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Highly Effective NPN-type Tridentate Ligands for Asymmetric Transfer Hydrogenation of Ketones

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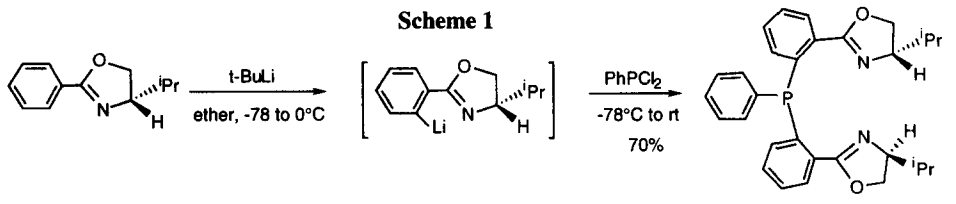
Summary: New chiral NPN-type tridentate ligands containing two oxazoline rings and one phosphine have been synthesized, and their Ru(II) complexes show high reactivity and enantioselectivity in transfer hydrogenations of both aryl alkyl and dialkyl ketones (with ee's up to 92% for a dialkyl ketone). Copyright © 1996 Elsevier Science Ltd

It has been more than 20 years since asymmetric transfer hydrogenation of prochiral ketones was first described.[1] However, only recently have major breakthroughs occurred in this area.[2-5] Although some tridentate ligands have been used for asymmetric transfer hydrogenation,[5] better ligands still are needed. In particular, asymmetric transfer hydrogenation of dialkyl ketones remains a challenging problem. Herein we present very promising preliminary results for asymmetric transfer hydrogenation of various aryl alkyl and dialkyl ketones catalyzed by Ru(II) complexes of new tridentate ligand systems containing two oxazoline rings and one phosphine.

Ligand systems incorporating chelating nitrogen groups have been investigated for asymmetric transfer hydrogenation, and some have shown high enantioselectivity and reactivity.[1-8] Based on these results, we have designed and synthesized NPN-type ligand **I**[9] (**Scheme 1**), which shows good conversion but low enantioselectivity in transfer hydrogenation of acetophenone.[10]

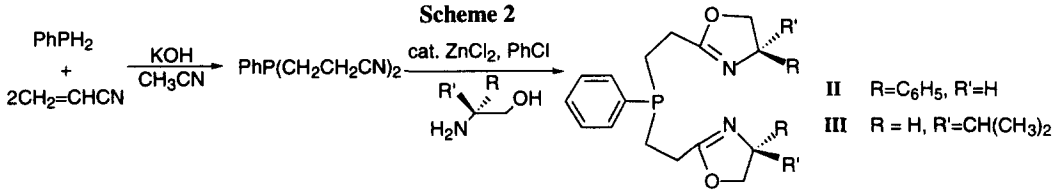
Scheme 1



I

The low enantioselectivity with ligand **I** may be due to two available propeller orientations of the phenyl groups on the phosphine, which confer conformational ambiguity on the ligand. To improve the catalytic system, we modified the design and prepared two other NPN-type ligands **II** and **III** (**Scheme 2**), where two methylene groups replace the 1,2-phenylene backbone in **I**. The synthesis of these ligands is straightforward. First, bis(2-cyanoethyl) phenylphosphine was synthesized through Michael addition of phenylphosphine to acrylonitrile (82%).[11] Then it was refluxed in chlorobenzene with amino alcohols in the presence of a catalytic amount of anhydrous zinc chloride,[12] resulting in formation of **II**[13] and **III**,[14] respectively (30%, **II**; 34%, **III**).

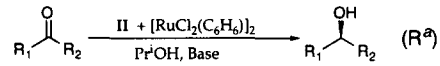
Scheme 2

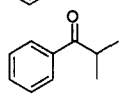
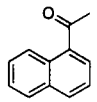
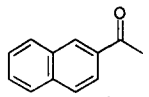
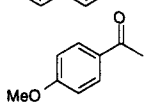
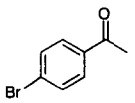
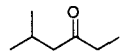
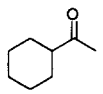


II & III

As shown in **Table 1**, the *in situ* complex made from $[RuCl_2(C_6H_6)]_2$ and ligand **II** is a highly efficient catalyst for transfer hydrogenation of ketones. Results with ligand **III** are provided in a footnote.[16]

Table 1. Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Ligand **II**-Ru(II) Complex[15]



Entry	Substrate	Temp(°C)	Time(h)	Yield(%)[b]	ee(%)[b]
1[c]		80	0.2	72	79
2		80	2.5	89	59
3		80	0.25	81	76
4		80	1.0	93	73
5		80	2.0	80	14
6		80	1.5	84	16
7		rt	24	100	63
8		rt	22	93	63
9[d]		rt	24.5	85	92

a. Absolute configurations were determined by comparing optical rotations with literature values. *b.* ee and yield were determined by GLC analysis with Supelco β-DEX120 and γ-DEX225 capillary chiral columns. *c.* Ru:L = 1:2 *d.* NaOMe was used as the base instead of NaH, and substrate:Ru=50:1

For aryl alkyl ketones, heating is generally required to achieve good conversion and enantioselectivity. For example, transfer hydrogenation of acetophenone gives the highest ee (79%) in refluxing 2-propanol (entry 1). However, we observed that prolonged heating increases the conversion but decreases the ee (sometimes severely) for these substrates. This erosion of selectivity may be attributed to the nature of transfer hydrogenation (the reaction is reversible and gives no enantioselectivity at equilibrium).[17] For dialkyl ketones, very good conversions (85-100%) and enantioselectivities (63-92%) have been observed, which are considerably *higher* than those for aryl alkyl ketones. Our best result (entry 9) is the highest enantioselectivity achieved so far for transfer hydrogenation of a dialkyl ketone as far as we are aware.

