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Amide catalysts with tetradentate ligands and the asymmetric transfer hydrogenation of carbonyl compounds

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Abstract

Amidic tetradentate catalysts comprising two *trans*-1,2-cyclohexanediamine units linked via a dicarbonyl spacer are shown to provide useful enantiomeric excesses in the asymmetric transfer hydrogenation from propan-2-ol to aromatic ketones. *N*-Benzylation of the terminal amino groups results, in several cases, in reversal of the absolute configuration of the major product.

The design of new ligands for catalytic asymmetric synthesis is a ceaseless quest. New features regarding ligand acceleration and the mechanism of catalysis can be revealed by ligands, which hitherto have been predominantly bidentate.[1] One notable exception is the class of chiral salen derivatives[2] extensively used in the epoxidation of unfunctionalised alkenes. However, multiple coordination of a metal to nitrogen is frequently observed in metalloproteins, e.g. Cu, Zn superoxide dismutase in which Cu(II) is tetragonally bound to four histidine ligands.[3] We sought tetradentate coordination as part of an amide network that might possess some essential features of metalloprotein catalysts.[4] Since metalloproteins are commonly involved in redox processes,[5] we selected the contemporary area of asymmetric transfer hydrogenation[6] as a probe reaction for catalyst design and optimisation. While a small-molecule mimic of metalloproteins has been designed,[7] tests on asymmetric induction were unsuccessful. The use of amides in catalytic asymmetric synthesis has been described only recently.[8] In the present work, the potentially tetradentate ligands **1** containing amides are shown to act as catalysts for enantioselective transfer hydrogenation (Scheme 1).[9]

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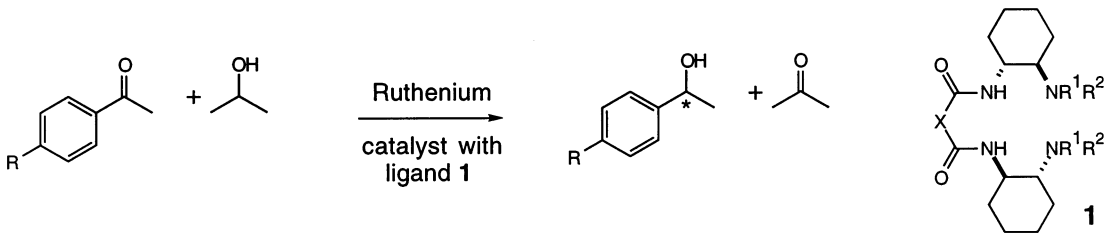
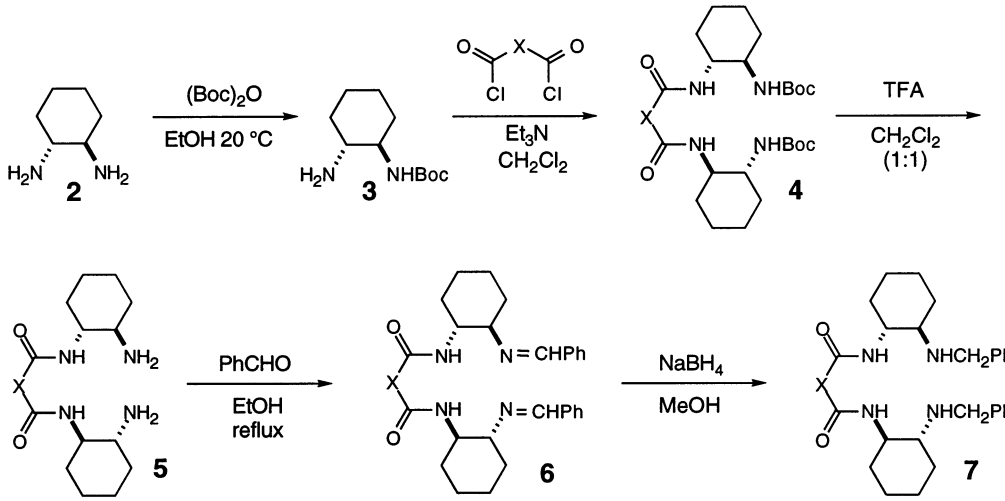


Scheme 1. Asymmetric transfer hydrogenation using (1*R*,2*R*)-*N*,*N*′-bis-[2-(aminocyclohexyl)]diamide catalysts

Catalysts of type **1** were synthesised according to Scheme 2. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane **2**[10] was monoprotected by vigorous stirring with $(Boc)_2O$ (ethanol, 20°C, 16 h) to give **3** (74%).[11] Oxamide **4a** was prepared in 77% yield by heating **3** (2 mmol) with diethyl oxalate (1 mmol) in ethanol at reflux (16 h). The malonamide **4b** was prepared in 75% yield by treating **3** (9.6 mmol) with dimethylmalonyl dichloride (4.8 mmol) and triethylamine (10 mmol) in dichloromethane at 0°C for 16 h. The succinamide **4c** was obtained in 90% yield from **3** (9.8 mmol) with succinyl dichloride (4.8 mmol) and triethylamine (10 mmol) in dichloromethane at 0°C for 16 h. For the Boc derivative **4a**, deprotection to give **5a** (99%) was accomplished by stirring in a 1:1 v/v mixture of dichloromethane and trifluoroacetic acid (13 mL per mmol of **4a**) at 20°C for 2 h; **4b** and **4c** were similarly deprotected.[12] The diimine **6a** was obtained in 95% yield by heating **5a** with benzaldehyde (4 mmol per mmol of **5a**) in ethanol at reflux for 16 h. The imine **6b** was similarly obtained (98%). Reduction of **6a** to **7a** (82%) was achieved with sodium borohydride (0.5 mmol per mmol of **6a**) in anhydrous methanol (20°C, 16 h). The diamine **7b** was similarly prepared in 65% yield.



