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The Evaluation of Novel Camphor-derived Ligands as Catalysts in the Asymmetric Henry Reaction

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ABSTRACT

The evaluation of a series of camphor-derived ligands as catalysts in the asymmetric Henry reaction is reported. The synthesis of two novel derivatives is detailed and these molecules are also screened as catalysts in this reaction. The single crystal X-ray structure of one of the novel compounds is reported. The reaction is catalyzed with moderate to excellent yields and moderate enantioselectivity.

KEYWORDS

Camphor, asymmetric catalysis, Henry reaction, chiral ligands.

1. Introduction

This is the third paper in a series of research results from our group in the field of chiral synthesis and catalytic applications. The first paper involved the synthesis of pentacycloundecane oxazolines and the application of the ligands in an asymmetric Diels-Alder reaction.[1] The second paper made use of camphor-derived ligands in the chiral alkylation of aldehydes with diethylzinc.[2]

The nitro-aldol or Henry reaction is one of the classic named reactions in organic synthesis. Since it was discovered in 1895 it has been widely used to generate β-nitroalcohols by coupling a nucleophile generated from a nitroalkane with a carbonyl electrophile.[3–5] These β-nitroalcohols are very versatile intermediates, commonly used in the synthesis of a variety of biologically-active compounds.[6,7] It is as a result of this that much effort has been invested in the development of the asymmetric version of this carbon–carbon bond forming reaction (Scheme 1).

Since the first reported incidence of the reaction being performed with a chiral catalyst more than sixteen years ago[8] a number of authors have reported ever-improving selectivity from a range of chiral catalysts.[9–25] These catalysts are predominantly metal complexes using chiral ligands, but several examples of organocatalysts[26,27] have also emerged. Camphor-derived ligands however have not been as widely investigated. Pedro *et al.* have reported the synthesis and evaluation of some very successful camphor-derived C_1-symmetric iminopyridine ligands in this reaction.[7,18,24] One of these ligands has, after reduction to the corresponding aminopyridine derivative (Scheme 2), been used to synthesize a precursor β-nitroalcohol which was subsequently used in the synthesis of the antifungal agent miconazole.[7]

We have recently reported the synthesis of a series of camphor-derived amino and pyridyl alcohol ligands **5**–**8** (Fig. 1).[2] These ligands differ from all other camphor ligands in that they

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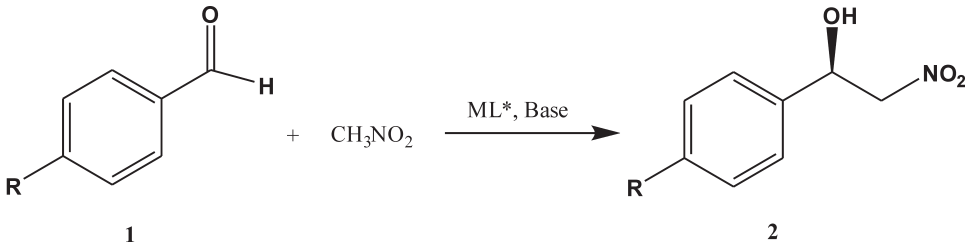
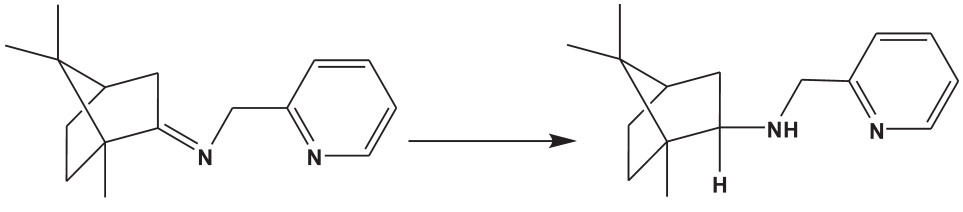


1 **2**

Scheme 1
The asymmetric Henry reaction.



3 **4**

Scheme 2
Example of a previously successful camphor-derived ligand[7].

