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Rapid, *in situ* synthesis of bidentate ligands: chromatography-free generation of catalyst libraries[†]

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The parallel synthesis of chiral bidentate ligands and their subsequent use *in situ* for a catalytic process is described. The ligands thus prepared gave comparable results to those obtained when the ligands were synthesized and purified by conventional means. This includes oxazolines and other compounds of similar complexity, meaning that for the first time these valuable compounds have been brought into the field of combinatorial catalysis.

While asymmetric catalysis is a highly successful and still burgeoning field of study, one common difficulty is identifying a suitable catalyst for a given reaction—a process that can be both time-consuming and expensive. As has been noted by Knowles, due to the fact that the energy differences between diastereomeric transition states leading to antipodal products are often very small (~2 kcal mol⁻¹ for 95% ee), it is extremely difficult to predict successful structures in advance.¹

One attractive solution to this problem is the combinatorial synthesis of ligands, *especially when those ligands can subsequently be used directly in a catalytic process without any purification.* A hugely successful example of this strategy is the MonoPhos instant ligand libraries and related systems developed by de Vries and others,² where chiral phosphoramidites were synthesised in parallel and used *in situ* for rapid screening. The ligands are typically formed with purities between 90–95%, and give levels of product enantiomeric excess only slightly reduced compared to the purified ligands.

Bidentate ligands on the other hand have proven more difficult to deal with, and this remains a problem today. While there are methods for the modular and high throughput synthesis of libraries of bidentate ligands, typically these methods require manipulation and purification of the resulting ligands.³⁴ Alternative methods have been employed, including solid phase⁵ and supramolecular⁶ approaches, and one case where a single tridentate ligand was synthesised *in situ*.⁷ However, *in situ* methods for the generation of solution phase bidentate ligand libraries are still lagging well behind the great strides taken for monodentate ligands, partly due to the greater synthetic difficulties associated with their synthesis.^{2b} Indeed this has been a factor which has stymied combinatorial asymmetric catalysis for some time, 6i and a general solution to this problem would represent a great step forward.^{3g}

Our initial approach to this problem is outlined in Fig. 1. We examined Schiff base formation as a route to P,N-ligands, reasoning that the high yields normally obtained in these reactions would make them ideal candidates for *in situ* generated libraries. Other advantages of this system include the fact that both fragments (aldehyde and amine) are readily available and independently variable, and that the only side product (water) could easily be removed by molecular sieves. This last point is important as it opens up the possibility of direct screening of crude reaction mixtures in catalytic reactions.



Fig. 1 Imine formation as a route to in situ ligand libraries.

A preliminary experiment (see Fig. 1) indicated that by mixing an equimolar amount of amine and aldehyde together in toluene in the presence of 4 Å molecular sieves at 70 °C overnight, ligand 1 could be generated in pure form (as shown by ¹H and ³¹P NMR). This operationally simple route proved applicable to the synthesis of many ligand types and very high purities were obtained (greater than 95%). Unfortunately ketones did not prove amenable to this process: when 2-acetylpyridine was used with the same amine the corresponding ketimine was produced with a conversion of 30%, with significant amounts of unreacted amine and ketone remaining.

The methodology could, however, easily be extended to similar functional groups. Use of secondary diamines allowed the generation of aminal-based ligands,⁸ while condensation using secondary amino alcohols furnished oxazolidines,⁸ another highly useful functionality in asymmetric catalysis.⁹ The only example we found where pure ligands were not obtained was the condensation of *primary diamines* with *one* equivalent of aldehyde: in this particular case, as expected, a mixture of bis- and mono-imine products was observed.⁸

Fig. 2 outlines some of the ligand structural diversity that is easily achievable by this methodology. From a very simple

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Fig. 2 Rapid ligand generation for direct use in asymmetric catalysis.

condensation reaction, solutions of chiral imine (3), aminal (4) and oxazolidine (5) ligands were accessible. Due to the ready availability of varied (and inexpensive) chiral amines, aminoalcohols and diamines, combined with the easy variability of the aldehyde fragment, we now possessed a methodology for the *in situ* synthesis of structurally varied ligands in very high purities.

While these ligands are useful and structurally diverse, an even greater challenge is the synthesis of highly successful-and complex-ligands such as oxazolines.10 To this end we examined the use of pyridyl imidate 6 (Fig. 2), a known precursor of oxazolines.¹¹ This route has the advantage of being a one-step process, again opening up the possibility of employing the ligands in situ in high throughput screening. Normally such oxazoline syntheses are carried out with an acid catalyst (e.g. HCl) and purified by column chromatography or recrystallization; however, we were keen to avoid the addition of any further additives or purification steps. We were gratified to find that simply heating the imidate with an aminoalcohol in the presence of molecular sieves was sufficient. We posited that the side products (ammonia and methanol) could be absorbed by 4 Å molecular sieves (or, if trace ammonia was a problem, simple evaporation of the solvent would yield pure compound). Initial tests supported this hypothesis, and

indicated that we could synthesize not just oxazolines (7), but also imidazolines (8) and thiazolines (9), in very high purities (>95% as measured by ¹H NMR spectroscopy).⁸

It was necessary to test if the *in situ* prepared ligands could be directly applied in catalytic reactions and, if so, whether they would exhibit similar efficacy to those associated with the corresponding isolated, purified ligands. As a test reaction we investigated the transfer hydrogenation of acetophenone in water (chosen due to the fact that variants of this process employing imine ligands are characterized by moderate levels of asymmetric induction, with levels of product enantiomeric excess of up to 51% using acetophenone as the electrophile).¹² Thus, in the context of the use of easily generated imine-based ligands, it represents a process with considerable scope for development.¹³ Ligand 10 has been employed in this reaction previously, and so we compared our in situ results with those obtained with the purified compound (see Fig. 3). Gratifyingly the level of performance of the in situ prepared material was almost identical to that of the isolated, purified version¹² (48% vs. 52% ee, 98% vs. 99% conversion), indicating that this methodology could provide a rapid method for evaluating ligand performance.



