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Synthesis of novel thiophene-based chiral ligands and their application in asymmetric Henry reaction

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Novel chiral thiolated amino alcohols were synthesized from norephedrine and thiophene carbaldehydes (methyl- or ethyl-substituted) and applied to the catalytic asymmetric Henry reaction of various aldehydes with nitromethane to provide β-hydroxy nitroalkanols in high conversion (92%). The reaction was optimized in terms of the metal, solvent, temperature and amount of chiral ligand. The corresponding catalyst with $Cu(OTf)_2$ and 2-propanol as the solvent provided the best enantioselectivities (up to 96% ee) of the corresponding nitroalcohols for aliphatic aldehydes. Copyright © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: enantioselective synthesis; Henry reaction; chiral amino alcohols; thiolated amino alcohols; copper complex

Introduction

The Henry or nitro aldol reaction is one of the most important methods for the formation of C–C bond in organic chemistry.[1] The resulting products of this reaction, a coupling between nitroalkanes and carbonyl groups, can be converted into synthetically useful derivatives such as carboxylic acids and amino alcohols and other useful compounds.[2,3] β-Nitroalkanols are useful intermediates in the asymmetric synthesis of the β-receptor agonists (−)-denopamine and arbutamine,[4] the β-blockers (*S*)-metoprolol,[5a] (*S*)-propranolol[5b] and (*S*)-pindolol,[5c] and pharmacologically important β-amino alcohol derivatives such as chloroamphenicol,[6a] ephedrine[6b] and sphingosine.[6c]

The first asymmetric Henry reaction was reported by Sasai *et al.*,[7] who used Lanthanide/1-1′-binaphthol (BINOL) complexes. Since then, various type of catalyst systems, containing metal such as Zn,[8] Co,[9] Mg,[10] Cu[11] and rare earth metal complexes[11a,12] and non-metal-based chiral catalysts have been reported for the asymmetric Henry reaction with chiral ligands such as BINOL,[13] amino alcohols,[8b,14] bisoxazolines,[15] bisoxazolidines,[8c,11c,16] (−)-sparteine,[17] sulfonamides,[18] chiral diimine,[19] *N*,*N*′-dioxides[20] and aminopyridines[21] such as **1a–e** (Scheme 1).

Although many chiral ligands derived from amino alcohols have found applications as catalysts in asymmetric reactions, only a few thiophene-based ligands have been employed in the Henry reaction[22,23] or other asymmetric reactions.[24] Bandini *et al.*[23a] reported a new type of C_2-symmetric diamino ligand (**4**), bearing oligothienyl groups, and their catalytic activity in the asymmetric Henry reaction (Scheme 2).

Thiophene-based ligands (**5**) were used as catalysts for asymmetric Henry reaction by Mansawat *et al.*,[25] who reported that homochiral amino alcohols carrying *N*-2-thienyl methyl substituent provided much better enantioselectivities compared to those with *N*-(2-alkylthio)benzyl substituent for the Henry reaction (Scheme 2).

In our previous studies, norephedrine-based chiral ligands with *N*-substituted chiral pyrrole have been synthesized and applied in the addition of diethylzinc to aldehydes.[26] We showed that the absolute configuration of the norephedrine moiety plays an important role in the configuration of addition products. Herein we report the synthesis of norephedrine-based amino alcohol ligands bearing a substituted thiophene ring and their application in the asymmetric Henry reaction. These ligands were readily prepared in two steps from quite inexpensive commercially available starting materials. These chiral ligands were prepared from the reaction of substituted thiophene-2-carbaldehydes (**6a**,**b**) with both enantiomers of norephedrine (**7**).

Results and Discussion

Synthesis of Chiral Ligands

As shown in Scheme 3, novel chiral ligands were synthesized from 5-substituted thiophene-2-carbaldehyde and both enantiomers of norephedrine.

The formylation of 2-substituted thiophene was performed according to the Vilsmeier–Haack method.[27] Formylated products were reacted with both of enantiomers of norephedrine to form imines in dry benzene under a Dean-Stark trap. Chiral ligands (8a,b and 9a,b) were obtained by reduction of these imines (Scheme 3). After purification of crude products by column chromatography, thiophene ring-containing norephedrine-based amino alcohols (**8a**,**b** and **9a**,**b**) were obtained with 68%, 73%, 70%, 75% chemical yields, respectively (Scheme 3 and Table 1).

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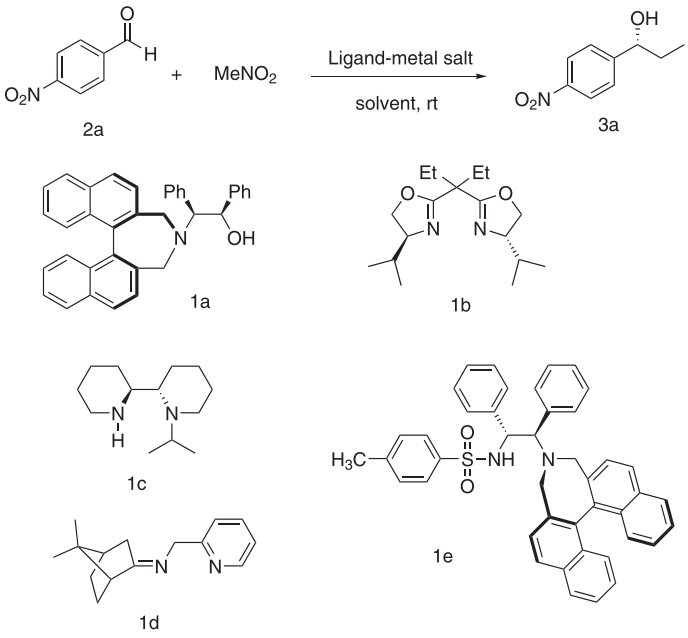
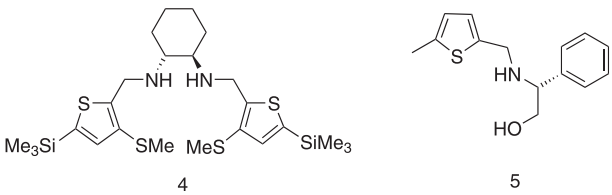


Scheme 1. Different chiral ligands used in asymmetric Henry reaction.



Scheme 2. Chiral thiophene ligands for asymmetric Henry reaction.

The Asymmetric Henry Reaction

The reactivity and enantioselectivity of chiral ligands **8** and **9a**,**b** for the Henry reaction were investigated. The reaction between *p*-nitrobenzaldehyde and nitromethane in the presence of chiral ligand (10% mol) and copper acetate monohydrate ($Cu(OAc)_2.H_2O$, 5 mol %) in 2-propanol (^{i}PrOH) at room temperature was chosen as a model reaction. Initially, all chiral ligands were screened in this model reaction (Scheme 4) and the results are listed in Table 1.

