Synthesis M. Mohebbi et al. Paper

Noscapine Derivatives as New Chiral Catalysts in Asymmetric Synthesis: Highly Enantioselective Addition of Diethylzinc to Aldehydes

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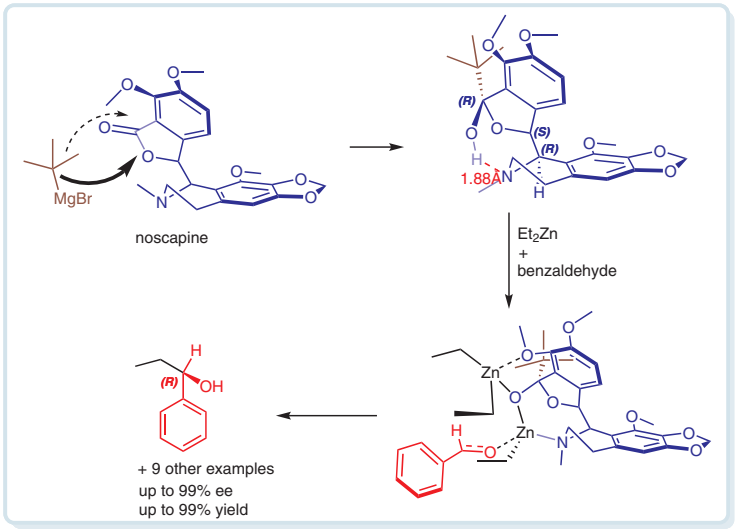

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Abstract Noscapine, a natural alkaloid, has never been used as a parent scaffold in chiral induction. The first examples of noscapinoid compounds as efficient catalysts in asymmetric synthesis are now reported. Three derivatives of noscapine were synthesized from its reaction with different Grignard reagents. Asymmetric addition of diethylzinc to aldehydes was performed in the presence of these catalysts in high yields and good to excellent ees.

Key words noscapine, asymmetric reaction, diethylzinc, alkaloids, MacroModel

Chirality is one of the most elegant features of creation. This feature can cause significant differences in biological function of enantiomers. Nature has always been inspiring for the enantioselective synthesis of chiral molecules.

Asymmetric addition of dialkylzinc to aldehydes is a noteworthy reaction because the produced chiral secondary alcohols are attractive intermediates in organic synthesis and also this is a standard reaction for benchmarking the efficiency of new chiral catalysts.[1]

In recent years, many catalysts with different backbones such as, amino alcohols,[2] diols,[3] and diamines[4] have been reported for this reaction, but synthesis of new catalysts with novel structures is still in demand.

In many reactions, amino alcohols are powerful catalysts. The majority of these are derived from natural compounds such as amino acids,[5] alkaloids,[6] or other natural scaffolds such as pinenes,[7] camphor,[8] etc. Catalysts with an alkaloidal backbone are among the most favorite organocatalysts because of their high efficiency in chiral induction. The natural structural complexity of alkaloids derived from nature can help us in approaching the synthesis of complex structures. The most famous structures of these groups are cinchona alkaloids with high potency, which have been used in many asymmetric reactions such as Sharpless asymmetric dihydroxylation,[9] asymmetric Baylis–Hillman,[10] aldol,[11] and Mannich reactions.[12] Despite the high potency of organocatalysts with alkaloidal backbones, high prices, adverse effects on health, and their sparse availability negatively counterbalance their advantages. Therefore, finding new alkaloids as potent catalysts to overcome the drawbacks of the previously reported catalysts, is a challenging issue in this field.

Noscapine is a benzylisoquinoline alkaloid and the second most abundant alkaloid in opium. Noscapine has been used as an antitussive agent since 1963 and in recent years it is being used as an anticancer lead compound (Figure 1).[13] The main advantages of noscapine are low toxicity and commercial availability. Despite numerous studies on biological activities of noscapine derivatives, their application as a chiral catalyst has not been reported in the literature so far. In continuation of our research on the application of natural-based catalysts in asymmetric reactions,[14] we report here the synthesis of novel derivatives from noscapine and their utilization as efficient catalysts in asymmetric addition of diethylzinc to aldehydes.

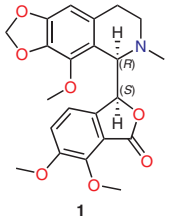
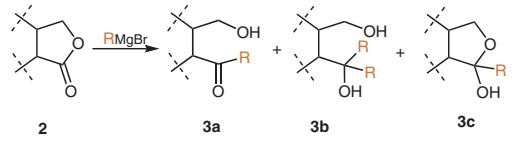


Figure 1 Noscapine structure

The masked functional groups of noscapine caught our attention for the design and synthesis of various derivatives for different catalytic roles. One of the active sites of noscapine available for modification and synthesis of new derivatives is the lactone ring. Our main strategy was based on nucleophilic opening of lactone ring by a Grignard reagent to form the golden β-amino alcohol moiety. According to the literature, three different products could be formed by the reaction of the Grignard reagent with γ-lactones, namely, a ketone **3a**, a tertiary alcohol **3b**, or a hemiacetal **3c** (Scheme 1).

