(1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol: An Effective Ligand for Asymmetric Catalysis of Transfer Hydrogenations of Ketones

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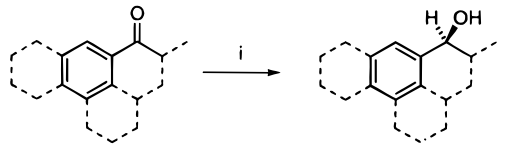
Introduction

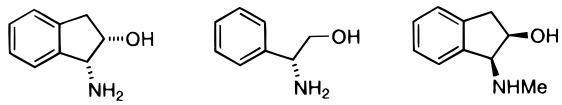
Dramatic developments in asymmetric catalysis have been recorded in recent years.[1] In particular, the reduction of ketones to enantiomerically enriched alcohols represents a pivotal transformation due to the combination of versatility and practical simplicity.[2] We have recently published the results of our ongoing studies of phosphinamide catalysts for the asymmetric reductions of ketones by borane.[3]

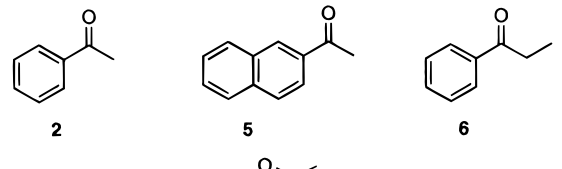
In a complementary series of investigations, we have studied the reduction of ketones using chiral transfer hydrogenation methodology. In principle, this approach benefits from the use of mild reagents and a requirement for very low quanitities of an appropriate catalyst. While many methods have been reported for this transformation,[4] recent years have witnessed a rapid development of the area thanks in particular to the efforts of Noyori[5] and others.[6] Specifically, we were intrigued by the use of amino alcohols in combination with ruthenium(II) arene complexes, a technique that provides remarkably high catalytic activities when even a very small amount of ligand is employed.[5b] In order to maximize asymmetric inductions, we felt that the use of a stereochemically rigid amino alcohol, and in particular, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**1**), would be beneficial. Amino alcohol **1**, which is commercially available in both enantiomeric forms, is an important component of the Merck anti-HIV compound Indinavir[7] and has been used as the basic component of a valuable series of oxazolidinone chiral auxiliaries[8] and bis-oxazolines for asymmetric catalysis of Diels−Alder reactions.[9]

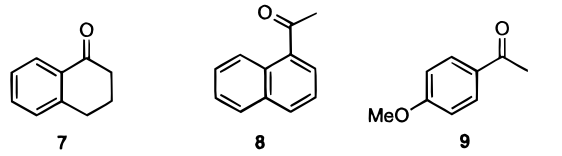
Scheme 1[a]

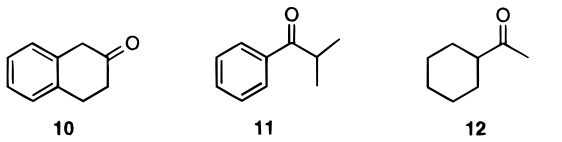


[a] Reagents and conditions: (i) 1 mol % of **1**, **3**, or **4**, 0.25 mol % of $[RuCl_2(arene)]_2$, 2.5 mol % of KOH, *i*-PrOH; see Table 1.









Results and Discussion

In the event, (1*R*,2*S*)-(+)-(**1**) proved to be an excellent ligand for this application (Scheme 1, Table 1). The use of 1 mol % in conjunction with 0.25 mol % of the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ and 2.5 mol % of KOH in propan-2-ol ([ketone] = 0.1 M) at room temperature[5b] resulted in reduction of acetophenone (**2**) to (*S*)-1-phenylethanol in 70% isolated yield and 91% ee after 1.5 (Table 1, entry 1). The use of other ruthenium arene complexes gave lower enantiomeric excesses, 69% and 82% ee using the benzene- and mesitylene-substituted