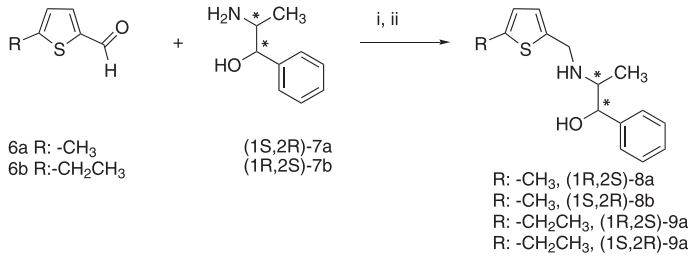
The use of enantiomeric chiral ligands (1*R*,2*S*)-**8a** and (1*S*,2*R*)-**8b** led to opposite enantiomers of β-nitroalkanol with 68% and 74% ee, respectively. It was found out that absolute configuration of β-nitroalkanol is mainly by the stereogenic centers of norephedrine on chiral ligands.[25] Chiral ligands (1*R*,2*S*)-**8a** with (*R*)-configuration at OH-bearing carbon gave the product with an (*R*)-configuration. Chiral ligand (1*S*,2*R*)-**8b** with an (*S*)-configuration at the same stereogenic center gave the (*S*)-product. Thus the configuration of β-nitroalkanol depended on the configuration of the alcohol part of the chiral ligand. Mansawat *et al.*[25] reported a homochiral thiolated amino alcohol which has asymmetric carbon bearing the amino groups. The use of (1*R*,2*S*)-**9a** and (1*S*,2*R*)-**9b** as chiral ligand afforded nitro aldol product **3a** in 90% yield with 65% ee and 87% yield with 67% ee for the major (*S*)-enantiomer, respectively (Table 1, entries 1 and 2).

Since (1*S*,2*R*)-**8b** gave the highest enantioselectivity in the Henry reaction, it was identified as more effective among the chiral ligand series (Table 1, entry 2) and was selected for optimizing further the reaction conditions.

The reactivity and enantioselectivity of the Henry reaction strongly depend upon the nature of the solvent used.[28] Therefore, the Henry reaction was performed in different solvents such as ethanol (EtOH), tetrahydrofuran (THF), CH_2Cl_2 (DCM), MeCN, toluene and *n*-propanol (^{n}PrOH) (Table 2). As can be seen in Table 2, ^{i}PrOH was the most appropriate solvent. MeCN, toluene, THF and DCM gave moderate yields and ee values. It is clear that protic alcoholic solvents are superior to aprotic solvents. It was found out that enantioselectivity increased in the order MeOH < EtOH < ^{n}PrOH < ^{i}PrOH (Table 2, entries 1–7).

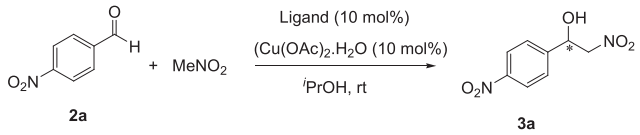
Next, a series of metal salts were screened for the enantioselective Henry reaction using ligand (1*S*,2*R*)-**8b** in ^{i}PrOH. The effect of metal salts was investigated for the model reaction at room temperature. Copper triflate ($Cu(OTf)_2$) was found to be best metal salt for the reaction (Table 3, entry 2). Other salts such as $NiCl_2.6H_2O$, AgOTf, CuI, $CuCl_2.2H_2O$ and $CoCl_2.2H_2O$ afforded nitroaldol adduct in moderate yield but with poor enantioselectivity.

Schätz *et al.*[29] reported that ligand/metal ratio influences enantioselectivity, and the effect of the ligand/metal ratio was tested at room temperature (Table 4). The influence of the ratio of ligand (1*S*,2*R*)-**8b** to metal source such as $Cu(OAc)_2.H_2O$ and $Cu(OTf)_2$ on reactivity and enantioselectivity was studied



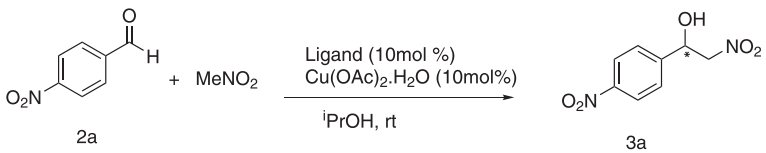
Scheme 3. Synthesis of chiral ligand derivatives – reagents and conditions: (*i*) norephedrine, benzene, reflux; (*ii*) $LiAlH_4$, ether, reflux.

Table 1. Optimization of chiral ligands for the enantioselective Henry reaction[a]



Entry	Sub. thiophene carbaldehyde (*R*)	Amino alcohol	Ligand (yield, %)	Yield (%)[b] **3a**	ee (%)[c] **3a**	Config.[d]
1	$-CH_3$ **6a**	(1*R*,2*S*)-**7a**	(1*R*,2*S*)-**8a** (68)	91	68	*R*
2	$-CH_3$ **6a**	(1*S*,2*R*)-7**b**	(1*S*,2*R*)-8**b** (73)	88	74	*S*
3	$-CH_2CH_3$ **6b**	(1*R*,2*S*)-**7a**	(1*R*,2*S*)-**8a** (70)	90	65	*R*
4	$-CH_2CH_3$ **6b**	(1*S*,2*R*)-7**b**	(1*S*,2*R*)-**8b** (75)	87	67	*S*

[a]All reaction were carried out with 0.2 mmol *p*-nitrobenzaldehyde and 0.6 ml nitromethane in 2 ml ^{i}PrOH in the presence of 10 mol% ligand and 10 mol% $Cu(OAc)_2.H_2O$, at room temperature.
[b]Values are isolated yields after chromatographic purification.
[c]Determined by HPLC analysis (Chiralcel OD-H).
[d]The absolute configuration of products was determined by comparison with literature values.[8b,12c,14b,15b]



Scheme 4. Asymmetric Henry reaction catalyzed by **8** and **9**-$Cu(OAc)_2.H_2O$ complex.

(Table 4). When the amount of $Cu(OAc)_2.H_2O$ was kept constant at 10 mol%, a gradual increase in the amount of ligand (1*S*,2*R*)-**8b** from 5 to 15 to 20 mol% gave comparable enantioselectivity. Decreasing the amount of ligand (1*S*,2*R*)-**8b** to 5 mol% resulted in lower ee value (68%) (entry 1). Changing the amount of ligand (1*S*,2*R*)-**8b** from 10 to 15 mol% had only a small effect on the enantioselectivity (74% and 75%, respectively) (entries 4 and 5). In the presence of 20 mol% ligand (1*S*,2*R*)-**8b**, the product was obtained in 65% yield with 80% ee (entry 4). The reaction was performed using different amounts of $Cu(OAc)_2.H_2O$ in the presence of 10 mol% ligand (1*S*,2*R*)-**8b** (Table 4). After changing the ratio of $Cu(OAc)_2.H_2O$ from 10 to 15 mol%, the enantioselectivity and yield decreased to 69 % and 71%, respectively. In the presence of 10 mol% (1S,2R)-8b and 5mol% $Cu(OAc)_2.H_2O$, the highest enantioselectivity obtained was 83%, but the yield of product decreased to 68% (entry 5).

Next, the effect of the amount of chiral ligand was examined in the presence of $Cu(OTf)_2$ as metal source (Table 4). By keeping the $Cu(OTf)_2$ ratio at 10 mol% and reducing the ligand (1*S*,2*R*)-**8b** . ratio from 10 mol% to 5 mol%, the product was obtained in 75% yield with 70% ee (entries 8 and 9). Increasing the amount of ligand (1*S*,2*R*)-**8b** to 20 mol%, the product was obtained in 86% ee, but the yield dropped to 58% (entry 11). When the amount of (1*S*,2*R*)-**8b** was kept at 10 mol%, a gradual increase in the amount of ligand $Cu(OTf)_2$ from 5 to 10 to 15 to 20 mol% led to a decrease in the enantioselectivity from 88% to 79% to 73% to 70%, respectively. The optimal ratio of ligand (1*S*,2*R*)-**8b** to $Cu(OTf)_2$ is 1:2 and the use of 5 mol% $Cu(OTf)_2$ gave the highest enantioselectivity.