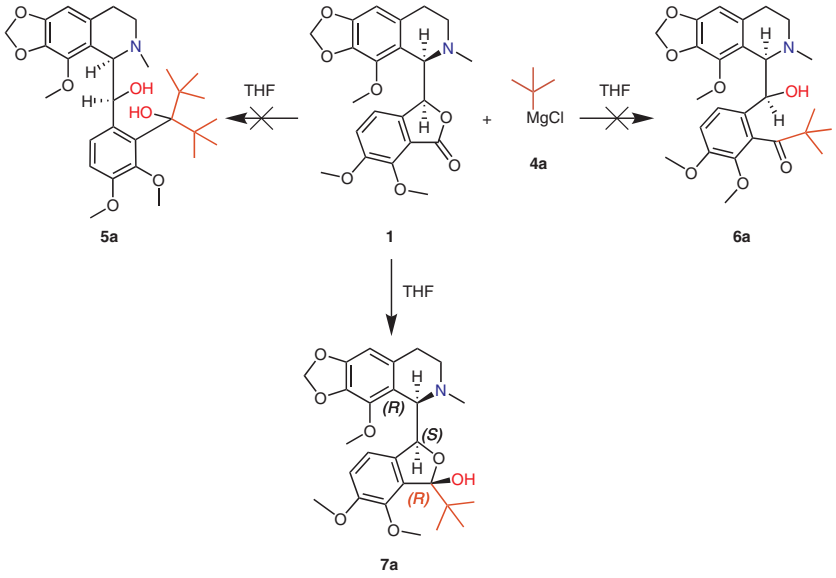


Scheme 1 Three possible products from the reaction of Grignard reagent with a γ-lactone ring

By the reaction of 2 equivalents of *t*-BuMgCl with noscapine at room temperature, only the hemiacetal **7a** was obtained (Scheme 2). By increasing the amount of Grignard reagent to 12 equivalents and the temperature to 60 °C, no difference in the pattern of the products was observed. A probable explanation for this behavior could be the formation of a strong complex between O–Mg–N after addition of the Grignard reagent, which locks the molecule in a way that no further progress to the corresponding ketone is possible. This effect was reflected in the downfield chemical shift of hydrogen-bonded OH equal to 7.55 ppm.

In spite of the predicted formation of two diastereomers, NMR spectra of the crude reaction mixture showed only one stereoisomer. This obviously can be explained by examining the structure of noscapine, which is crowded in the *Re*-face of the carbonyl group for the nucleophilic attack (Figure 2). X-ray crystal structure analysis on a single crystal of the product **7a** confirmed the hemiacetal structure with 1*R*,3*S*,5*R*-configuration. Its ORTEP view is depicted in Figure 3. The strong hydrogen bond between the OH and the amine was obvious. Conformational analysis of **7a** with MacroModel in solution and the structure of more stable conformer (Figure 3) showed a shorter O–H–N distance (1.88 Å) than in the crystal structure (1.92 Å) (for details of the X-ray crystal structures, see the Supporting Information).

Although we did not synthesize the targeted structure (β-amino alcohol), the short distance between the OH and amine N atom of the group in **7a** aroused our curiosity and prompted us to examine the catalytic potency of this molecule (Table 1). Efficiency of this compound in asymmetric addition of Et_2Zn was amazing. At room temperature, excellent enantioselectivity (99% ee) was observed for the formation of *R*-enantiomer with 10 mol% of the catalyst in 99% yield after 3 hours (Table 1, entry 4).



Scheme 2 Expected and isolated products for Grignard reaction with noscapine

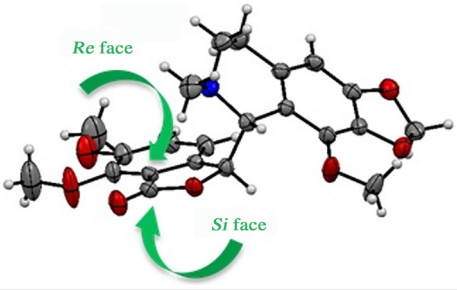


Figure 2 Crystal structure of noscapine

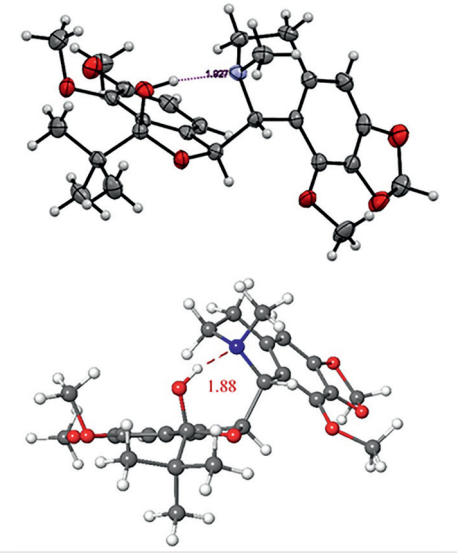
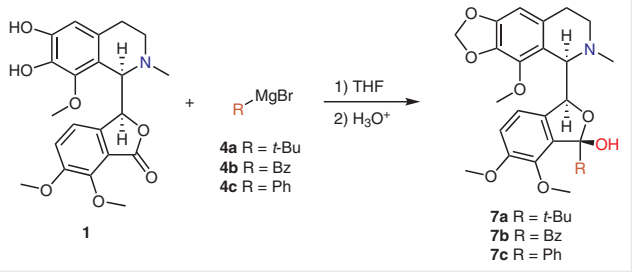


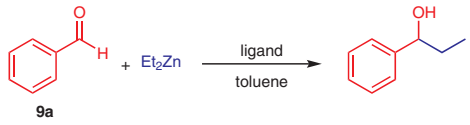
Figure 3 a) ORTEP view of compound **7a**, b) structure of more stable conformer of **7a** in solution

In parallel, we also synthesized two other noscapine derivatives with benzyl **7b** and phenyl groups **7c** by the same Grignard reaction (Scheme 3). The efficiency of new catalysts was also examined by adding of diethylzinc to benzaldehyde in toluene as solvent with different mol% of **7b** and **7c** (Table 1, entries 7–17). The best enantioselectivity for **7b** was obtained with 10 mol% of the catalyst at 0 °C in 96% yield and 96% ee in 1.5 hours (entry 13).



