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Catalytic Asymmetric Hydrosilylation of Ketones Using Mixed-Ligand Ruthenium Complexes

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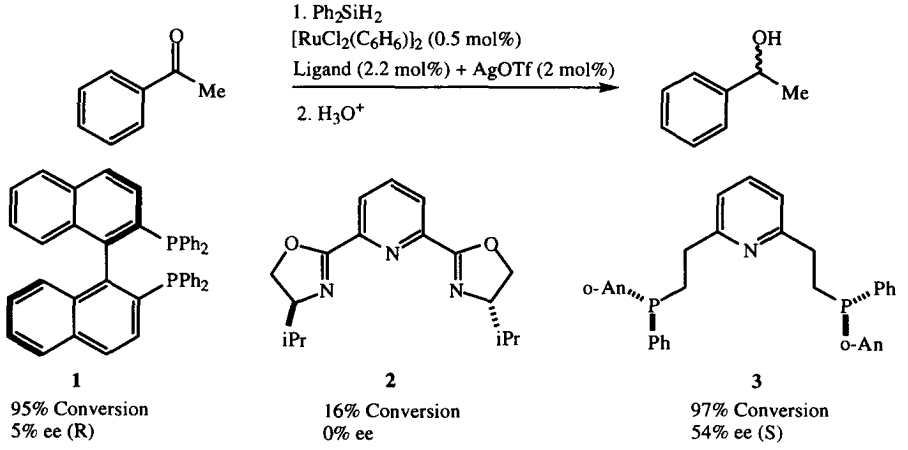
Abstract: An efficient ruthenium catalysed asymmetric hydrosilylation of ketones has been developed using high-throughput, parallel screening to optimise ligand combinations.

Keywords. Ruthenium; Asymmetric catalysis; Mixed-ligands; High-throughput screening.

The ruthenium catalysed asymmetric hydrosilylation of ketones remains a relatively undeveloped reaction compared to its rhodium counterpart.[1] The foremost study by Zhang and co-workers revealed that enantiomerically pure P-P chelating ligands such as **1** or the trusty tridentate nitrogen ligand **2** were either non-selective or inactive in the ruthenium catalysed hydrosilylation of acetophenone. The key discovery was that mixed P-N ligands were necessary for activity and selectivity (Scheme 1).[2] The best result for an asymmetric ruthenium catalysed hydrosilylation reaction was realised when utilising the enantiomerically pure tridentate ligand **3** to afford the product alcohol with 54% ee.



1
95% Conversion
5% ee (R)

2
16% Conversion
0% ee

3
97% Conversion
54% ee (S)

Scheme 1

In this communication we wish to highlight the key results obtained in a parallel screening programme directed towards the discovery of new ruthenium catalysts for enantioselective hydrosilylation reactions. Mixed-ligand ruthenium complexes have proved to be efficient pre-catalysts for the enantioselective hydrogenation of ketones (up to 99% ee).[3] Ruthenium complexes of the type shown in Figure 1 can be prepared by the sequential

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treatment of $[RuCl_2(C_6H_6)]_2$ with first (S)-BINAP then (S,S)-DPEN to afford an air stable pre-catalyst. The preparation of ruthenium complexes from different enantiopure phosphorus and nitrogen-containing ligand components allows the assembly of an array of pre-catalysts suitable for parallel screening.[4] The strategy is illustrated in Scheme 2 along with the ligand components necessary to prepare a small library of 50 pre-catalysts.

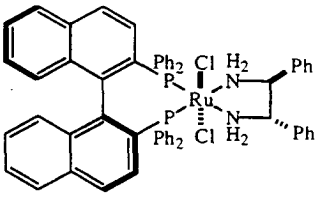
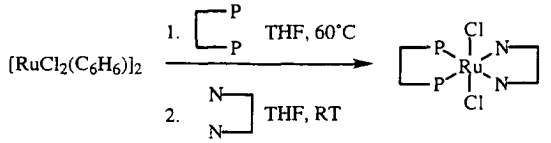
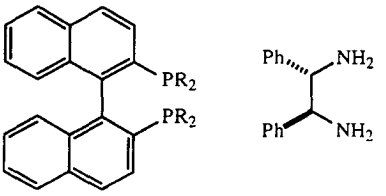