The reaction temperature also plays an important role in the chemical yield and ee value of nitroalkanols.[30] When the reaction temperature was reduced from room temperature to −20 °C, the corresponding product was obtained in 72% yield with 53% ee (Table 4, entry 16). The highest ee (89%) was achieved at 0 °C with 75% yield (entry 15). The homochiral *N*-thienylmethyl-substituted amino alcohol ligand **2**, which has a asymmetric carbon bearing the amino group,[25] gave a high yield (92%) and the ee value was moderate (63%). Chiral ligands **8** and **9a**,**b** with two chiral centers gave a higher enantioselectivity than amino alcohol carrying *N*-thienylmethyl substituted **5**.

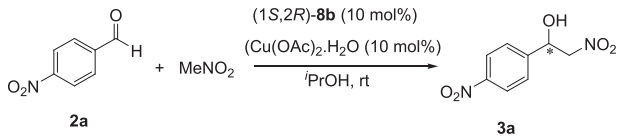
Overall, the optimized reaction conditions were found to be $Cu(OTf)_2$–(1*S*,2*R*)-**8b** (1:2) complex catalyst, ^{i}PrOH used as solvent, at 0 °C.

With the optimized conditions in hand, the catalytic efficiency of ligand (1*S*,2*R*)-**8b** was also tested in the Henry reaction between nitromethane and various aldehydes. As can be seen from Table 5, aromatic aldehydes with either electron-donating or electron-withdrawing groups gave the products with moderate to good ee values and yields. High ee values are observed for aromatic aldehydes bearing substituents in the *ortho* position. The heteroaromatic aldehyde furan-2-carbaldehyde also furnished the nitro aldol product with 83% ee. Next, the scope of the asymmetric Henry reaction was studied with aliphatic aldehydes using (1*S*,2*R*)-**8b**. The aliphatic aldehydes provided the corresponding adduct with higher enantioselectivity than did aromatic aldehydes. For aliphatic aldehydes, the enantioselectivity increased with an increase of the chain length of aldehydes. Branched aliphatic aldehydes such as cyclohexanecarboxaldehyde gave the corresponding products with excellent enantioselectivities of up to 96% (entries 18, 20 and 22).

Conclusion

We synthesized thiophene ring-containing chiral amino alcohols from 5-substituted thiophene-2-carbaldeydes and both enantiomers of norephedrine. Their catalytic activity was determined in enantioselective Henry reaction between nitromethane and aromatic aldehydes. High enantioselectivities were obtained with (1*S*,2*R*)-**8b** and (1*S*,2*R*)-**9b** in the Henry reaction. The chiral ligand pairs induced opposite enantioselectivity and the absolute configuration of β-nitroalkanol is similar to the configuration of the alcohol part of the chiral ligand. Further investigation is being carried out on the application of these ligands for the diastereoselective Henry reaction and the other asymmetric reactions.

Table 2. Effects of solvents on the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane under the chiral ligand (1*S*,2*R*)-**8b**[a]



2a 3a

Entry	Solvent	Yield (%)[b] **3a**	ee (%)[c] **3a**
1	MeOH	82	62
2	EtOH	88	70
3	^{i}PrOH	92	74
4	MeCN	70	30
5	Toluene	60	50
6	THF	65	54
7	CH_2Cl_2	75	60
8	^{n}PrOH	89	72

[a]All reaction were carried out with 0.2 mmol *p*-nitrobenzaldehyde and 0.6 ml nitromethane in 2 ml solvent in the presence of 10 mol% ligand and 10 mol% $Cu(OAc)_2.H_2O$, at room temperature.
[b]Values are isolated yields after chromatographic purification.
[c]Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (*S*) was determined by comparison with literature values.[8b,12c,14b,15b]

Experimental

General Methods

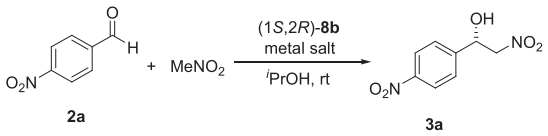
All solvents were dried before use according to standard procedures. Melting points were obtained using an electrothermal digital melting point apparatus (Gallenkamp). ^{1}H and ^{13}C NMR spectra were measured with a Bruker 400 MHz NMR spectrometer using $CDCl_3$ as solvent at room temperature. Chemical shifts (ppm) were reported relative to Me_4Si. Coupling constants were expressed as *J* values in hertz units. Optical rotations were measured with an Autopol IV polarimeter. All reactions were carried out under Ar atmosphere and monitored by thin-layer chromatography (TLC) on Merck silica gel plates (60 F-254) using UV light or phosphomolybdic acid in methanol. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Enantiomeric excesses were determined by HPLC analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column.

Synthesis of Ligands

Formylation of 2-substituted thiophenes

DMF (2.56 ml, 33 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C and $POCl_3$ (2.94 ml, 32 mmol) was added dropwise very slowly.

Table 3. Influence of metal salts on the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane under the chiral ligand (1*S*,2*R*)-**8b**[a]

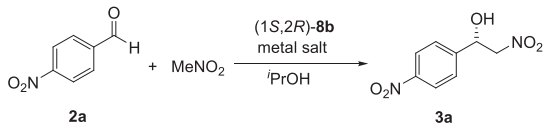


2a 3a

Entry	Metal salt	Yield (%)[b] **3a**	ee (%)[c] **3a**
1	$Cu(OAc)_2.H_2O$	92	74
2	$Cu(OTf)_2$	68	79
3	$NiCl_2.6H_2O$	68	21
4	AgOTf	30	12
5	$Cu(OAc)_2.H_2O$	82	70
6	CuCl	55	68
7	CuI	73	45
8	CuBr	48	64
9	$CuCl_2.2H_2O$	15	22
10	$CuBr_2$	62	50
11	$Zn(OTf)_2$	17	21
12	$CoCl_2.2H_2O$	57	40

[a]All reactions were carried out with 0.2 mmol *p*-nitrobenzaldehyde and 0.6 ml nitromethane in 2 ml ^{i}PrOH in the presence of 10 mol% ligand (1*S*,2*R*)-**8b** and 10 mol% metal salt, at room temperature.
[b]Values are isolated yields after chromatographic purification.
[c]Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (*S*) was determined by comparison with literature values.[8b,12c,14b,15b]

Table 4. Effects of ligand loading, solvents and reaction temperature on the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane under the chiral ligand (1*S*,2*R*)-**8b**[a]



2a **3a**

Entry	Metal salt	Metal salt (mol %)	(1*S*,2*R*)-**8b** (mol %)	Temp. (°C)	Yield (%)[b]	ee (%)[c]
1	$Cu(OAc)_2.H_2O$	10	5	r.t.	80	68
2	$Cu(OAc)_2.H_2O$	10	10	r.t.	92	74
3	$Cu(OAc)_2.H_2O$	10	15	r.t.	68	75
4	$Cu(OAc)_2.H_2O$	10	20	r.t.	65	80
5	$Cu(OAc)_2.H_2O$	5	10	r.t.	68	83
6	$Cu(OAc)_2.H_2O$	15	10	r.t.	71	69
7	$Cu(OAc)_2.H_2O$	20	10	r.t.	80	66
8	$Cu(OTf)_2$	10	5	r.t.	75	70
9	$Cu(OTf)_2$	10	10	r.t.	68	79
10	$Cu(OTf)_2$	10	15	r.t.	70	81
11	$Cu(OTf)_2$	10	20	r.t.	58	86
12	$Cu(OTf)_2$	5	10	r.t.	65	88
13	$Cu(OTf)_2$	15	10	r.t.	80	73
14	$Cu(OTf)_2$	20	10	r.t.	80	70
15	$Cu(OTf)_2$	5	10	0	75	89
16	$Cu(OTf)_2$	5	10	−20	72	53

[a]All reaction were carried out with 0.2 mmol of *p*-nitrobenzaldehyde and 0.6 ml nitromethane in 2 ml solvent in the presence of ligand (1*S*,2*R*)-**6a**, using $Cu(OAc)_2.H_2O$ or $Cu(OTf)_2$, at room temperature.