Scheme 3 Synthesis of ligands **7a–c**

Table 1 Optimization of Diethylzinc Addition Reaction Catalyzed by **7a–c**



Entry	Ligand	mol%	Temp (°C)	Time (h)	Conv. (%)[a]	ee (%)[b] (Config.)[c]
1	**7a**	2	r.t.	3	nr[d]	–
2	**7a**	5	r.t.	3	84	39 (*R*)
3	**7a**	7	r.t.	3	65	95 (*R*)
4	**7a**	10	r.t.	3	99	99 (*R*)
5	**7a**	10	40	3	99	80 (*R*)
6	**7a**	10	0	3	80	98 (*R*)
7	**7b**	2	r.t.	3	80	6 (*R*)
8	**7b**	5	r.t.	3	96	44 (*R*)
9	**7b**	7	r.t.	3	97	70 (*R*)
10	**7b**	10	r.t.	3	97	91 (*R*)
11	**7b**	12	r.t.	3	98	84 (*R*)
12	**7b**	10	40	3	93	88 (*R*)
13	**7b**	10	0	1.5	96	96 (*R*)
14	**7b**	10	–10	16	94	96 (*R*)
15	**7c**	10	–20	16	43	64 (*R*)
16	**7c**	10	r.t.	2	96	92 (*R*)
17	**7c**	10	0	2	98	99 (*R*)

[a] Measured as % conversion by GC.
[b] Determined by capillary chiral GC.
[c] Absolute configuration was determined by comparing the sign of specific rotations with those reported in the literature.
[d] No reaction.

The optimum conditions for **7c** used 10 mol% of the catalyst at 0 °C in 2 hours with 99% ee and in 98% yield (Table 1, entry 17). With the optimized conditions in hand for **7a–c**, the asymmetric addition of diethylzinc to other aromatic and aliphatic aldehydes was investigated. The results are summarized in Table 2.

Excellent ees were observed for *p*-substituted benzaldehydes in almost quantitative yields (Table 2, entries 4–12, 19–21). A slight decrease in enantioselectivities was observed for *o*-substituted benzaldehydes (entries 13–18). 1-Naphthaldehyde has also undergone the asymmetric reactions in high yields and enantioselectivities with all three catalysts (entries 22–24). The reaction of 3-phenylpropanal as an aliphatic aldehyde ended up with 76% ee in the presence of **7a** after 16 hours at room temperature (entry 28).

To investigate the role of OH group in asymmetric induction of the catalysts, dehydration reaction of **7b** was carried out by heating it in the presence of *p*-toluenesulfonic acid (Scheme 4). Interestingly, we observed that asym-

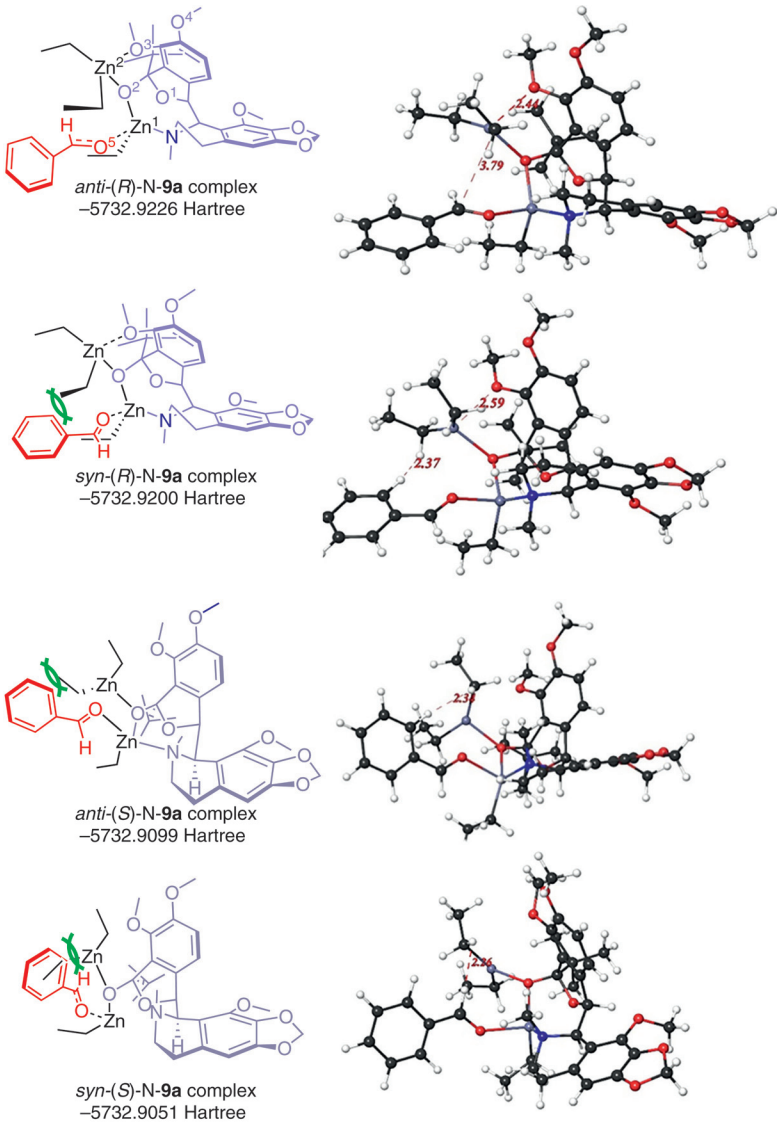
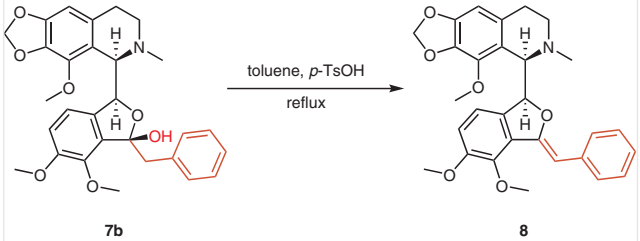