Our study reveals that the enantioselectivity of the catalyst system is very sensitive to both substrate structures and ligand substituent (R/R') groups.[16] For instance, as the steric difference for the two sides of the dialkyl ketones diminishes, the ee goes down dramatically (entries 7-9). Moreover, introduction of either electron donating or withdrawing groups at the *para* phenyl position slows the reaction and decreases the ee (entries 1, 5, 6). Due to the simplicity of our ligand synthesis, we can use various α-amino alcohols to change the size and configuration of the R/R' groups on the ligand. The systematic change of ligand structures should allow us to fine-tune the catalyst system and optimize the ee for different substrate classes.

In conclusion, this new NPN-type tridentate ligand system gives promising results in asymmetric transfer hydrogenation for a variety of ketones. We are currently investigating other reactions catalyzed by transition metals with these ligands.

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9. *Bis[2-[4'-(R)-isopropyl-oxazolin-2'-yl]phenyl]phenylphosphine* (**I**) ^{1}H-NMR ($CDCl_3$): δ = 0.70 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 11.1 Hz, 3H), 0.79 (d, J = 11.1 Hz, 3H), 1.56 (m, 2H), 3.89 (m, 4H), 4.14 (m, 2H), 6.93, 7.28 and 7.87 (m, 13H). ^{13}C-NMR ($CDCl_3$): δ = 18.38 (m), 32.57 (s), 69.79 (s), 72.79 (d, J = 12.3 Hz), 127.51(d, J = 2.4 Hz), 128.04 (m), 129.43 (m), 129.94 (d, J = 9.8 Hz), 132.17 (m), 133.72 (s), 134.14 (d, J = 3.8 Hz), 134.40 (s), 138.73 (d, J = 13.4 Hz), 139.57 (s), 139.94 (d, J = 9.7 Hz), 140.37 (s), 163.02 (m). ^{31}P-NMR ($CDCl_3$): δ = -6.61.
10. Conversions were up to 94% and ee's up to 31% (S) within 48 h at rt under the general experimental conditions given in note 15.
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13. *Bis[4-(R)-phenyl-oxazolin-2-yl-ethyl]phenylphosphine* (**II**) ^{1}H-NMR ($CDCl_3$): δ = 2.17 (m, 4H), 2.46 (m, 4H), 4.03 (dd, J = 8.2, 8.3 Hz, 2H), 4.54 (m, 2H), 5.11 (m, 2H), 7.21-7.58 (m, 15H). ^{13}C-NMR ($CDCl_3$): δ = 24.30 (d, J = 12.4 Hz), 24.33 (d, J = 12.4 Hz), 24.70 (d, J = 17.6 Hz), 24.75 (d, J = 17.9 Hz), 69.56 (s), 74.63 (s), 126.56 (s), 127.47 (s), 128.60 (d, J = 7.7 Hz), 129.33 (s), 132.60 (d, J = 19.2 Hz), 136.62 (d, J = 14.8 Hz), 142.30 (s), 168.40-168.53 (m). ^{31}P-NMR ($CDCl_3$): δ = -22.36.
14. *Bis[4-(S)-isopropyl-oxazolin-2-yl-ethyl]phenylphosphine* (**III**) ^{1}H-NMR ($CDCl_3$): δ = 0.84 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.70 (m, 2H), 2.04 (m, 4H), 2.26 (m, 4H), 3.86-3.88 (m, 4H), 4.13 (m, 2H), 7.38-7.52 (m, 5H). ^{13}C-NMR ($CDCl_3$): δ = 17.99 (s), 18.8 (s), 24.26 (d, J = 12.2 Hz), 24.30 (d, J = 12.8 Hz), 24.66 (d, J = 17.8 Hz), 24.70 (d, J = 17.7 Hz), 69.89 (s), 72.05 (s), 128.51 (d, J = 7.0Hz), 129.17 (s), 132.51 (d, J = 19.6 Hz), 136.64 (d, J = 14.7 Hz), 166.93 (d, J = 13.3 Hz), 167.00 (d, J = 13.3 Hz). ^{31}P-NMR ($CDCl_3$): δ = -21.99.
15. General experimental procedure: To a 25 mL Schlenk tube were added $[RuCl_2(C_6H_6)]_2$ (5 mg, 0.01 mmol), the ligand solution (0.1 M in toluene, 0.22 mL, 0.022 mmol) and 10 mL of 2-propanol. The mixture was stirred at rt for 1h, followed by addition of base (NaH unless otherwise noted, 7.2 mg, 0.3 mmol) and ketone substrate (2 mmol). The reaction mixture was then stirred at rt or heated at 80°C, after which it was eluted through a silica gel plug with ether and analyzed by GLC to determine product ee and yield.
16. Compared with ligand **II** in asymmetric transfer hydrogenation of various ketones, ligand **III** shows much lower enantioselectivity and yields of alcohol products with the opposite absolute configuration (S). Substrate (temp., time, yield %, ee %): acetophenone (80°C, 1 h, 92, 4); pinacolone (rt, 48h, 33, 47); 4-methyl-2-pentanone (rt, 89 h, 93, 8); cyclohexylmethyl ketone (80°C, 1.5 h, 90, 16).
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