Scheme 2. Synthesis of (1*R*,2*R*)-*N*,*N*′-bis-[2-(aminocyclohexyl)]diamide catalysts: (a) X = -; (b) $X = (CH_3)_2C$; (c) $X = CH_2CH_2$

Ruthenium catalysed asymmetric transfer hydrogenation takes advantage of low redox potentials and the strong affinities of ruthenium for heteroatoms, and has emerged as an efficient system for the asymmetric reduction of carbonyl groups.[6] Consequently, it was used to test the amide ligands **5**–**7** (Table 1) under standard conditions, in which the catalysts are preformed by heating the amide (2 mol%) with $RuCl_2(PPh_3)_3$ (1 mol%)[13] in propan-2-ol at 80°C

for 1 h. After cooling to 20°C, KOH (10 mol%) was added, then acetophenone (0.1 M) or a derivative. The major conclusions to be drawn are: first, that the oxamide ligand **5a**, possessing terminal NH_2 groups, afforded e.e.'s (39–48%) that depended little on the *p*-substituent R of the aryl ketone (Scheme 1). Secondly, compared with NH_2 as the terminal group, an *N*-benzyl group generally furnishes higher yields (e.g. entries 4 and 5, Table 1), although in only low e.e.'s. Thirdly, an oxamide linker gave the best yields but poor e.e.'s (9–15%, *S* or *R*); in contrast, a malonamide spacer gave poorer yields but substantially higher e.e.'s (e.g. entries 1 and 2 compared with entries 6 and 7); a succinamide linker was unsuccessful. Lastly, and most significantly, *N-benzylation leads in every case for the oxamide catalysts to a greatly increased proportion of the (R)-enantiomer, and for the examples R = H and Cl, even results in a reversal of the absolute configuration of the major product*. Thus, for R = H, entries 1 and 4, and entries 2 and 5 show switching to enantiomeric excess in favour of the (*R*)-configuration, using the *N*-benzyl catalysts, as do the runs for R = Cl (entries 10 and 11). For both R = F and OMe, a shift in favour of the (*R*)-configuration is again observed, but to a lesser extent. These examples of reversal[14] of enantiomeric excess designation are apparently the first to be reported for asymmetric transfer hydrogenation. Thus, although rhodium catalysed reduction of ketones with diurea ligands containing four chiral centres exhibited matched and mismatched effects, depending on the diastereoisomerism of the ligands, *N*-methylation did not lead to reversal of enantioselectivity.[15] The potential of the same ligand skeleton to provide both enantiomers, thus obviating the need to prepare both enantiomeric ligands, is a major advantage of these new tetra-aza catalysts that deserves further study.

Table 1
Reduction of acetophenone and derivatives with propan-2-ol catalysed by $RuCl_2(PPh_3)_3$ at 20°C[a]

Entry	Ketone (R)	Ligand	Ligand linker X	Terminal group	Reaction time (h)	Conversion (%)[b]	e.e. (%)[c]	Configuration[c]
1	H	**5a**	–	NH_2	24	29	48	(*S*)
2	H	**5a**	–	NH_2	48	44	44	(*S*)
3	H	**6a**	–	N=CHPh	24	45	<2	–
4	H	**7a**	–	$NHCH_2Ph$	24	64	16	(*R*)
5	H	**7a**	–	$NHCH_2Ph$	48	71	15	(*R*)
6	H	**5b**	$(CH_3)_2C$	NH_2	24	8	62	(*R*)
7	H	**5b**	$(CH_3)_2C$	NH_2	48	8	61	(*R*)
8	H	**7b**	$(CH_3)_2C$	$NHCH_2Ph$	48	0	–	–
9	H	**6c**	CH_2CH_2	NH_2	48	0	–	–
10	Cl	**5a**	–	NH_2	72	28	39	(*S*)
11	Cl	**7a**	–	$NHCH_2Ph$	72	49	13	(*R*)
12	F	**5a**	–	NH_2	72	29	46	(*S*)
13	F	**7a**	–	$NHCH_2Ph$	72	71	9	(*S*)
14	OMe	**5a**	–	NH_2	72	22	43	(*S*)
15	OMe	**7a**	–	$NHCH_2Ph$	72	13	12	(*S*)

[a] Standard conditions of KOH (10 mol%), ligand (2 mol%) and $RuCl_2(PPh_3)_3$ (1 mol%) were used.
[b] Conversions were determined by ^1H NMR spectroscopy.
[c] The e.e.'s and absolute configurations of the alcohols were determined in accordance with literature methods.[16]

Although tetradentate ligation of these catalysts through four nitrogen atoms is possible, it has yet to be investigated. Amide coordination to metals is known in both the neutral amide and

the anionic amide forms.[17,18] The possibility of coordination through either nitrogen or oxygen atoms presents further options.[17,18] Dianionic bis-amides are known to stabilise high oxidation states of coordinated metal ions,[19] an important factor for asymmetric transfer hydrogenation. Amide ligands have been used in catalysts for asymmetric nucleophilic ring opening,[17,20] in asymmetric Michael additions,[8b] and in C–H oxidations.[21] The present study shows that significant enantiomeric excesses can also be obtained for asymmetric transfer hydrogenation using catalysts containing amide groups in the ligand. Consequently, these results hold promise for the design of new amidic catalysts that mimic redox processes carried out by enzyme complexes.

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