Figure 4 Schematic description and 3D structure of four possible diastereomeric complexes of **9a** with calculated energies

metric addition of diethylzinc to benzaldehyde did not proceed at all in the presence of **8** under different conditions. This showed that the oxygen of hydrofuran ring did not participate in the reaction and the presence of OH group in the right position was vital for the success of this reaction.



Scheme 4 Dehydration of ligand **7b**

To gain insight into the conformational analysis of chiral active species in this reaction, DFT calculations of mixed complexes of **7a**, diethylzinc, and benzaldehyde (**9a**) were conducted. Combination of *R* or *S* configurations of nitrogen group and *syn* or *anti* arrangements of the amino alkoxide ring with C=O bond, resulted in four diastereomeric complexes (Figure 4). Comparison of the optimized energies for different structures indicate that stability decreases in the order *anti*-(*R*)-N-**9a** > *syn*-(*R*)-N-**9a** > *anti*-(*S*)-N-**9a** > *syn*-(*S*)-N-**9a**. The *anti*-(*R*)-N-**9a** and *syn*-(*R*)-N-**9a** are stabilized by a coulombic interaction between Zn^2 (1.23 au) and O^3 (–0.55 au), which is shorter (2.44 Å) in the *anti* complex than in the *syn* (2.59 Å).

Table 2 Enantioselective Addition of Diethylzinc Addition to Various Aldehydes Catalyzed by Ligands **7a–c**[a,b]

Entry	Aldehyde	Ligand	Time (h)	Yield (%)[c]	ee (%)[d]
1	PhCHO	**7a**	3	99	99
2	PhCHO	**7b**	1.5	99	96
3	PhCHO	**7c**	2	99	98
4	*p*-FC_6H_4CHO	**7a**	3	99	98
5	*p*-FC_6H_4CHO	**7b**	1.5	99	98
6	*p*-FC_6H_4CHO	**7c**	2	99	97
7	*p*-MeC_6H_4CHO	**7a**	3	99	98
8	*p*-MeC_6H_4CHO	**7b**	1.5	99	97
9	*p*-MeC_6H_4CHO	**7c**	2	99	97
10	*p*-ClC_6H_4CHO	**7a**	3	99	96
11	*p*-ClC_6H_4CHO	**7b**	1.5	99	97
12	*p*-ClC_6H_4CHO	**7c**	2	99	98
13	*o*-ClC_6H_4CHO	**7a**	3	99	88
14	*o*-ClC_6H_4CHO	**7b**	1.5	93	93
15	*o*-ClC_6H_4CHO	**7c**	2	93	96
16	*o*-$MeOC_6H_4CHO$	**7a**	3	99	89
17	*o*-$MeOC_6H_4CHO$	**7b**	1.5	97	90
18	*o*-$MeOC_6H_4CHO$	**7c**	2	97	84
19	*p*-$F_3CC_6H_4CHO$	**7a**	1.5	96	98
20	*p*-$F_3CC_6H_4CHO$	**7b**	2	98	97
21	*p*-$F_3CC_6H_4CHO$	**7c**	3	96	97
22	1-naphthaldehyde	**7a**	1.5	99	95
23	1-naphthaldehyde	**7b**	2	99	96
24	1-naphthaldehyde	**7c**	3	99	94
25	4-pyridylCHO	**7a**	1.5	60	85
26	4-pyridylCHO	**7b**	2	75	85
27	4-pyridylCHO	**7c**	3	74	80
28	$PhCH_2CH_2CHO$	**7a**	16	93	76
29	$PhCH_2CH_2CHO$	**7b**	16	80	53
30	$PhCH_2CH_2CHO$	**7c**	16	90	44

[a] Ligand **7a** (10 mol%), r.t.
[b] Ligand **7b** (10 mol%), 0 °C. Ligand **7c** (10 mol%), 0 °C.
[c] Isolated yield.
[d] The ee was determined by chiral GC or HPLC.