[b]Values are isolated yields after chromatographic purification.

[c]Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (*S*) was determined by comparison with literature values.[8b,12c,14b,15b]

After the addition the mixture was stirred for 30 min at 0 °C. 2-Substituted thiophene (methyl- or ethyl-) (25 mmol) was dissolved in 10 ml CH_2Cl_2 and added to the mixture dropwise over 45 min at 0 °C. After warming to room temperature, the mixture was heated further and at about 70 °C a vigorous reaction occurred. Immediately an ice bath was put under the vessel until no further HCl gas evolved. The mixture was then heated for 1 h at 110 °C. After cooling to room temperature the mixture was poured into ice water (200 ml) and neutralized with sodium bicarbonate. The mixture was extracted with diethyl ether (3 × 100 ml) and dried (Na_2SO_4).After evaporation of the solvent the crude product was purified by flash column chromatography (EtOAc–hexane, 1:5).

5-Methyl thiophene-2-carbaldehyde (**6a**) was characterized by comparing their ^1H and ^{13}C NMR spectra with those published in the literature.[27b]

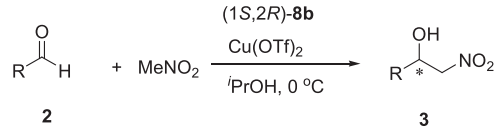
5-Ethyl thiophene-2-carbaldehyde (**6b**): brown oil; 85% yield; R_f 0.41 (EtOAc–hexane, 1:3); ^1H NMR (400 MHz $CDCl_3$) δ 9.74 (s, 1H, CO*H*), 7.54 (d, 1H, J = 3.7 Hz, C(3)*H*), 6.85 (d, 1H, J = 3.7 Hz, C(4)*H*), 2.84 (q, 2H, J = 7.5, CH_2CH_3), 1.27 (t, 2H, J = 7.5 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 182.72 (CHO), 159.21 (thiophene ring, *C*(2)), 141.6 7 (thiophene ring, *C*(5)), 137.16 (thiophene ring, *C*(3)), 125.55 (thiophene ring, *C*(4)), 24.22 (CH_3CH_2), 15.60 (CH_3CH_2). IR (KBr) ν (cm^{-1}) 3077, 2973, 2925,1661, 1454, 1228, 1082, 1030, 812, 757, 665 Anal. Calcd for C_7H_8OS: C, 59.97; H,5.75; O, 11.41; S, 22.87. Found: C,59.86; H, 4.84; O, 11.46; S, 22.91 (See supporting information for ^1H and ^{13}C NMR of **6b**).

General procedure for the synthesis of thiophene-based chiral amino alcohols

5-Substituted thiophene-2-carbaldehydes (5 mmol, **6a** or **6b**) were dissolved in 10 ml benzene to which was added norephedrine (0.756 g, 5 mmol) under nitrogen atmosphere. The mixture was refluxed for 4 h and water was removed in a Dean–Stark trap. Reaction was controlled by TLC. Imine was concentrated to dryness without purification. The synthesized imine was dissolved in 15 ml Et_2O and added to a suspension of 1.35 mmol $LiAlH_4$ in 10 ml Et_2O. The mixture was refluxed for 8 h and controlled by TLC. When the reaction was completed, the mixture was cooled to room temperature and quenched with 15 ml water. It was extracted with ether (3 × 10 ml) and dried over $MgSO_4$. The mixture was filtered and the solvent was evaporated. Crude products **8a**,**b** and **9a**,**b** were purified by flash column chromatography (EtOAc–hexane, 1:5) (See supporting information for ^1H and ^{13}C NMR of chiral ligands **8,9a-b**).

(1*R*,2*S*)- 2-((5-Methylthiophen-2-yl)methylamino-1-phenylpropanol ((1*R*,2*S*)-(**8a**)): brown oil; 68% yield; R_f 0.32 (EtOAc–hexane, 1:1); $[\alpha]_D^{25} = -0.78$ (c = 0.54, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.18 (m, 5H, Ar*H*), 6.64 (d, 1H, J = 3.2 Hz, thiophene ring, C (3)*H*), 6.51 (d, 1H, J = 3.2 Hz, thiophene ring, C(4)*H*,), 4.67 (d, 1H, J = 3.6 Hz, *CH*OH), 3.99 (d, 1H, J = 14.4 Hz, NHCH_2), 3.88 (d, 1H, J = 14.4 Hz, NHCH_2), 2.99–2.89 (m, 1H, *CH*CH_3), 2.40 (s, 3H, CH_3), 0.77 (d, 3H, J = 6.4, CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.70 (Ar−*C*), 151.41 (thiophene ring, *C*(2)), 141.25 (thiophene ring, *C*

Table 5. Asymmetric Henry reaction of nitromethane with various aromatic aldehydes[a]



2 3

Entry	Aldehyde	Product **3**	Yield (%)[b] **3**	ee (%)[c] **3**
1	4-$NO_2C_6H_4$	**3a**	92	89
2	2-$NO_2C_6H_4$	**3b**	89	90
3	3-$NO_2C_6H_4$	**3c**	80	83
4	PhCHO	**3d**	74	65
5	4-$MeOC_6H_4$	**3e**	70	69
6	2-$MeOC_6H_4$	**3f**	69	72
7	3-$MeOC_6H_4$	**3g**	78	67
8	4-MeC_6H_4	**3h**	66	62
9	2- MeC_6H_4	**3i**	70	67
10	3- MeC_6H_4	**3j**	68	63
11	4-ClC_6H_4	**3k**	82	71
12	2-ClC_6H_4	**3l**	80	75
13	2-FC_6H_4	**3m**	82	79
14	1-Naphthyl	**3n**	80	78
15	2-Naphthyl	**3o**	82	77
16	$PhCH_2CH_2$	**3p**	78	87
17	2-Furfuryl	**3q**	75	83
18	Cyclohexyl	**3r**	78	87
19	^{n}Pr	**3s**	77	90
20	^{i}Pr	**3t**	68	93
21	^{n}Bu	**3u**	70	96
22	^{i}Bu	**3v**	74	96

[a]All reactions were carried out with 0.2 mmol aromatic aldehyde and 0.6 ml nitromethane in 2 ml ^{i}PrOH in the presence of 10 mol% ligand and 5 mol% $Cu(OTf)_2$, 0 °C.

[b]Values are isolated yields after chromatographic purification.

[c]Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (*S*) was determined by comparison with literature values.[8b,12c,14b,15b]

(5)), 128.25–126.13 (Ar—*C*), 108.08 (thiophene ring, *C*(3)), 105.94 (thiophene ring, *C*(4)), 72.97 (*C*HOH), 57.23 (*C*HCH$_3$), 43.54 (*C*H$_2$NH), 14.1125 (*C*H$_3$), 13.58 (CH*C*H$_3$), IR (KBr) ν (cm^{-1}) 3419, 2975, 2919, 1490, 1448,1339, 1254, 1117, 796, 697. Anal. Calcd for $C_{15}H_{19}NOS$: C, 69.78; H, 7.69; N, 5.09; O, 5.81; S, 11.64. Found: C, 69.77; H, 7.64; N, 5.12; O, 5.84; S, 11.63.