Fig. 3 Comparison of purified vs. in situ ligands.

The behavior of ligands derived from imidates was also evaluated. Ligand 14 was synthesized and purified by column chromatography. The results obtained from the purified ligand were again closely matched to the results of the ligand simply formed by the condensation of L-phenylalaninol with imidate 6, followed by direct use in the reaction (13% ee in both cases, 12% conversion for *in situ vs.* 15% for purified). This was a particularly important result, as it showed that we could now bring the powerful and complex oxazoline ligands into combinatorial catalysis.

Encouraged by these findings we made a small proof-of-concept library and screened this in the reaction (see Table 1 and Fig. 4). Generating each of the ligands was facile, and could be carried out in parallel; a library of this size (or even larger) could easily be produced in one day.



Fig. 4 Ligands employed in this study. [^(a) Compound 5 consisted of a 5.6:1 ratio of the two diastereomers. ^(b) Compound 12 consisted of an equilibrium mixture of monoimine 12 (70%) with bis-imine 11 + unreacted cyclohexane diamine (30%). See the ESI for details†].

Some trends could be observed in the results obtained. All of the best results obtained were with imine ligands, in common with the results reported by Himeda.¹² P,N-ligands uniformly gave low conversions, although the enantioselectivities were more variable. Increasing the bulk on the aldehyde fragment had a detrimental effect on both the conversion and selectivity (*cf.* 1 *vs.* **16**, **10** *vs.* **19** and **17** *vs.* **20**), perhaps by inhibiting binding at the metal centre. The effect of increasing the steric bulk in the amine fragment had a variable effect. In pyridine-based imine ligands it appeared to reduce conversions but not selectivities (**10** *vs.* **20**), whereas in the phosphine imine case it greatly reduced both (**1** *vs.* **23**). Electronic effects were somewhat more difficult to probe; for instance compound **15** produced 1-phenylethanol in 40% ee, but the addition of either electron withdrawing (**21**) or electron donating (**22**) groups decreased this value.

The enantiomeric excess of the product obtained was moderate (albeit it in a challenging system), with a maximum of 68% achieved with ligand **12**. As mentioned previously, in the case of this type of ligand there were three species in equilibrium (monoimine **12**, bisimine **11** and cyclohexane diamine). Ordinarily this would have lead to the rejection of **12** as a candidate; however,

 Table 1
 Asymmetric transfer hydrogenation in water with *in situ* generated ligands

	O H	[RhCp*Cl ₂] ₂ (1 mol%) L* (1.05 mol%)	ОН	
ĺ	Me	HCO ₂ H/HCO ₂ Na (pH 3.5) H ₂ O, 40 °C		* Me
Entry	Ligand	Conversion (%)	ee (%)	Config.
1	1	5	41	(S)
2	5	7	<5	
3	8	79	8	(S)
4	10	98	48	<i>(S)</i>
5 ^a	10	99	51	(S)
6	11	11	51	(R)
7	12	18	68	(R)
8	13	8	26	(R)
9	14	12	13	(S)
10 ^a	14	15	13	(S)
11	15	29	40	(R)
12	16	2	<5	
13	17	6	<5	
14	18	25	43	(S)
15	19	15	<5	(S)
16	20	7	47	(S)
17	21	4	<5	
18	22	6	15	(R)
19	23	5	<5	
20	24	58	49	(S)
21	25	5	<5	
22	26	10	9	(S)

" Ligands isolated and purified prior to use

the simplicity of this system encourages the chemist to access structures that would otherwise not be considered. It appears likely that the most selective species is the major component (ligand 12). While it was not possible to isolate this ligand in pure form the other species in solution—bisimine 11 and cyclohexane diamine starting material—both furnished the alcohol with lower enantiomeric excess (51% and 43% respectively).

While none of the ligands in this library allowed the formation of the product with outstanding levels of enantiomeric excess, even using a small, rapidly generated library such as that described above we were able to significantly improve upon the literature benchmark for catalysis of this reaction using an imine-based ligand. Much more importantly we demonstrated the ease with which our methodology could be used to generate bidentate ligand libraries of synthetically useful structures to test directly in asymmetric reactions, and that the results obtained by the *in situ* ligands were a reliable measure of the results obtained by the purified ligands.

In conclusion, we have developed an operationally simple method for the rapid generation of ligand libraries. A great deal of structural diversity is easily achievable, not only P,N-, N,N- and N,O-imine-based ligands, but also the more complex oxazoline and imidazoline ligands have now been brought into the repertoire of combinatorial catalysis. *It is worth noting that ligands of such complexity have previously been beyond the scope of in situ synthesis*, and the advantages this brings to the field are clear. Finally, this methodology is not only time effective, but also can reduce cost and waste—instead of synthesizing each ligand on a reasonably large scale and subsequently purifying, simply microlitre quantities of the two fragments can be heated together to generate sufficient ligand quantities for screening. Once a hit has been found the ligand can either be synthesized and purified as normal or subjected to a further round of combinatorial chemical space exploration around that structure. Studies to further extend this proof-of-concept to diverse ligand classes for application in challenging asymmetric transformations are underway.

Acknowledgements

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