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Table 1

entry	ketone	ligand	complex[a]	*T*/°C	*t*/h	yield/%[b]	% ee[c] (*R*/*S*)
1	**2**	**1**	A	rt	1.5	70	91 (*S*)
2	**2**	**1**	B	rt	1.6	68	69 (*S*)
3	**2**	**1**	C	rt	2	73	82 (*S*)
4	**2**	**3**	A	rt	2	95	23 (*S*)
5	**2**	**4**	A	rt	15	33	27 (*S*)
6	**2**	**1**	A	0	6.5	49	93 (*S*)
7	**2**	**1**	A	−20	24	47	90 (*S*)
8	**2**	**1**	A	−20	72	47	84 (*S*)
9	**5**	**1**	A	rt	1.7	94	86 (*S*)
10	**5**	**1**	A	rt	18	89	81 (*S*)
11	**6**	**1**	A	rt	1.5	84	86 (*S*)
12	**6**	**1**	A	rt	20	70	85 (*S*)
13	**7**	**1**	A	rt	4	40	98 (*S*)
14	**7**	**1**	A	rt	16	39 (85)	98 (*S*)
15	**7**	**1**	A	rt	46	60	67 (*S*)
16	**7**	**1**	A	45	4	63 (88)	95 (*S*)
17	**7**[d]	**1**[d]	A	rt	4	60 (94)	87 (*S*)
18	**8**	**1**	A	rt	1.75	79	94 (*S*)
19	**9**	**1**	A	rt	1.5	56	84 (*S*)
20	**10**	**1**	A	45	6	85	81 (*S*)
21	**11**	**1**	A	rt	15	52 (90)	43 (*S*)
22	**12**	**1**	A	45	3	63	7 (*S*)

[a] (A) arene = *p*-cymene, (B) arene = benzene, (C) arene = mesitylene. [b] Isolated yields: yields corrected for recovered starting material in parentheses. [c] Enantiomeric excesses were determined using chiral HPLC with a Chiralcel OD column. [d] 4 mol % of **1**, 1 mol % $[RuCl_2(p\text{-cymeme})]_2$ used.

analogues, for example (Table 1, entries 2 and 3). Although purification by flash chromatography was employed in most cases, the reaction could be worked up simply by filtration of the reaction mixture through a plug of silica followed by removal of solvent under vacuum. In order to determine the importance of the rigid structure of the ligand, we repeated the reaction under identical conditions using (*R*)-phenylglycinol (**3**). In this reaction, (*S*)-phenylethanol was obtained in 95% yield but only 23% enantiomeric excess (Table 1, entry 4), a dramatically inferior result.

Although we have not yet investigated a systematic series of ligand modifications, the use of the *N*-methyl derivative **4** resulted in an inferior asymmetric induction (Table 1, entry 5). It therefore appears that a primary amine function in the ligand is essential. The ratio of ligand to ruthenium(II) is also critical; the use of 0.5 mol % of $[RuCl_2(p\text{-cymene})]_2$ with 1 mol % **1** under conditions identical to those in entry 1 of Table 1 resulted in a decrease of the ee to 68%.

Concerned that the enantiomeric excesses of the reduction products might be reduced under extended reaction times, we studied the progress of the reduction by taking samples for analysis by chiral HPLC. The results of this study reveal that over the reaction time studied (typically 2 h), no significant erosion of the ee was observed. However, further results (see below) suggest that erosion of enantiomeric excesses does take place over longer reaction times. This erosion is presumably a result of the known reversability of the reaction.[5a,d] The use of formic acid/triethylamine has been reported, for certain systems,[5d] to be capable of promoting transfer hydrogenation without the associated reversible reaction. In the case of the ligand **1**, however, no reduction was observed using this hydride source.

Further improvements to the selectivity could be achieved upon reduction of the reaction temperature, although the rate was reduced. Hence, using the same reaction conditions as given above, at 0 °C rather than room temperature, the selectivity increased to 93% ee but the yield of 49% reflected the incomplete reaction (Table 1, entry 6). No improvement was recorded at −20 °C, at which temperature an incomplete reaction was observed, even after a reaction time of 24 h. In an attempt to improve the yield, a longer reaction time (72 h) was employed; however, this merely resulted in a further erosion of the asymmetric induction (Table 1, entries 7 and 8).

Reduction of a series of aromatic ketones under identical conditions using ligand **1** resulted in reduction to the corresponding alcohols in good to excellent yields and enantiomeric excesses (Table 1, entries 9−22). The sense of the reductions appears to be controlled by steric factors in each case. In the cases of both **5** and **6** a decrease in selectivity was observed when prolonged reaction times were employed. The reduction of 1-tetralone (**7**) gave the most remarkable result: up to 98% enantiomeric excess under the room temperature reduction conditions. Extended reaction times (Table 1, entry 15) and increased catalyst loading (Table 1, entry 17) resulted in considerable loss of enantioselectivity, although the use of higher reaction temperatures did not (Table 1, entry 16). High ee's in the case of 1-tetralone (**7**) reduction were achieved, but at the cost of conversion. Isolated yields of 39−63% were obtained; however, when account was taken of the quantity of recovered starting material the mass balance is generally excellent (see Table 1).