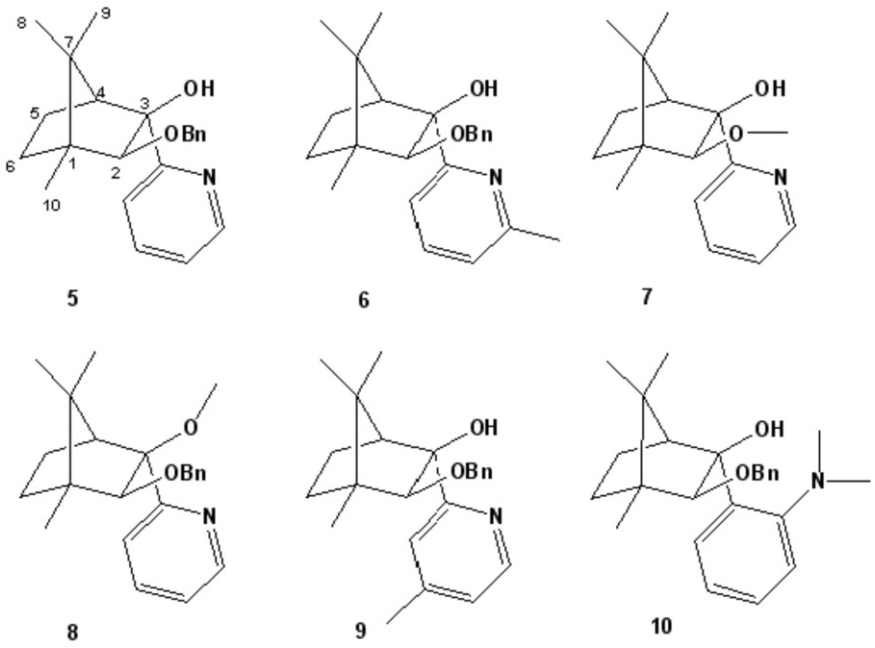
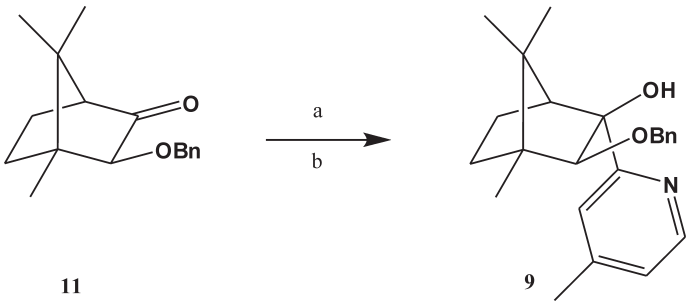


Figure 1 Novel camphor-derived ligands.



Scheme 3
Synthesis of Ligand **9**. Key: (**a**) 11, $CeCl_3$, RT, 30 min; (**b**) 4-methyl pyridyllithium, –78 °C → RT, 12 h.

are the first examples of molecules with the pyridyl alcohol moieties pendant at the C3 position of the camphor skeleton. Herein we report the synthesis of two additional derivatives (**9** and **10**) and the evaluation of these ligands as catalysts in the asymmetric Henry reaction of a series of aldehydes with nitromethane. This screening was carried out as part of an ongoing study to develop an overall picture of how successful these novel ligands are when applied as catalysts in different chiral reactions.

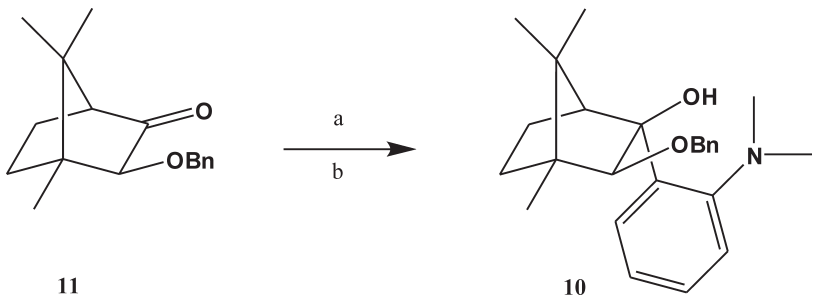
2. Results and Discussion

The two new derivatives were synthesized according to similar procedures to those reported previously.[2] For ligand **9** the benzyl ether ketone **11** was reacted with the pyridyllithium freshly prepared by reacting 2-bromo-4-methylpyridine with butyllithium at –78 °C using the same procedure as previously reported (Scheme 3).

Ligand **10** was synthesized similarly, except an aniline derivative (2-bromo-*N*,*N*-dimethylaniline) was used in place of the pyridine (Scheme 4).

On isolation of this compound it was discovered that it was possible to crystallize the free ligand from a chloroform/methanol solution to yield crystals of high enough quality for single-crystal X-ray analysis. The analysis confirmed the structure of **10** (Fig. 2).

A survey of the literature revealed that copper is a very successful metal for use in catalyzing the Henry reaction.[10,11,15,18,19] The first step in screening the ligands was to determine which



Scheme 4 Synthesis of Ligand **10**. Key: (**a**) **11**, $CeCl_3$, RT, 30 min; (**b**) 2-(dimethylamino)phenyllithium, –78 °C → RT, 12 h.