The lower stability of the *syn*-(*R*)-N-**9a** could be related to the steric repulsion between one of the ethyl groups on Zn^2 and the phenyl ring of the aldehyde. In addition, in the *anti*-(*R*)-N-**9a** the benzaldehyde molecule has a tight contact with the catalyst and the carbonyl carbon atom is positioned closer to one of the ethyl groups (3.79 Å) than in the *syn*-(*R*)-N-**9a** (4.38 Å). This facilitated the alkylation reaction leading to *R*-configured alcohols.

In summary, we have reported the synthesis of three derivatives of noscapine and their applications as chiral catalysts in the asymmetric addition of diethylzinc to aldehydes in high yields and with good to excellent enantioselectivities. To the best of our knowledge, this is the first report on the application of noscapine derivatives as chiral catalysts in asymmetric synthesis. Noscapine could be considered as a parent alkaloid for the synthesis of new organocatalysts, which can be used in other asymmetric reactions.

Melting points were measured on an Electrothermal 9200 instrument. HR-ESIMS spectra were recorded on a Bruker microTOF ESI-MS system. IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ascend 600 spectrometer at 600.15 and 150.92 MHz, respectively, in $CDCl_3$ using TMS as internal standard and reported in ppm. Et_2Zn was purchased from Sigma-Aldrich Co. LLC. Noscapine was purchased from Temad Co. Silica gel (70–230 mesh) used for column chromatography and pre-coated silica gel F_{254} (20 × 20 cm) plates for TLC were purchased from Merck Co. The enantiomeric ratios of the optically active products were determined by gas chromatoghraphy (GC) analysis. GC analysis was performed on an Agilent 4890 D instrument equipped with a Supelco β-DEX™ 120 fused silica capillary column (0.25 nm/0.25 µm, 30 m).

Grignard Reaction Noscapine; General Procedure

To a 1 M solution of the respective Grignard reagent in THF (15 mmol, 15 mL) was added a solution of noscapine (**1**; 4.2 g, 10 mmol) in THF (15 mL) dropwise at r.t. The reaction mixture was stirred for 2 h, then quenched with sat. aq NH_4Cl, and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed using a rotary evaporator under reduced pressure. The crude product was purified by column chromatography (*n*-hexane/EtOAc).

(1*R*,3*S*)-1-*tert*-Butyl-6,7-dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl]-1,3-dihydro-2-benzofuran-1-ol (7a)

Yield: 3.7 g (78%); white crystals; mp 178–179 °C.

FTIR (KBr): 3445, 2943, 1621, 1479, 1263, 1086, 1045 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.55 (br s, 1 H, OH), 6.57 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 6.25 (s, 1 H, H_{Ar}), 5.93 (d, *J* = 1.3 Hz, 1 H, OCH_2O), 5.90 (d, *J* = 1.3 Hz, 1 H, OCH_2O), 5.70 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 5.45 (d, *J* = 4.8 Hz, 1 H, CHO), 4.07 (s, 3 H, OCH_3), 4.05 (d, *J* = 4.8 Hz, 1 H, CHN), 3.80 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 2.48–2.54 (m, 1 H, CH_2N), 2.43 (s, 3 H, NCH_3), 2.17–2.20 (m, 1 H, CH_2N), 1.75 (dt, *J* = 16, 4.02 Hz, 1 H, CH_2), 1.52–1.57 (m, 1 H, CH_2) 1.14 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.0 (C), 148.0 (C), 144.2 (C), 140.8 (C), 137.7 (C), 134.1 (C), 133.3 (C), 129.6 (C), 117.3 (CH), 116.2 (C), 113.6 (C), 112.2 (CH), 102.4 (CH), 100.6 (CH_2), 81.6 (CH), 62.0 (CH), 60.7 (CH_3), 59.4 (CH_3), 56.2 (CH_3), 45.6 (CH_2), 44.5 (CH_3), 38.8 (C), 26.2 (CH_3), 22.9 (CH_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{34}NO_7$: 472.2335; found: 472.2343.

(1*R*,3*S*)-1-Benzyl-6,7-dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl]-1,3-dihydro-2-benzofuran-1-ol (7b)

Yield: 4.3 g (85%); pale yellow solid; mp 99–100 °C.

FTIR (KBr): 3450, 2939, 1618, 1483, 1265, 1030 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.80 (br s, 1 H, OH), 7.31 (d, *J* = 7.38 Hz, 2 H, H_{Ar}), 7.08–7.10 (m, 2 H, H_{Ar}), 7.01–7.03 (m, 1 H, H_{Ar}), 6.49 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 6.26 (s, 1 H, H_{Ar}), 5.89 (d, *J* = 1.3 Hz, 1 H, OCH_2O), 5.88 (d, *J* = 1.3 Hz, OCH_2O), 5.59 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 5.35 (d, *J* = 3.9 Hz, 1 H, CHO), 4.09 (d, *J* = 3.9 Hz, 1 H, CHN), 4.03 (s, 3 H, CH_3), 3.97 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 3.71 (d, *J* = 13.9 Hz, 1 H, CH_2), 3.49 (d, *J* = 13.9 Hz, 1 H, CH_2), 2.51–2.57 (m, 1 H, CH_2N), 2.45 (s, 3 H, CH_3), 2.21–2.25 (m, 1 H, CH_2N), 1.81–1.85 (m, 1 H, CH_2), 1.69–1.74 (m, 1 H, CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.3 (C), 148.1 (C), 143.8 (C), 140.8 (C), 137.3 (C), 136.9 (C), 134.1 (C), 132.4 (C), 130.5 (CH), 129.5 (C), 127.4 (CH), 125.6 (CH), 117.4 (CH), 116.1 (C), 112.7 (CH), 108.1 (C), 102.3 (CH), 100.6 (CH_2), 82.8 (CH), 61.5 (CH), 61.3 (CH_3), 59.4 (CH_3), 56.1 (CH_3), 45.6 (CH_2), 44.4 (CH_3), 42.9 (CH_2), 22.7 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{33}NO_7$: 506.2179; found: 506.2149.

