08 (major of *trans*-isomer), 17.10 (minor of *trans*-isomer), 18.32 (major of *cis*-isomer) and 28.56 min (minor of *cis*-isomer).

4.2.8. (2R,4S)-2-Methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline-7-carbonitrile (**9h**)

Yellow solid, m.p. 140–141 °C, 25 mg, 55% yield, $[\alpha]_D^{20}$ = +16.4 (c 0.34, $CHCl_3$), *cis*/*trans* = 84/16, >99% ee for *cis*-isomer, 98% ee for

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trans-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 7.01 (d, J = 8.0 Hz, 1 H), 6.90 (d, J = 8.0 Hz, 1 H), 6.75 (s, 1 H), 4.90 (dd, J = 12.4, 5.2 Hz, 1 H), 4.44 (dd, J = 12.4, 9.2 Hz, 1 H), 3.99 (br. s, 1 H), 3.72–3.80 (m, 1 H), 3.47–3.52 (m, 1 H), 2.06–2.10 (m, 1 H), 1.49–1.70 (m, 3 H), 1.26 (d, J = 6.4 Hz, 3 H); δ (*trans*-isomer, incomplete data) 7.08 (d, J = 7.6 Hz, 1 H), 6.88 (d, J = 8.4 Hz, 1 H), 4.52 (d, J = 8.0 Hz, 2 H), 4.01 (br. s, 1 H), 1.99–2.02 (m, 1 H), 1.88–1.93 (m, 2 H), 1.28 (d, J = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer) 145.7, 126.9, 123.4, 120.5, 118.8, 117.4, 111.8, 79.4, 46.5, 35.0, 34.5, 22.1; δ (*trans*-isomer, incomplete data) 130.1, 120.1, 117.1, 80.0, 42.3, 35.4, 31.1, 22.2. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 12.56 (major of *trans*-isomer), 16.87 (minor of *trans*-isomer), 18.51 (major of *cis*-isomer) and 25.13 min (minor of *cis*-isomer).

4.2.9. (2R,4S)-2,7-Dimethyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**9k**)

Yellow solid, m.p. 71–73 °C, 23 mg, 52% yield. $[\alpha]_D^{20}$ = +12.8 (c 0.60, $CHCl_3$), *cis*/*trans* = 77/23, 99% ee for *cis*-isomer, 99% ee for *trans*-isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (*cis*-isomer) 6.85 (d, J = 7.6 Hz, 1 H), 6.50 (dd, J = 7.6, 0.8 Hz, 1 H), 6.37 (s, 1 H), 4.91 (dd, J = 12.0, 4.8 Hz, 1 H), 4.35 (dd, J = 12.0, 10.0 Hz, 1 H), 3.70–3.78 (m, 2 H), 3.38–3.43 (m, 1 H), 2.22 (s, 3 H), 2.04 (ddd, J = 8.8, 6.0, 2.8 Hz, 1 H), 1.45–1.54 (m, 1 H), 1.22 (d, J = 6.0 Hz, 3 H); δ (*trans*-isomer, incomplete data) 6.92 (d, J = 7.6 Hz, 1 H), 6.48 (dd, J = 7.6, 1.2 Hz, 1 H), 6.35 (s, 1 H), 4.54 (s, 1 H), 4.52 (d, J = 1.6 Hz, 1 H), 3.61–3.60 (m, 1 H), 3.44–3.49 (m, 1 H), 1.84 (dt, J = 14.0, 2.4 Hz, 1 H), 1.63–1.71 (m, 1 H), 1.24 (d, J = 6.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (*cis*-isomer) 145.3, 138.0, 126.2, 118.8, 115.5, 114.9, 80.6, 46.5, 35.7, 34.7, 22.3, 21.0; δ (*trans*-isomer) 144.5, 138.4, 129.3, 118.5, 115.8, 114.6, 80.9, 42.1, 35.2, 31.9, 22.4, 21.1. HRMS (ESI) m/z calcd for $C_{12}H_{17}N_2O_2$ $[M+H]^+$: 221.1285, found 221.1287. HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 17.68 (major of *trans*-isomer), 22.73 (minor of *trans*-isomer), 25.43 (major of *cis*-isomer) and 45.83 min (minor of *cis*-isomer).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.08.052.

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[14] 6-Methyl-[1,3]dioxolo[4,5-g]quinolone (**10**): white solid, m.p. 152–154 °C, 20 mg, 54% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, J = 8.4 Hz, 1 H), 7.31 (s, 1 H), 7.13 (d, J = 8.4 Hz, 1 H), 7.01 (s, 1 H), 6.08 (s, 2 H), 2.67 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 156.6, 150.5, 147.1, 146.1, 135.0, 123.1, 120.1, 105.4, 102.6, 101.5, 24.9. 2-Methylbenzo[*h*]quinolone (**11**): Pale yellow oil, 24 mg, 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.33 (d, J = 8.0 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 1 H), 7.76 (d, J = 8.8 Hz, 1 H), 7.72 (dt, J = 8.0, 1.6 Hz, 1 H), 7.67 (dt, J = 8.0, 1.6 Hz, 1 H), 7.66 (d, J = 8.8 Hz, 1 H), 2.85 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 157.7, 145.9, 135.9, 133.7, 131.3, 127.9, 127.7, 126.7, 126.6, 125.2, 124.4, 124.1, 122.1, 25.4.
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