In the case of 2-tetralone (**10**), the asymmetric induction was somewhat reduced, while for **11** the drop in ee was greater still. The suggestion that the enantioselectivity of the reaction is driven by the steric difference between the substituents that flank the ketone is supported by these results, since the difference in steric demand between flanking groups is low in each case. The reduction of the nonaromatic ketone **12** gave a reduction product with a very low ee, a result that underlies the key requirement for an aromatic system in the substrate. In the case of reduction of **10** and **12** it is noteworthy that reasonable reaction rates and conversions were only achieved when the hydrogenations were run at 45 °C.

Conclusions

We have demonstrated that (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**1**) is an excellent ligand for the control of asymmetric ruthenium-catalyzed transfer hydrogenation of ketones. The required ligand loading is very low (typically 1 mol %), and yields and enantiomeric excesses are generally excellent. We are presently examining the extension of this methodology to novel substrates and methods by which the undesirable reaction reversibility can be prevented.

Experimental Section

General Methods. Reactions were run under an atmosphere of nitrogen in flame- or oven-dried Schlenk flasks. Propan-2-ol (HPLC grade) was degassed prior to use. All ketones were purified by short path distillation or passing through a plug of deadened silica. Reactions were monitored by TLC using aluminum-backed silica gel 60 (F_{254}) plates, visualized using UV_{254nm} and PMA dip. Flash column chromatography was carried out routinely using 60 Å silica gel. Proton NMR spectra were recorded on a 250 MHz instrument. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD column.

General Procedure for Transfer Hydrogenation of Ketones. A solution of (*p*-cymene)ruthenium(II) chloride dimer (7.7 mg, 0.0125 mmol) and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (7.5

mg, 0.05 mmol) in dry propan-2-ol (4 mL) was heated at 80 °C for 20 min under nitrogen. After being cooled to room temperature, the light brown solution was transferred *via* cannula to a large sealed Schlenk flask. A solution of ketone (5 mmol) in dry degassed propan-2-ol (45 mL) was added *via* cannula, followed by KOH (1.25 mL, 0.1 M in propan-2-ol, 0.125 mmol). The reaction was run at room temperature and monitored by TLC until substantially complete (generally 2 h). Workup consisted of filtering the dark brown solution through a pad of silica under vacuum (with ethyl acetate washings, 2 × 50 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (SiO_2, ethyl acetate−petroleum ether).

(*S*)-1-Phenylethanol: 91% ee (*S*) by HPLC (Chiralcel OD, ethanol:hexane = 5:95 (0.5 mL/min), *S* isomer 17.1 min, *R* isomer 14.8 min); $[\alpha]_D$ −48.8° (*c* 1.0, CH_2Cl_2) (lit.[10a] $[\alpha]_D$ +48.6° (*c* 1.0, CH_2Cl_2), 96% ee (*R*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.37−7.25 (m, 5 H), 4.86 (q, *J* = 6.41 Hz, 1 H), 1.92 (br s, 1 H), 1.48 (d, *J* = 6.41 Hz, 3 H).

(*S*)-1-(2′-Naphthyl)ethanol: 86% ee (*S*) by HPLC (Chiralcel OD, ethanol:hexane = 5:95 (0.5 mL/min), *S* isomer 26.4 min, *R* isomer 29.3 min); $[\alpha]_D$ −34.3° (*c* 1.10, EtOH) (lit.[10b] $[\alpha]_D$ −41.9° (*c* 4.92, EtOH), (*S*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.86−7.81 (m, 4 H), 7.53−7.42 (m, 3 H), 5.07 (dq, *J* = 3.20, 6.39 Hz, 1 H), 1.94 (d, *J* = 3.20 Hz, 1 H), 1.59 (d, *J* = 6.68 Hz, 3 H).

(*S*)-1-(1′-Naphthyl)ethanol: 94% ee (*S*) by HPLC (Chiralcel OD, ethanol:hexane = 5:95 (0.5 mL/min), *S* isomer 24.4 min, *R* isomer 42.2 min); $[\alpha]_D$ −79.6° (*c* 1.02, Et_2O) (lit.[10c] $[\alpha]_D$ +82.1° (*c* 1.0, Et_2O), 99% ee (*R*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 8.16−8.09 (m, 1 H), 7.91−7.84 (m, 1 H), 7.80−7.77 (d, *J* = 8.14 Hz, 1 H), 7.70−7.67 (d, *J* = 7.26 Hz, 1 H), 7.56−7.45 (m, 3 H), 5.68 (q, *J* = 6.39 Hz, 1 H), 1.91 (br s, 1 H), 1.68 (d, *J* = 6.39 Hz, 3 H).