(1*R*,3*S*)-6,7-Dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl]-1-phenyl-1,3-dihydro-2-benzofuran-1-ol (7c)

Yield: 3.9 g (80%); yellow solid; mp 67–69 °C.

FTIR (KBr): 3445, 2943, 1621, 1479, 1263, 1086, 1045 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.54 (br s, 1 H, OH), 7.66 (dd, *J* = 7.2, 1.14 Hz, 2 H, H_{Ar}), 7.31 (m, 2 H, H_{Ar}), 7.25 (m, 1 H, H_{Ar}), 6.61 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 6.34 (s, 1 H, H_{Ar}), 5.94 (d, *J* = 1.4 Hz, 1 H, OCH_2O), 5.91 (d, *J* = 1.4 Hz, 1 H, OCH_2O), 5.86 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 5.77 (d, *J* = 3.8 Hz, 1 H, CHO), 4.17 (d, *J* = 3.8 Hz, 1 H, CHN), 4.06 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.24 (s, 3 H, OCH_3), 3.23 (s, 3 H, NCH_3), 2.56–2.62 (m, 1 H, CH_2N), 2.49 (s, 3 H), 2.30–2.33 (m, 1 H, CH_2N), 1.90–1.94 (m, 1 H, CH_2), 1.83–1.87 (m, 1 H, CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.9 (C), 148.2 (C), 143.8 (C), 142.2 (C), 140.8 (C), 139.2 (C), 134.1 (C), 132.1 (C), 129.5 (C), 127.6 (CH), 127.5 (CH), 126.7 (CH), 117.1 (CH), 116.0 (C), 113.3 (CH), 106.4(C), 102.5 (CH), 100.6 (CH_2), 83.45 (CH), 61.5 (CH), 59.9 (CH_3), 59.4 (CH_3), 56.2 (CH_3), 45.6 (CH_2), 44.3 (CH_3), 22.6 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{31}NO_7$: 492.2022; found: 492.1991.

(5*R*)-5-[(1*R*)-4,5-Dimethoxy-3-[(*Z*)-phenylmethylidene]-2-benzofuran-1(1*H*)-yl]-4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (8)

Ligand **7b** (1 g, 2 mmol) and *p*-TsOH (70 mg, 0.4 mmol) were dissolved in toluene (50 mL) in a 2-necked round-bottomed flask equipped with a Dean–Stark apparatus and refluxed for 3 h. After completion of the reaction, the solvent was evaporated, and the residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc as eluent to afford **8**; yield: 0.78 g (80%); pale yellow crystals; mp 188–190 °C.

FTIR (KBr): 2945, 1645, 1619, 1492, 1270, 1033, 1003 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.4 Hz, 1 H, H_{Ar}), 7.26–7.29 (m, 2 H, H_{Ar}), 7.1 (t, *J* = 7.3 Hz, 1 H, H_{Ar}), 6.72 (d, *J* = 8.2 Hz, 1 H, H_{Ar}), 6.37 (s, 1 H, C=CH), 6.29 (s, 1 H, H_{Ar}), 6.20 (d, *J* = 8.2 Hz, 1 H, H_{Ar}), 5.87 (d, *J* = 1.5 Hz, 1 H, OCH_2O), 5.84 (d, *J* = 1.5 Hz, 1 H, OCH_2O), 5.71 (d, *J* = 3.8 Hz, 1 H, CHO), 4.39 (d, *J* = 3.8 Hz, 1 H, CHN), 3.92 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 2.79–2.83 (m, 1 H, CH_2N), 2.50 (s, 3 H, NCH_3), 2.45–2.49 (m, 1 H, CH_2N), 2.39–2.43 (m, 1 H, CH_2), 2.20–2.24 (m, 1 H, CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.1 (C), 152.3 (C), 148.0 (C), 13.6 (C), 140.6 (C), 137.4 (C), 135.4 (C), 133.7 (C), 131.7 (C), 129.1 (CH), 128.1 (CH), 128.0 (CH), 124.8 (CH), 117.8 (C), 117.5 (CH), 113.1 (CH), 102.5 (CH), 100.4 (CH_2), 100.1 (CH), 87.3 (CH), 62.5 (CH), 60.0 (CH_3), 59.1 (CH_3), 56.4 (CH_3), 49.6 (CH_2), 45.8 (CH_3), 27.9 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{31}NO_6$: 488.2073; found: 488.2039.