(1*S*,2*R*)-2-((5-Methylthiophen-2-yl)methylamino-1-phenylpropanol ((1*S*,2*R*)-(**8b**)): brown oil; 73% yield; R_f 0.32 (EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ = +0.74 (*c* = 0.57, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.17 (m, 5H, Ar*H*), 6.65 (d, 1H, *J* = 3.2 Hz, thiophene ring, C(3)*H*), 6.52 (ss, 1H, thiophene ring, C(4)*H*), 4.69 (d, 1H, *J* = 3.6 Hz, *C*HOH), 3.96 (d, 1H, *J* = 14.4 Hz, NHC*H*$_2$), 3.88 (d, 1H, *J* = 14.4 Hz, NHC*H*$_2$), 2.98–2.95 (m, 1H, *C*HCH$_3$), 2.39 (s, 3H, *C*H$_3$), 0.78 (d, 3H, *J* = 6.4, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.67 (Ar—*C*), 151.43 (thiophene ring, *C*(2)), 141.24 (thiophene ring, *C*(5)), 128.64–126.08 (Ar—*C*), 108.06 (thiophene ring, *C*(3)), 105.97 (thiophene ring, *C*(4)), 72.94 (*C*HOH), 57.21 (CH$_3$*C*H), 43.55 (NHC*H*$_2$), 14.06 (*C*H$_3$), 13.67 (*C*H$_3$CH). IR (KBr) ν (cm^{-1}) 3422, 2973, 2914, 1487, 1452,1337, 1250, 1115, 780, 695. Anal. Calcd for $C_{15}H_{19}NOS$: C, 69.78; H, 7.69; N, 5.09; O, 5.81; S, 11.64. Found: C, 69.77; H, 7.64; N, 5.12; O, 5.84; S, 11.63.

(1*R*,2*S*)- 2-((5-Ethylthiophen-2-yl)methylamino-1-phenylpropanol ((1*R*,2*S*)-(**9a**)): brown oil; 70% yield; R_f 0.30 (EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ = −1.38 (*c* = 0.42, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 5H, Ar*H*), 6.68 (d, 1H, *J* = 3.6 Hz, thiophene ring, C(3)*H*), 6.54 (d, 1H, *J* = 3.6 Hz, thiophene ring, C(4)*H*), 4.68 (d, 1H, *J* = 3.6 Hz, *C*HOH), 3.95 (d, 1H, *J* = 14.4 Hz, NHC*H*$_2$), 3.86 (d, 1H, *J* = 14.4 Hz, NHC*H*$_2$), 2.99–2.94 (m, 1H, NHC*H*CH$_3$), 2.74 (q, 2H, *J* = 7.2 Hz, *C*H$_2$CH$_3$), 1.97 (s, 3H, *C*H$_3$), 0.79 (d, 3H, *J* = 6.4, NHCHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.97 (Ar—*C*), 141.19 (thiophene ring, *C*(2)), 140.80 (thiophene ring, *C*(5)), 128.12–126.15 (Ar—*C*), 124.79 (thiophene ring, *C*(3)), 122.82 (thiophene ring, *C*(4)), 73.22 (*C*HOH), 57.25 (NH*C*HCH$_3$), 45.96 (NHCH$_2$), 23.59 (CH$_3$*C*H$_2$), 15.94 (*C*H$_3$CH$_2$), 1462 (NHCHCH$_3$). IR (KBr) ν (cm^{-1}) 3412, 2977, 2922, 1492, 1450, 1383, 1217, 1018, 784, 736, 697. Anal. Calcd for $C_{16}H_{21}NOS$: C, 68.93; H, 7.33; N, 5.36; O, 6.12; S, 12.27. Found: C, 69.77; H, 7.64; N, 5.12; O, 5.84; S, 11.63.

(1*S*,2*R*)- 2-((5-Ethylthiophen-2-yl)methylamino-1-phenylpropanol ((1*S*,2*R*)-(**9b**)): brown oil; 75% yield; R_f 0.30 (EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ = +1.27 (*c* = 0.46, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.17 (m, 5H, Ar*H*), 6.66 (d, 1H, *J* = 3.60 Hz, thiophene ring C(3)*H*), 6.55 (d, 1H, *J* = 3.6 Hz, thiophene ring, C(4)*H*,), 4.69 (d, 1H, *J* = 4.0 Hz, *C*HOH), 3.96 (d, 1H, *J* = 14.4 Hz, NHC*H*$_2$), 3.89 (d, 1H, *J* = 14.0 Hz, NHC*H*$_2$), 2.97–2.95 (m, 1H, NHC*H*CH$_3$), 2.75 (q, 2H, *J* = 7.20 Hz, *C*H$_2$CH$_3$), 1.22 (t, 3H, *J* = 7.20 Hz, *C*H$_3$), 0.78 (d, 3H, *J* = 6.80, NHCHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.92 (Ar—*C*). 141.17 (thiophene ring, *C*(2)), 140.82 (thiophene ring, *C*(5)), 126.04–128.34 (Ar—*C*), 124.78 (thiophene ring, *C*(3)), 122.78 (thiophene ring, *C*(4)) 73.19 (*C*HOH), 57.22 (NH*C*HCH$_3$), 45.92 (NHCH$_2$), 23.57 (CH$_3$*C*H$_2$), 15.93 (*C*H$_3$CH$_2$), 14.59 (NHCHCH$_3$). IR (KBr) ν (cm^{-1}) 3415, 2974, 2919, 1495, 1448, 1385, 1216, 1020, 790, 738, 693. Anal. Calcd for $C_{16}H_{21}NOS$: C, 68.93; H, 7.33; N, 5.36; O, 6.12; S, 12.27. Found: C, 69.77; H, 7.64; N, 5.12; O, 5.84; S, 11.63. Found: C, 69.75; H, 7.62; N, 5.13; O, 5.86; S, 11.64.

General procedure for the catalytic enantioselective Henry reaction

The representative procedure for enantioselective Henry reaction is available online as supporting information. The enantiomeric purity of the product was determined by HPLC analysis. The absolute configuration of the products was assigned by comparison to the literature data and the details can be found in the Supporting Information.

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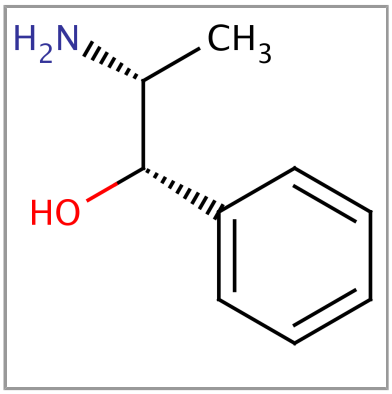
7a



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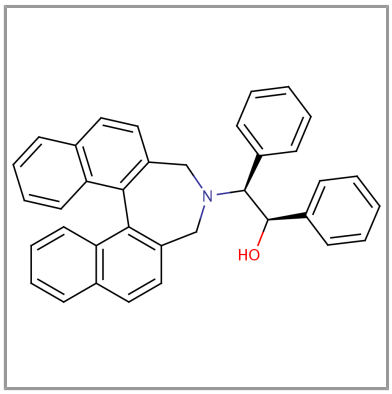

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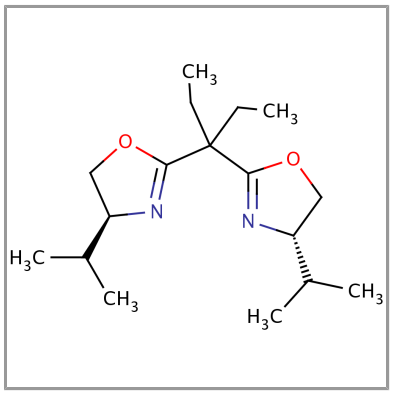