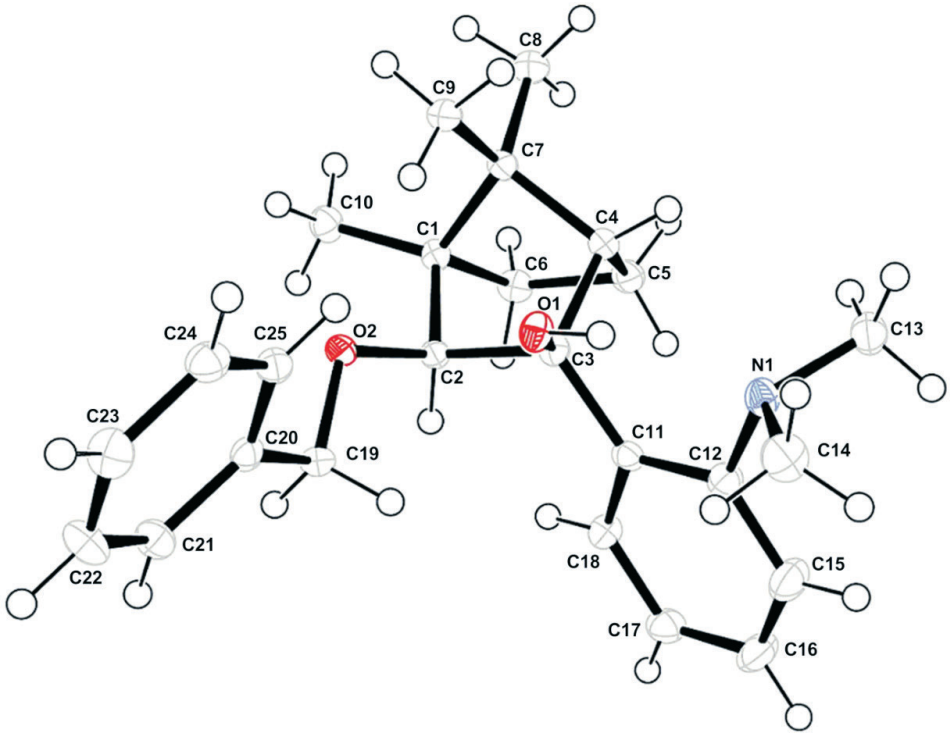


Figure 2 ORTEP diagram of novel ligand **10**.

copper salt was the most effective in catalyzing the reaction when combined with our ligands. A series of copper salts was screened in the Henry reaction of *p*-nitrobenzaldehyde with nitromethane (see Table 1).

Table 1 Reaction of *p*-nitrobenzaldehyde with nitromethane catalyzed by ligand **5** using various copper salts in ethanol.

Copper salt	Time/h	Yield/%	*ee*/%[a]	Configuration[a]
$Cu(OTf)_2$	96	10	rac	–
$Cu(OAc)_2{\cdot}H_2O$	72	75	48	*S*
$CuCl_2$	96	4	rac	–
$Cu(ClO_4)_2$	96	12	44	*S*

[a] Determined by HPLC (Chiralpak IB).

Initially, ligand **5** (10 mol %) was used in the absence of base with ethanol as the solvent. No special precautions were taken for the exclusion of moisture or air. All reactions were carried out at room temperature. A control reaction without any ligand resulted in no product formation. Of the salts investigated, $Cu(OAc)_2{\cdot}H_2O$ and $Cu(ClO_4)_2$ showed some selectivity. Due to the poor yield and long reaction time when $Cu(ClO_4)_2$ was used, this salt was not investigated further. The addition of organic bases has been shown to affect the rate of reaction as well as the selectivity.[28] This was investigated using a range of amine bases in ethanol as the solvent for the reaction (see Table 2).

Table 2 Reaction of *p*-nitrobenzaldehyde with nitromethane catalyzed by ligand **5** using various amine bases and $Cu(OAc)_2{\cdot}H_2O$ in ethanol.

Base	Time/h	Yield/%	*ee*/%[a]	Configuration[a]
DIPEA	1	79	18	*R*
DBU	1	55	2	*R*
Et_3N	48	98	56	*S*
Piperidine	1	85	3	*R*
2,6-Lutidine	24	92	46	*S*

[a] Determined by HPLC (Chiralpak IB).