Enantioselective Addition of Diethylzinc to Aldehydes; General Procedure

The ligand **7** (0.10 mmol) was dissolved in anhyd toluene (1 mL) in a test tube. The solution was stirred for 5 min. A 1.0 M solution of Et_2Zn in *n*-hexane (2.0 mmol, 2.0 mL) was then added, and after the mixture had been stirred for 5 min at the appropriate temperature, a solution of aldehyde (1.0 mmol) in anhyd toluene (1 mL) was added by syringe. The mixture was stirred for the time reported in Table 2. Sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The collected organic phases were combined, washed with H_2O, dried (Na_2SO_4), and concentrated.

GC or HPLC analysis was done after suitable dilution. General method for GC analysis: T_{Inj}: 260 °C, T_{Det}: 260 °C (FID), H_2: 1 mL/min, split 100:1.

1-Phenylpropan-1-ol

Yield: 0.134 g (99%); colorless oil; $[\alpha]_D^{20}$ +41.5 (*c* 1.0, $CHCl_3$) {Lit.[15] $[\alpha]_D^{20}$ +46.90 (*c* 1.0, $CHCl_3$)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 90 → 110 °C (1.5 °C/min)]. t_R = 24.3 min (*R*); t_R = 25.1 min (*S*).

FTIR (neat): 3360, 2963, 1490, 1450, 1377, 1200, 974 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.40 (m, 5 H, H_{Ar}), 4.59 (t, *J* = 6.6 Hz, 1 H, C*H*OH), 1.69–1.91 (m, 2 H, CH_2), 0.93 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 128.5, 127.6, 126.1, 75.9, 31.9, 10.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{12}ONa$: 159.0786; found: 159.0780.

1-(4-Fluorophenyl)propan-1-ol

Yield: 0.152 g (99%); colorless oil; $[\alpha]_D^{20}$ +38.5 (*c* 1.0, $CHCl_3$) {Lit.[16] $[\alpha]_D^{37}$ +37.0 (*c* 1.0, $CHCl_3$)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 90 → 110 °C (1.5 °C/min)]. t_R = 14.5 min (*R*); t_R = 15.5 min (*S*).

FTIR (neat): 3358, 2965, 1605, 1509, 1458 1379, 1223, 1157 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 2 H, H_{Ar}), 7.01–7.07 (m, 2 H, H_{Ar}), 4.59 (t, *J* = 6.6 Hz, 1 H, C*H*OH), 2.01 (br s, 1 H, OH), 1.65–1.86 (m, 2 H, CH_2), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 127.6, 127.5, 115.3, 1149, 75.2, 31.9, 10.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}FONa$: 177.0692; found: 177.0689.

1-(*p*-Tolyl)propan-1-ol

Yield: 0.148 g (99%); colorless oil; $[\alpha]_D^{20}$ +31.5 (*c* 1.0, $CHCl_3$) {Lit.[16] $[\alpha]_D^{32}$ +31.5 (*c* 1.0, C_6H_6)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 80 → 110 °C (1.0 °C/min)]. t_R = 24.3 min (*R*); t_R = 25.7 min (*S*).

FTIR (neat): 3361, 2962, 1450, 1377, 1200, 1042, 973 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 7.17 (d, *J* = 7.8 Hz, 2 H, H_{Ar}), 4.54 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 2.37 (s, 3 H, CH_3), 2.05 (br s, 1 H, OH), 1.66–1.87 (m, 2 H, CH_2), 0.92 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7, 129.1, 127.6, 125.9, 75.8, 31.9, 21.1, 10.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{14}ONa$: 173.0942; found: 173.0945.

1-(4-Chlorophenyl)propan-1-ol

Yield: 0.168 g (99%); colorless oil; $[\alpha]_D^{30.1}$ +39.2 (*c* 1.2, $CHCl_3$) {Lit.[16] $[\alpha]_D^{37}$ +38.9 (*c* 1.2, $CHCl_3$)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 100 → 130 °C (1.0 °C/min)]. t_R = 22.0 min (*R*); t_R = 21.3 min (*S*).

FTIR (neat): 3358, 2965, 1460, 1410, 1198, 1013, 975 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 7.23 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 4.55 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 2.31 (br s, 1 H, OH), 1.65–1.83 (m, 2 H, CH_2), 0.89 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 133.0, 128.4, 127.4, 75.2, 31.8, 10.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}ClONa$: 193.0396; found: 193.0392.

1-(2-Chlorophenyl)propan-1-ol

Yield: 0.168 g (99%); colorless oil; $[\alpha]_D^{20}$ +45.2 (*c* 3, $CHCl_3$) {Lit.[17] $[\alpha]_D^{25}$ +42.2 (*c* 3.2, $CHCl_3$)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 100 → 140 °C (1.5 °C/min)]. t_R = 15.6 min (*R*); t_R = 16.5 min (*S*).

FTIR (neat): 3358, 2963, 1595, 1460, 1437, 1260, 1012 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 7.21–7.32 (m, 2 H, H_{Ar}), 5.05 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 2.87 (br s, 1 H, OH), 1.67–1.87 (m, 2 H, CH_2), 0.98 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 132.5, 129.2, 128.6, 127.0, 126.9, 71.8, 30.5, 10.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}ClONa$: 193.0396; found: 193.0391.

1-(2-Methoxyphenyl)propan-1-ol

Yield: 0.164 g (99%); colorless oil; $[\alpha]_D^{20}$ +48.1 (*c* 1, $CHCl_3$) {Lit.[18] $[\alpha]_D^{20.4}$ +31.0 (*c* 1.35, $CHCl_3$)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 100 → 180 °C (10 °C/min)]. t_R = 10.6 min (*R*); t_R = 11.5 min (*S*).