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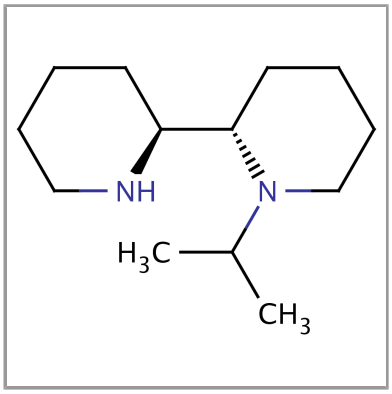

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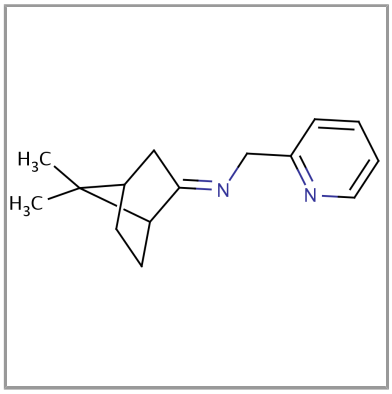

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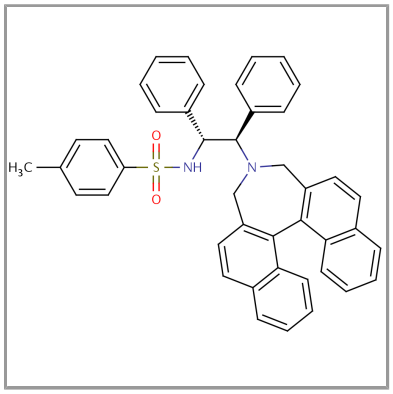

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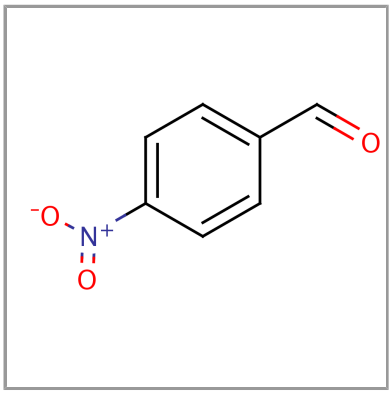

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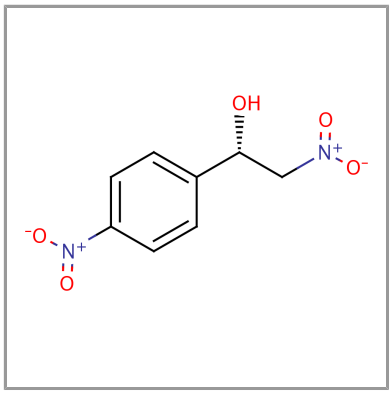

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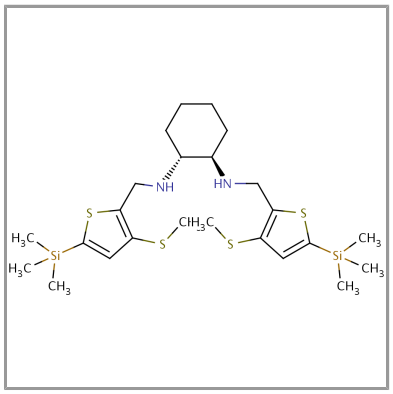

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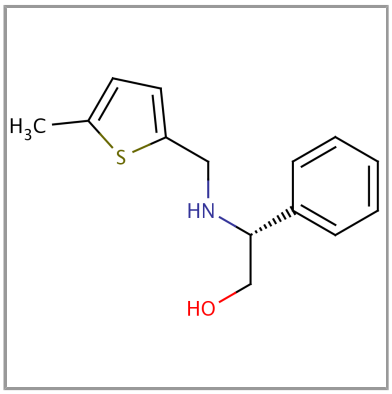

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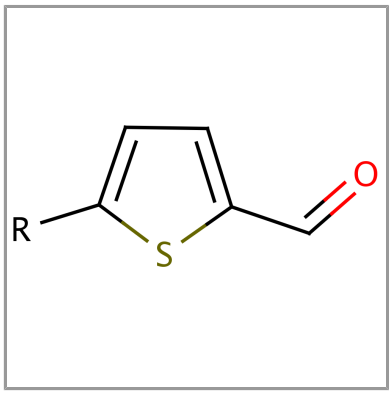

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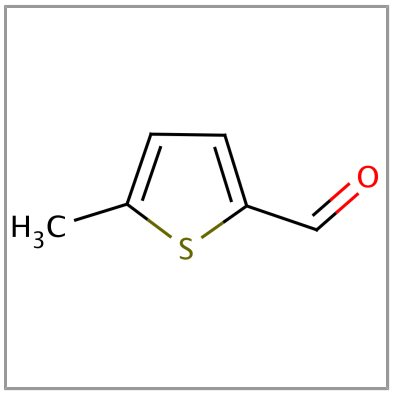

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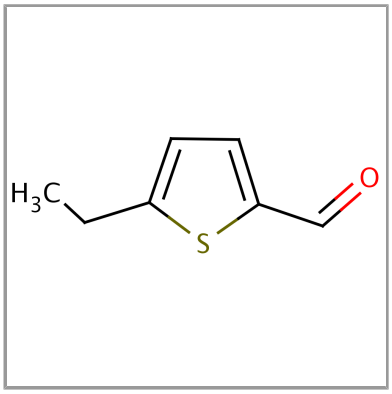

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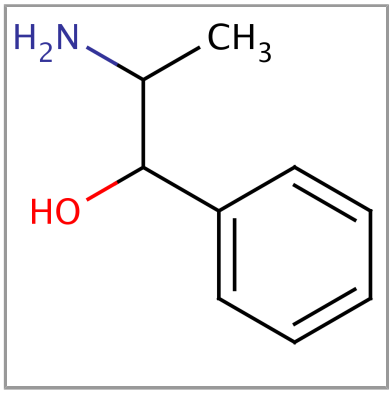

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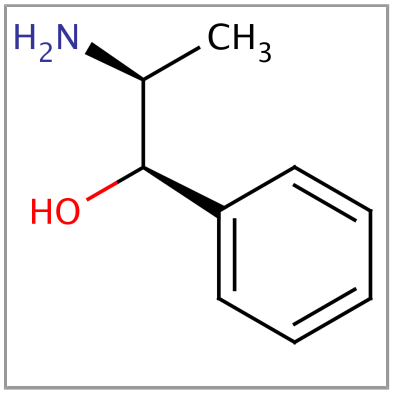

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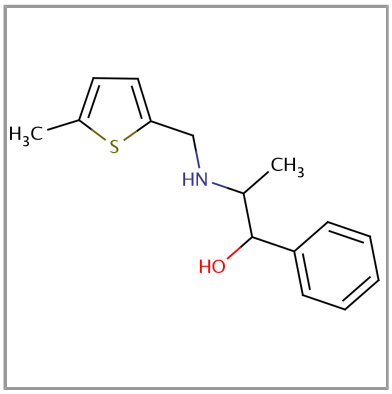

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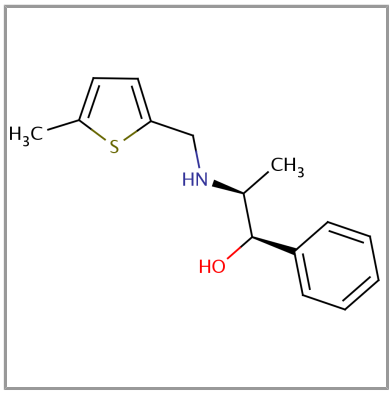