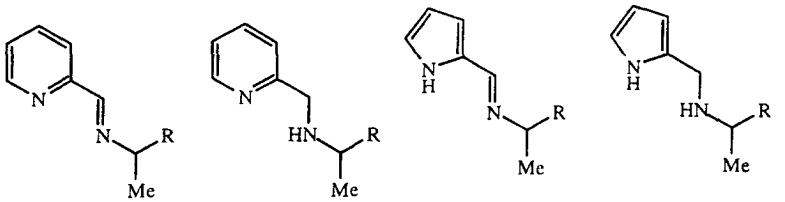
Figure 1





(R)-R=p-$CH_3C_6H_4$ **4**
(S)-R=p-$CH_3C_6H_4$ **5**

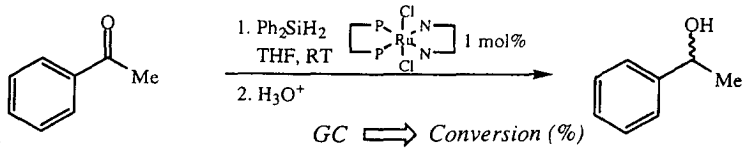
6



(R)-R=C_6H_5 **7**	(R)-R=C_6H_5 **13**	(R)-R=C_6H_5 **19**	(R)-R=C_6H_5 **25**
(S)-R=C_6H_5 **8**	(S)-R=C_6H_5 **14**	(S)-R=C_6H_5 **20**	(S)-R=C_6H_5 **26**
(R)-R=C_6H_{11} **9**	(R)-R=C_6H_{11} **15**	(R)-R=C_6H_{11} **21**	(R)-R=C_6H_{11} **27**
(S)-R=C_6H_{11} **10**	(S)-R=C_6H_{11} **16**	(S)-R=C_6H_{11} **22**	(S)-R=C_6H_{11} **28**
(R)-R=2-naphthyl **11**	(R)-R=2-naphthyl **17**	(R)-R=2-naphthyl **23**	(R)-R=2-naphthyl **29**
(S)-R=2-naphthyl **12**	(S)-R=2-naphthyl **18**	(S)-R=2-naphthyl **24**	(S)-R=2-naphthyl **30**

Scheme 2

We adopted the screening strategy pioneered by Burgess which involves performing the transformations in parallel in individual reaction vessels and following the reactions by automated GC and chiral HPLC analysis.[5] This approach is most viable when the basic features of the reaction are established and optimisation involves a narrow range of variables. In our case this was the different permutations of phosphorus and nitrogen ligands that could comprise a mixed-ligand ruthenium complex. The complexes were tested in the hydrosilylation of acetophenone as outlined in Scheme 3, the screening experiments revealed some interesting and unanticipated results which confirms the benefits of evaluating all ligand combinations.[6]



Scheme 3

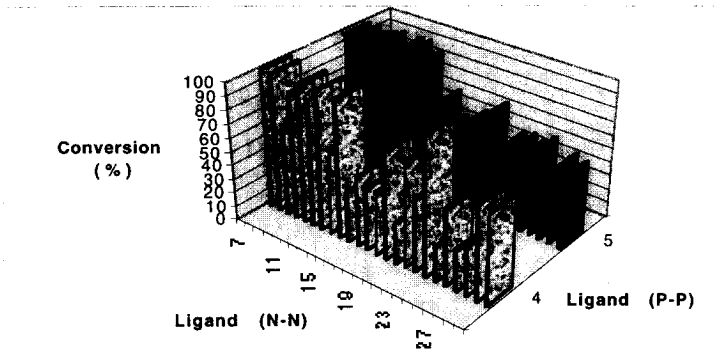


Chart 1

The first point to note was that the Noyori system employing ligand **6** was completely inactive under the screening conditions. The most significant "hits" featured the pyridine based ligand combinations and despite this being a rare transformation we observed several very high conversions (Chart 1). The highest enantioselectivity of 63% was observed with the combination of ligands **4** and **16** (Chart 2). The cyclohexyl substituent was significantly superior to both the phenyl and naphthyl substituted ligands in the same ligand set, this was confirmed in the case of pyrrole ligand **28** which in combination with **4** afforded the product alcohol with 52% ee . The complexes containing the (R)-enantiomer of tol-BINAP **4** predominantly gave the (R)-enantiomer of product.