Table 3 Reaction of *p*-nitrobenzaldehyde with nitromethane catalyzed by ligand **5** using various solvents and $Cu(OAc)_2{\cdot}H_2O$ with Et_3N as base.

Solvent	Time/h	Yield/%	*ee*/%[a]	Configuration[a]
Ethanol	48	98	56	*S*
Methanol	12	61	rac	–
Isopropanol	4	79	4	*R*
DCM	16	70	rac	–
THF	16	83	7	*R*
CH_3CN	12	58	3	*R*

[a] Determined by HPLC (Chiralpak IB).

From the results it was determined that Et_3N was the most suitable base. This served to reduce the reaction time compared with the reaction without base, as well as to increase the selectivity slightly. The yield for the reaction also increased quite markedly from 75 % to 98 %. Consequently, it was decided that all subsequent reactions would be carried out with this combination of salt and base. Next, the effect of solvent was investigated. The reaction was carried out in a variety of protic and aprotic solvents. Ethanol was found to be the best solvent for the reaction (see Table 3).

Once we had determined the best combination of metal salt, solvent and base, it was decided to screen the remaining ligands in order to determine which would give the best selectivity in the reaction of *p*-nitrobenzaldehyde with nitromethane (see Table 4).

Surprisingly, it was discovered that the initial ligand screened was in fact the most successful in terms of both yield and selectivity for the chosen reaction. All the other ligands showed little or no selectivity.

Table 4 Screening of ligands **6**–**10** in the Henry reaction of *p*-nitrobenzaldehyde with nitromethane using the optimized conditions for solvent, base and Cu salt.

Ligand	Time/h	Yield/%	*ee*/%[a]	Configuration[a]
6	72	96	23	*S*
7	1	88	rac	–
8	1	74	rac	–
9	1	94	4	*R*
10	72	78	3	*R*

[a]Determined by HPLC (Chiralpak IB).

The next step was to investigate the ligand (**5**) with a variety of different substrates. The reactions were carried out using the optimized conditions at room temperature (see Table 5).

The results obtained from the substrate screening were disappointing. Only the cyclohexanecarboxaldehyde substrate resulted in any significant selectivity and even in this case the selectivity was considered poor.

Table 5 Screening of different substrates with nitromethane using the optimized conditions.

Substrate	Time/h	Yield /%	*ee* /%[a]	Configuration[a]
o-Anisaldehyde	24	43	22	*S*
p-Anisaldehyde	24	44	15	*S*
Benzaldehyde	4	64	9	*S*
Cinnamaldehyde	4	68	6	*S*
o-Methoxycinnamaldehyde	4	41	14	*S*
o-Tolualdehyde	24	73	2	*S*
p-Tolualdehyde	12	50	2	*S*
o-Chlorobenzaldehyde	24	72	6	*S*
p-Chlorobenzaldehyde	12	67	2	*S*
Cyclohexanecarboxaldehyde	12	59	39	*S*

[a] Determined by HPLC (Chiralpak IB).

3. Conclusion

Two novel ligands have been synthesized to add to the series of C3 pendant ligands synthesized previously. The ligands were screened as catalysts in the asymmetric Henry reaction with excellent yields, but with only moderate selectivity.

4. Experimental

4.1. General

All NMR spectra were recorded on Bruker (Karlsruhe, Germany) AVANCE III 400 MHz or 600 MHz instruments. Infrared spectra were recorded on a Perkin-Elmer (Waltham, MA, USA) Spectrum 100 instrument equipped with a Universal ATR attachment. Optical rotation data were acquired using a Perkin-Elmer Model 341 polarimeter. Accurate mass measurements were obtained on a Bruker MicroTOF Q2 instrument with the ESI ionization method. All solvents were dried using standard procedures prior to use. All reagents were purchased from Fluka (St Louis, MO, USA) or Sigma-Aldrich (St Louis, MO, USA) and were used without further purification. Column chromatography was carried out on silica gel 60 particle size 0.063–0.200 mm (230–400 mesh). Full analytical data are reported for novel compounds only.

4.2. Synthesis of Ligands 5–8

The synthesis of all precursor compounds and ligands **5**–**8** was reported previously.[2]

4.3. General Procedure for the Synthesis of Ligands 9 and 10

Anhydrous $CeCl_3$ (1.5 eq) was weighed into a dry two-neck round bottom flask.