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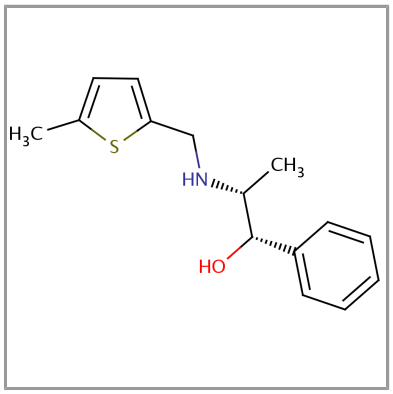
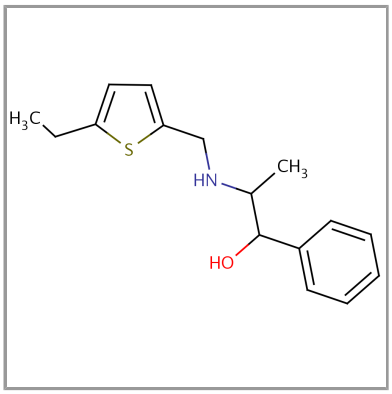


Compound Details Structure Search

9



Compound Details Structure Search

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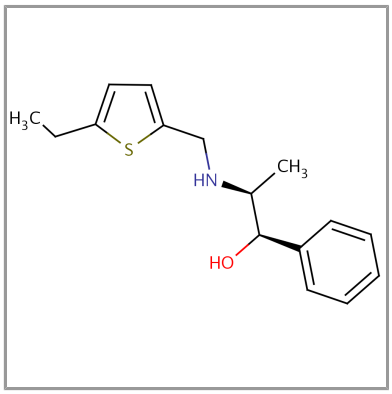

Compound Details Structure Search

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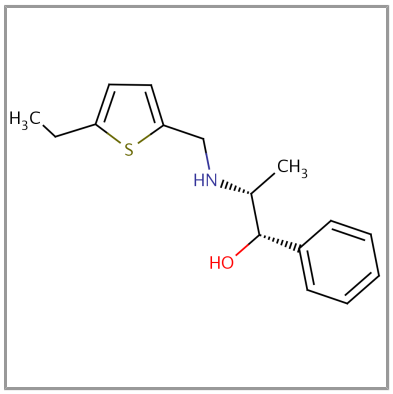

Compound Details Structure Search

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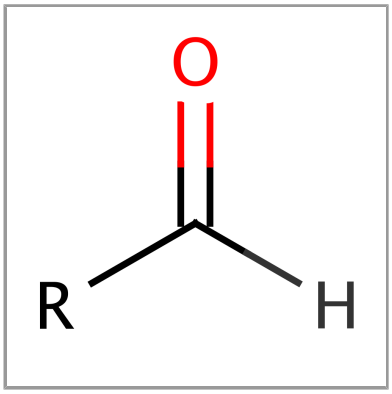

Compound Details Structure Search

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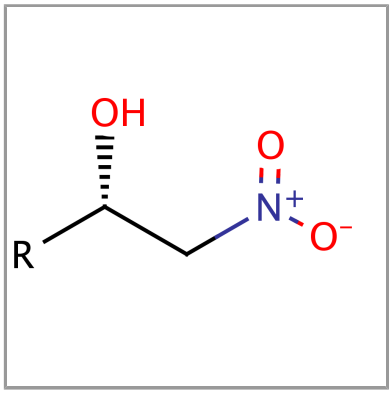

Compound Details Structure Search

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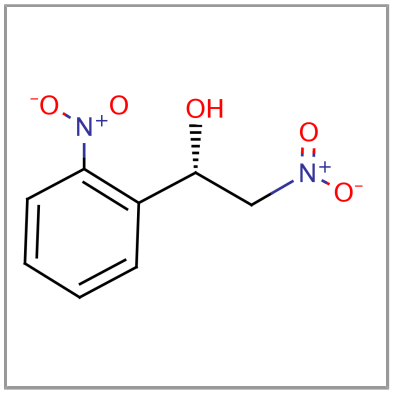

Compound Details Structure Search

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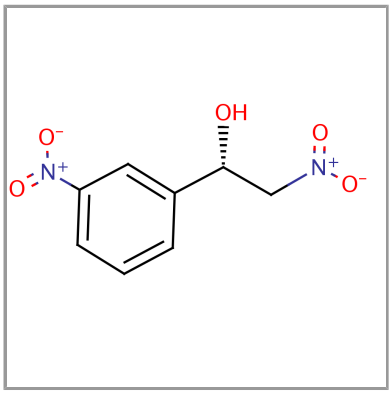

Compound Details Structure Search

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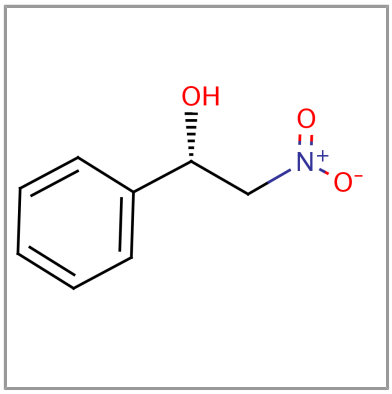

Compound Details Structure Search

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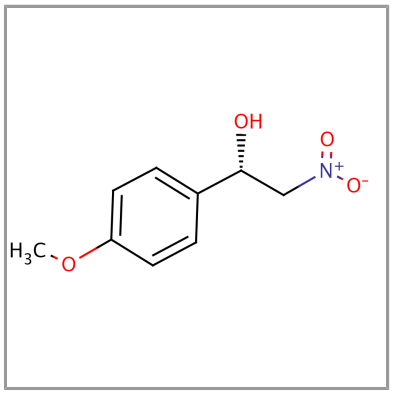

Compound Details Structure Search

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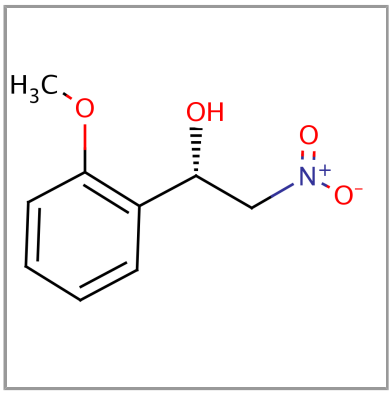

Compound Details Structure Search

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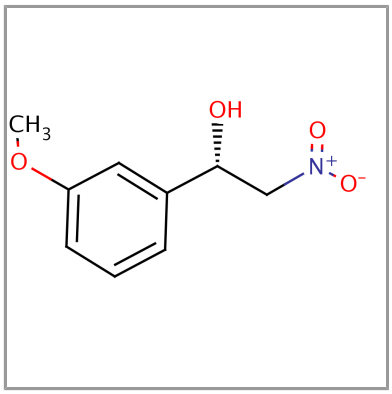

Compound Details Structure Search

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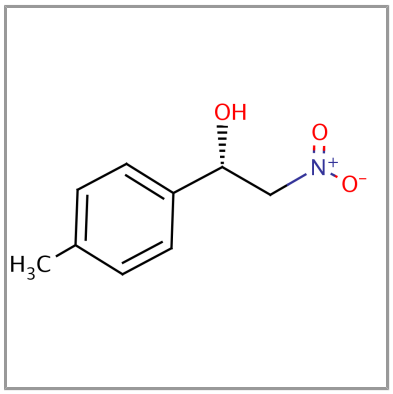

Compound Details Structure Search

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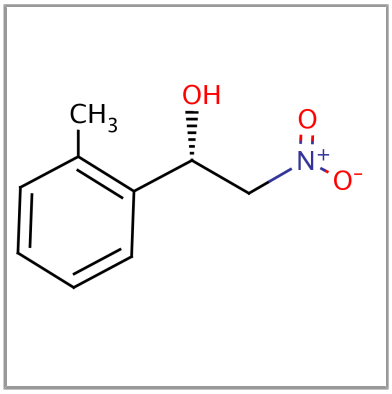