(*S*)-1-Phenylpropanol: 86% ee (S) by HPLC (Chiralcel OD, ethanol:hexane = 5:95 (0.5 mL/min), *S* isomer 16.1 min, *R* isomer 14.2 min); $[\alpha]_D$ −33.0° (*c* 5.15, EtOH) (lit.[5d] $[\alpha]_D$ −34.0° (*c* 5.03, EtOH), 97% ee (*S*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.36−7.23 (m, 5 H), 4.60 (t, *J* = 6.60 Hz, 1 H), 1.91−1.69 (m, 2 H), 1.88 (br s, 1 H), 0.92 (t, *J* = 7.51 Hz, 3 H).

(*S*)-1-Tetralol: 98% ee (*S*) by HPLC (Chiralcel OD, propan-2-ol:hexane = 2:98 (0.9 mL/min), *S* isomer 17.4 min, *R* isomer 19.8 min); $[\alpha]_D$ +34.4° (*c* 1.01, $CHCl_3$) (lit.[10d] $[\alpha]_D$ +25.8° (*c* 3.10, $CHCl_3$), (*S*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.46−7.41 (m, 1 H), 7.23−7.17 (m, 2 H), 7.12−7.09 (m, 1 H), 4.79 (br s, 1 H), 2.87−2.69 (m, 2 H), 1.99−1.60 (m, 5 H).

(*S*)-2-Tetralol: 81% ee (*S*) by HPLC of (*S*)-Mosher ester (Chiralcel OD, propan-2-ol:hexane = 0.1:99.9 (0.9 mL/min), *S* isomer 34.4 min, *R* isomer 38.4 min); $[\alpha]_D$ −54.4° (*c* 0.70, $CHCl_3$) (lit.[10e] $[\alpha]_D$ −55.4° (*c* 0.70, $CHCl_3$), 95.5% ee (*S*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.15−7.07 (m, 4 H), 4.16 (m, 1 H), 3.14−2.72 (m, 4 H), 2.11−2.01 (m, 1 H), 1.90−1.75 (m, 1 H), 1.68 (s, 1 H).

(*S*)-2-Methyl-1-phenylpropanol: 43% ee (*S*) by HPLC (Chiralcel OD, propan-2-ol:hexane = 2:98 (0.5 mL/min), *S* isomer 25.4 min, *R* isomer 28.8 min); $[\alpha]_D$ −21.0° (*c* 1.05, Et_2O) (lit.[10f] $[\alpha]_D$ +34.8° (*c* 4.90, Et_2O), 73% ee (R)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.37−7.23 (m, 5 H), 4.36 (d, *J* = 6.68 Hz, 1 H), 1.96 (dsept, *J* = 6.69, 6.69 Hz, 1 H), 1.83 (br s, 1 H), 1.00 (d, *J* = 6.68 Hz, 3 H), 0.80 (d, *J* = 6.98 Hz, 3 H).

(*S*)-1-(*p*-Methoxyphenyl)ethanol: 84% ee (S) by HPLC (Chiralcel OD, propan-2-ol:hexane = 10:90 (0.5 mL/min), *S* isomer 16.9 min, *R* isomer 15.9 min); $[\alpha]_D$ −44.2° (*c* 1.06, $CHCl_3$) (lit.[5d] $[\alpha]_D$ −51.9° (*c* 1.04, $CHCl_3$), 97% ee (*S*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 7.13 (AB, *J* = 9.01 Hz, $\Delta\upsilon$ = 105 Hz, 4 H), 4.85 (q, *J* = 6.40 Hz, 1 H), 3.81 (s, 3 H), 1.81 (br s, 1 H), 1.48 (d, *J* = 6.40 Hz, 3 H).

(*S*)-1-Cyclohexylethanol: 7% ee (S) by HPLC of 4-nitrobenzoyl ester (Chiralcel OD, propan-2-ol:hexane = 0.1:99.9 (0.9 mL/min), *S* isomer 19.5 min, *R* isomer 21.4 min); $[\alpha]_D$ +0.3° (*c* 12.3, $CHCl_3$) (lit.[10g] $[\alpha]_D$ −3.4° (*c* 1.1, $CHCl_3$), 94% ee (*R*)); ^{1}H NMR ($CDCl_3$, 250 MHz) 3.60−3.50 (m, 1 H), 1.93−1.63 (m, 5 H), 1.50 (br s, 1 H), 1.15 (d, *J* = 6.10 Hz, 3 H), 1.34−0.88 (m, 6 H).

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