The ketone **11** (1 eq) in dry THF (20 mL) was added and the mixture was stirred under nitrogen at room temperature until a homogeneous gel-like mixture was obtained (usually about 30 min). The mixture was cooled to –78 °C and the appropriate pyridyllithium or lithioaniline solution (3 eq) in THF was added. The solution was stirred for *ca.* 1 h at –78 °C before being allowed to warm to room temperature. The mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 mL) and 2 mol L^{-1} HCl was added. The solution was then extracted with 2 mol L^{-1} HCl (2 × 30 mL) and the acidic extract retained. The acid layer was neutralized with solid sodium bicarbonate before being extracted with diethyl ether (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane 5:95).

4.3.1. *(1R, 2S, 3S, 4S)-(+)-2-benzyloxy-1,7,7-trimethylbicyclo [2.2.1]heptan-3-(4-methylpyridine)-3-ol* (**9**)

Pale yellow waxy solid (59 %): R_f = 0.59 on TLC EtOAc:hexane 25:75; $[\alpha]^{20}_D$ + 20.7 ° (c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.54–0.59 (m, 1H), 0.86 (s, 3H), 1.01 (s, 3H), 1.21–1.59 (m, 6H), 2.01 (s, 1H), 2.34 (s, 3H), 3.82 (s, 1H), 4.60–4.68 (q, 2H), 4.81 (s, 1H), 6.96–6.98 (d, 1H), 7.25–7.37 (m, 6H), 8.32–8.34 ppm (d, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 12.0 (q), 21.1 (q), 22.2 (t), 22.4 (q), 22.5 (q), 33.1 (t), 49.8 (s), 50.4 (s), 56.4 (d), 74.4 (t), 83.4 (d), 87.9 (d), 122.9 (d), 123.2 (d), 127.6 (d), 127.7 (d), 128.3 (d), 138.4 (s), 146.8 (d) 164.6 ppm (s); IR (ATR): ν_{max} 3499 (br,m), 2945 (m), 1603 (s), 1065 (vs), 695 (s) cm^{-1}; HRMS calcd. for $C_{23}H_{29}NO_2$ ([M+H]$^+$) 352.227654, found 352.230899.

4.3.2. *(1R, 2S, 3S, 4S)-(-)-2-benzyloxy-1,7,7-trimethylbicyclo [2.2.1]heptan-3-[(2-dimethylamino)-phenyl]-3-ol* (**10**)

White solid (62 %): R_f = 0.57 on TLC EtOAc:hexane 25:75; m. p. 106–110 °C; $[\alpha]^{20}_D$ –35.5 °(c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.63–0.67 (m, 1H), 0.86 (s, 3H), 1.01 (s, 3H), 1.10–1.18 (m, 1H), 1.50–1.58 (m, 6H), 1.97 (s, 1H), 2.69 (s, 6H), 4.05 (s, 1H), 4.28–4.31 (d, 1H), 4.78–4.81 (d, 1H), 7.08–7.41 (m, 8H), 7.94 ppm (s, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 12.5 (q), 22.4 (q), 22.7 (t), 22.8 (q), 33.6 (q), 49.8 (s), 49.9 (s), 58.3 (s), 72.6 (d), 83.6 (d), 89.2 (t), 123.9 (d), 125.1 (d), 126.3 (d), 126.9 (d), 127.4 (d), 127.7 (d), 128.0 (d), 139.7 (s) 142.7 (s), 152.9 ppm (s); IR (ATR): ν_{max} 2942 (m), 1455 (s), 1112 (s), 736 (vs), 559 (s) cm^{-1}; HRMS calcd. for $C_{25}H_{33}NO_2$ ([M+H]$^+$) 380.258954, found 380.260591. Elemental analysis: calculated C = 79.11 %, H = 8.76 %, N = 3.69 %, O = 8.43 %; found C = 79.85 %, H = 8.59 %, N = 3.51 %, O = 8.05 %.

4.4. General Procedure for Asymmetric Henry Reaction

The ligand (10 mol %) was dissolved in ethanol (2 mL) in a Schlenk tube. The copper salt (1.2 mol equivalent relative to ligand) was added and the resulting blue solution was stirred at room temperature for 1 h. Triethylamine (1 mol equivalent relative to substrate) was added, followed by the substrate (50 mg). The mixture was stirred at room temperature until no starting material remained (TLC). The green solution was evaporated *in vacuo* and the product isolated using flash chromatography. The enantiomeric excess was determined by HPLC analysis [Daicel Chiralpak IB column (hexane:*i*-PrOH 90:10) flow rate = 0.8 mL min^{-1}, *t*(*R*) 19.0 min, *t*(*S*) 21.0 min]. The configurations were assigned by comparison of HPLC elution order with literature values.[6,28]

4.5. X-ray details

CCDC 721782 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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