Compound Details Structure Search

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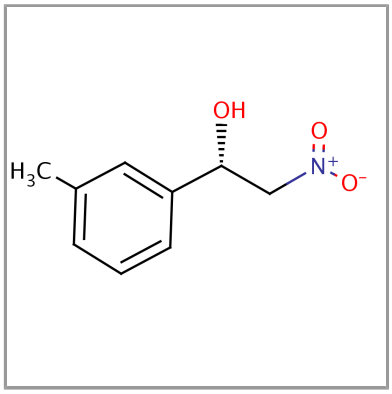

Compound Details Structure Search

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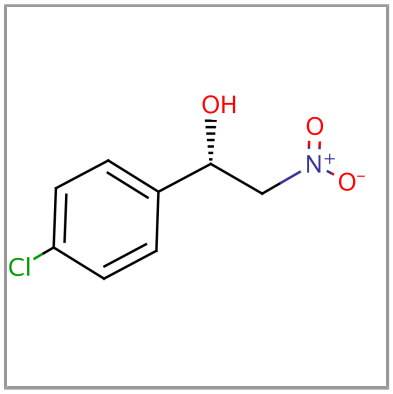

Compound Details Structure Search

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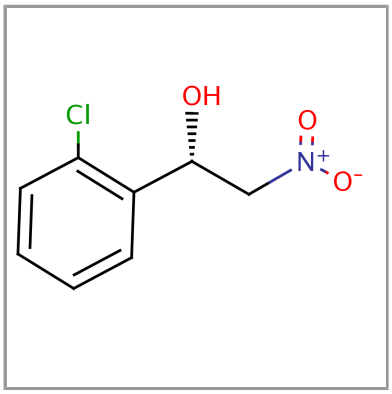

Compound Details Structure Search

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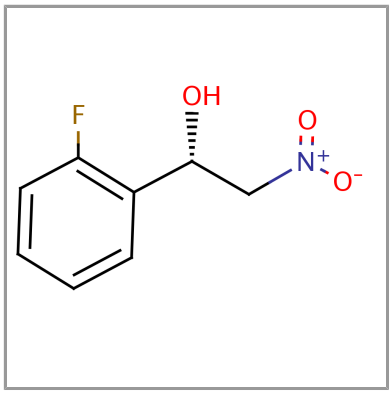

Compound Details Structure Search

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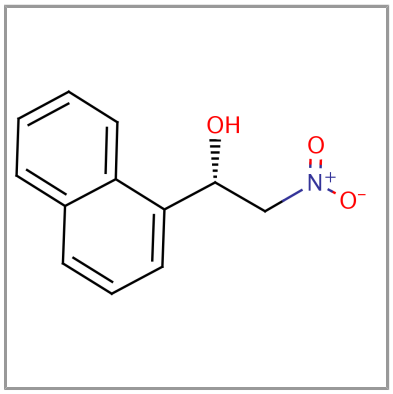

Compound Details Structure Search

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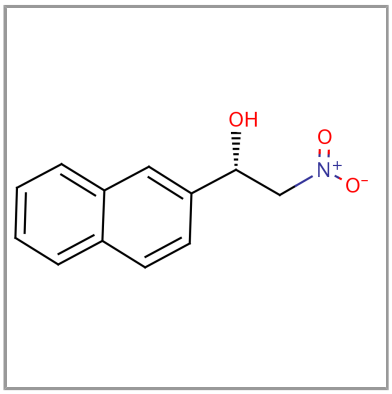

Compound Details Structure Search

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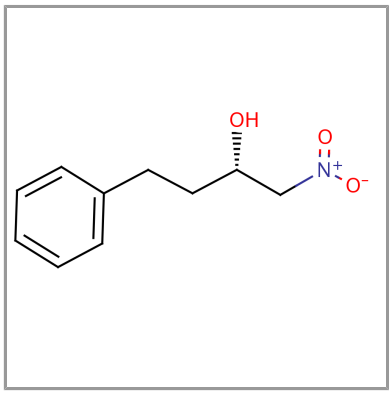

Compound Details Structure Search

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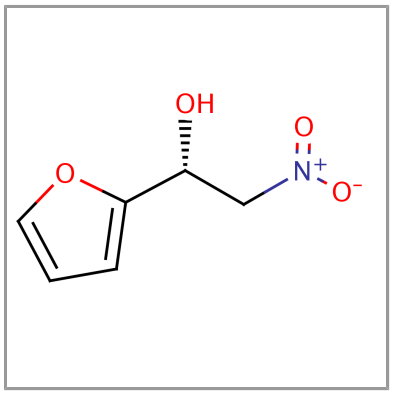

Compound Details Structure Search

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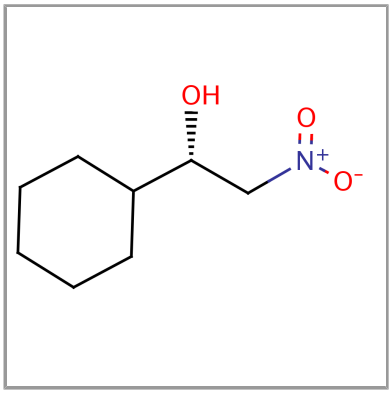

Compound Details Structure Search

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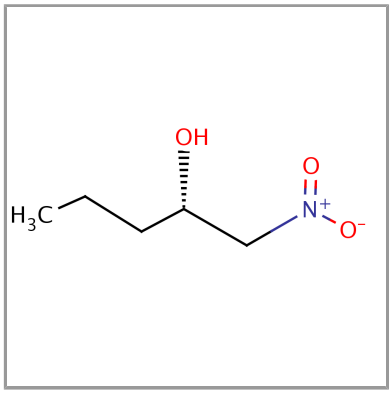

Compound Details Structure Search

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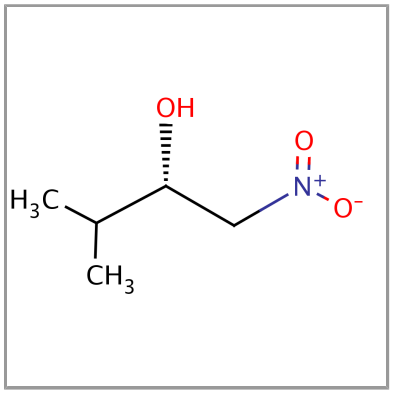

Compound Details Structure Search

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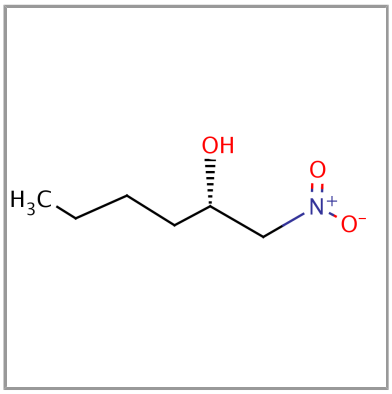

Compound Details Structure Search

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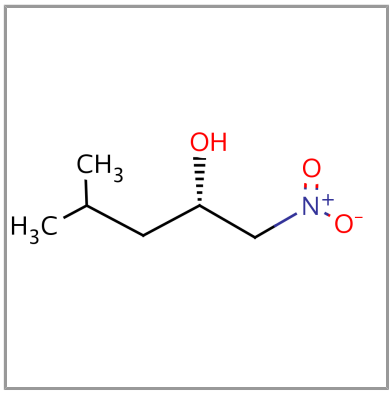

Compound Details Structure Search