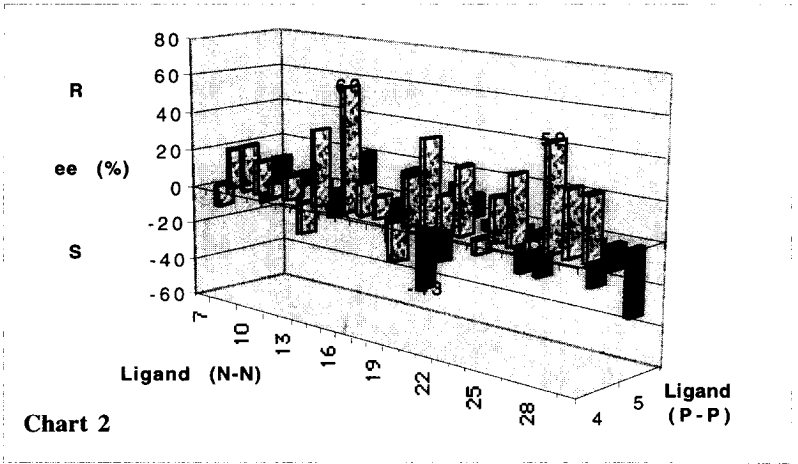


Chart 2

This was not reflected in the case of the enantiomeric ligand **5**. It was not surprising to note that the relative stereochemistry of the two ligands had a significant effect on reaction enantioselectivity. For example, the diastereomeric combinations of **4/15** and **4/16** gave 0% ee and 63% ee (R) respectively. This indicates the likelihood of "matched" and "mis-matched" ligand pairs.

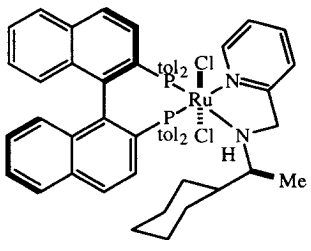
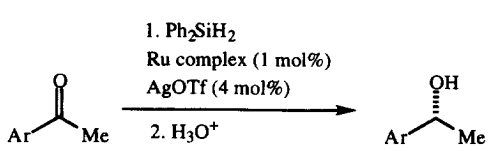
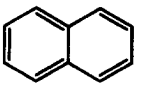
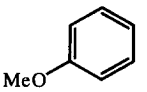


Figure 2 Complex **4/16**

To confirm the validity of the results from parallel screening, the complex that gave the highest enantioselectivity (Figure 2) was isolated and tested in the hydrosilylation of acetophenone by traditional serial experiments. The results obtained were consistent with the parallel experiments, the product alcohol being repeatedly obtained in 60-63% ee. Changing the reaction solvent had a detrimental effect on the enantioselectivity: MeCN (8% yield, 10% ee (R)); CCl_4 (11% yield, 12% ee (S)); DME (92% yield, 12% ee (R)); toluene (24% yield, 21% ee (R)). The addition of AgOTf increased the enantioselectivity further to 82% ee.[7] This is consistent with the observations reported previously for both ruthenium and rhodium catalysed hydrosilylation and is due to the generation of coordination sites for binding the ketone and

activating the Si-H bond.[8] The optimised system proved to be effective for the hydrosilylation of different ketones (Scheme 4).



Ar	Yield (%)	ee (%)
	53	82
	88	68
	90	58

Scheme 4

In conclusion, a parallel screening approach has been used to identify mixed-ligand ruthenium complexes that are effective pre-catalysts for the asymmetric hydrosilylation of ketones. The study revealed unusual ligand combinations that gave reproducible good enantioselectivities and activities at low loadings. It is important to note that neither the diphosphine ligand nor the bidentate nitrogen ligand are effective on their own, only in combination do we observe any enantioselectivity. Work is in progress to ascertain the origin of the asymmetric induction in this process and other systems are being tested to build on these preliminary results.

Acknowledgments

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References and Notes

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4. For examples of catalyst identification by parallel screening, see; Sigman, M. S.; Jacobsen, E. N., *J. Am. Chem. Soc.*, **1998**, 120, 4901 and references therein.
5. Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A., *Angew. Chem. Int. Ed.*, **1996**, 35, 220.
6. Many ligand combinations gave low conversion and low enantioselectivity. An analysis of all the data will be given in a subsequent full paper.
7. The enantioselectivity was reproducible in both parallel and serial experiments.
8. Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K., *Organometallics*, **1989**, 8, 846.