FTIR (neat): 3360, 2963, 1487, 1459, 1378, 1290, 1008 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.33 (m, 2 H, H_{Ar}), 7.00–6.89 (m, 2 H, H_{Ar}), 4.80 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 3.86 (s, 3 H, CH_3), 2.67 (br s, 1 H, OH), 1.81–1.89 (m, 2 H, CH_2), 0.97 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 132.4, 128.1, 127.0, 110.5, 75.1, 55.2, 30.2, 10.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{14}O_2Na$: 189.0891; found: 189.0889.

1-[4-(Trifluoromethyl)phenyl]propan-1-ol

Yield: 0.174 g (99%); colorless oil; $[\alpha]_D^{20}$ +24.2 (*c* 1, $CHCl_3$) {Lit.[17] $[\alpha]_D^{25}$ +20.02 (*c* 1.1, $CHCl_3$)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 100 → 140 °C (1.5 °C/min)]. t_R = 15.6 min (*R*); t_R = 16.5 min (*S*).

FTIR (neat): 3357, 2968, 1619, 1458, 1418, 1018, 975 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.2 Hz, 2 H, H_{Ar}), 7.42 (d, *J* = 8.2 Hz, 2 H, H_{Ar}), 4.55 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 1.65–1.83 (m, 2 H, CH_2), 0.90 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 126.2, 125.3, 75.3, 32.0, 9.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}F_3O$: 205.8400; found: 205.8360.

1-(Naphthalen-1-yl)propan-1-ol

Yield: 0.184 g (99%); colorless oil; $[\alpha]_D^{20}$ +53.5 (*c* 0.5, $CHCl_3$) {Lit.[17] $[\alpha]_D^{25}$ +24.5 (*c* 4, C_6H_6)}.

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 120 °C (40 °C/min)]. t_R 32.1 min (*R*); t_R 33.9 min (*S*).

FTIR (neat): 3385, 2963, 1590, 1509, 1376, 1094, 970 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 9.0 Hz, 1 H, H_{Ar}), 7.89–7.92 (m, 1 H, H_{Ar}), 7.81 (d, *J* = 8.2 Hz, 1 H, H_{Ar}), 7.65 (d, *J* = 7.1 Hz, 1 H, H_{Ar}), 7.28–7.54 (m, 3 H, H_{Ar}), 5.39 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 2.38 (br s, 1 H, OH), 1.88–2.38 (m, 2 H, CH_2), 1.05 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 133.8, 130.6, 128.9, 128.5, 127.8, 127.0, 125.9, 125.5, 123.3, 123.0, 72.5, 31.1, 10.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}ONa$: 209.0942; found: 209.0937.

1-(Pyridin-4-yl)propan-1-ol

Yield: 0.113 g (60%); colorless oil; $[\alpha]_D^{20}$ +50.4 (*c* = 0.5, $CHCl_3$).

Enantiomeric excess determined by GC using Chiralsil-Dex CB column [Oven 150 °C (20 °C/min)]. t_R = 13.7 min (*R*); t_R = 14.1 min (*S*).

FTIR (neat): 3218, 2963, 1604, 1458, 1414, 1120, 1093, 984 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 5.3 Hz, 1 H, H_{Ar}), 7.28 (d, *J* = 5.3 Hz, 1 H, H_{Ar}), 4.55 (t, *J* = 6.7 Hz, 1 H, C*H*OH), 2.28 (br s, 1 H, OH), 1.65–1.83 (m, 2 H, CH_2), 0.89 (t, *J* = 7.5 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 149.5, 121.0, 74.0, 31.7, 9.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{11}NO$: 138.0919; found: 138.0910.

1-Phenylpentan-3-ol

Yield: 0.152 g (93%); colorless oil; $[\alpha]_D^{20}$ –22.5 (*c* 1, $CHCl_3$) {Lit.[19] $[\alpha]_D^{20}$ –22.5 (*c* 1.0, EtOH)}.

Enantiomeric excess was determined by HPLC analysis: Chiralcel OD-H, hexane/*i*-PrOH (95:5), flow rate 1.0 mL/min. t_R = 11.02 min (*R*); t_R = 16.13 min (*S*).

FTIR (neat): 3357, 2926, 1603, 1496 1377, 1030, 965 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.36 (m, 5 H, H_{Ar}), 3.56–3.65 (m, 1 H, C*H*OH), 2.67–2.90 (m, 2 H, CH_2), 1.76–1.86 (m, 2 H, CH_2), 1.45–1.67 (m, 2 H, CH_2), 1.00 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 128.5, 125.8, 72.6, 38.7, 32.2, 30.3, 10.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{16}ONa$: 187.1099; found: 187.1097.

Computational Methods

The optimization of structures was carried out using the density function theory (DFT) with the B3LYP functional and the 6-31G(d,p) basis-set as implemented with the Gaussian 09 program package in toluene using the 'self-consistent reaction field' method (SCRF) with the conductor-like polarizable calculation model (CPCM). As MacroModel does not contain parametrization for zinc–carbon bonds, the initial structures of feasible complexes (catalyst + reactant) were generated using silicon instead of zinc and constraining the Si–C and Si–O bond lengths to 2.0 ± 0.1 Å.

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Supporting Information

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