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Rapid in-situ Synthesis of Bidentate Ligands and its Application in Rhodium Catalyzed Transfer Hydrogenation

Tariq Zaman[1+], Habib Nasir[1], Robin Frauenlob[2] and Enda Bergin[2]

[1]School of Chemical & Materials Engineering, NUST, H-12, Islamabad, 44000, Pakistan.
[2] School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland.

Abstract. The parallel synthesis of chiral oxazoline, imine and bisimine bidentate ligands and their in situ use for catalytic transfer hydrogenation of ketone is described. The ligands thus prepared in situ gave nearly same results with compare to the purified versions. The ligands which gave more than 60% ee and best conversions were readily identified.

Keywords: Combinatorial chemistry, Asymmetric catalysis, Transfer hydrogenation, Ligand libraries.

1. Introduction

The development of asymmetric synthesis is driven by the importance of stereochemically pure compounds in the field of pharmaceutical industry, agrochemicals and flavours [1]. The synthesis of molecules containing one or more chiral centers is remained challenging for chemists [2]. The majority of enantiomerically pure compounds are generally sourced from natural products or by the resolution of racemic compounds [3], as according to knowels, the structure cannot be predicted in advance due to the small difference of energy (~2kcal/mol) between two diastereomeric transition states [4]. In general, finding new and improved catalysts can be time consuming, cost expensive and an inefficient method for mass production [5].

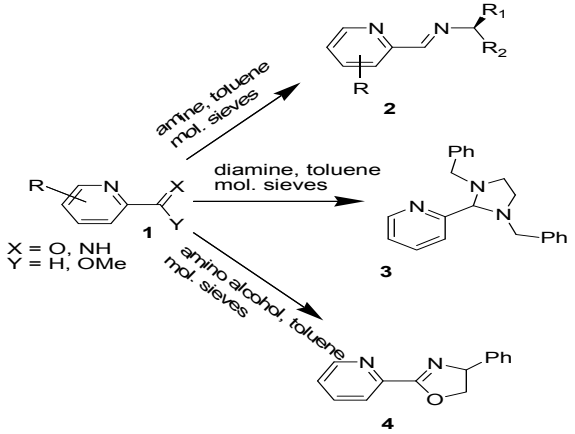


Fig. 1: Synthesis of bidentate ligands.

Combinatorial chemistry creates a new methodology for the production of a vast variety of potential ligands which can be categorized in libraries, screened and then tuned to a particular substrate [6]. De Vries has developed a successful example of this by introducing instant libraries of MonoPhose [7, 8] where chiral ligands were synthesized and used in situ which gave slightly reduced results than the purified ligands. Inspite of the modular and high throughput synthesis, Bidentate ligands remains a problem that require

+ Corresponding author. Tel.: + (923065673015); fax: + (925190855002).
E-mail address: (tariq@scme.nust.edu.pk).

purification of resulting ligands [9, 10] for which solid phase [11-13] and supramolecular [14-17] methods have been employed. Due to the greater synthetic difficulties [18] of bidentate ligands, its use in combinatorial catalysis was halt until E. Bergin and co-workers used it with efficient enantiomeric excesses [19]. Herein we demonstrate a library of bidentate ligands for the in situ transfer hydrogenation of ketones and the comparison of results with the purified ligands.

2. Results and Discussions

At first equimolar of amine and aldehyde were mixed together for 24 hours in toluene with molecular sieves and gratifyingly a pure ligand was obtained after column chromatography. The main advantage of this method is the available variation in both starting materials and the formation of by product (water, HCl) which can easily be removed with the help of 4A^{o} molecular sieves. Three families of ligands imines, aminals and oxazolines were synthesized and used in situ. These ligands were easily obtained by combining aldehyde with amine [20], diamine [21, 22] and amino alcohol [23, 24] respectively figure 1. The readily availability (and inexpensive) fragments of the above mentioned compounds enabled us the generation of a library of ligands to be tested in situ and in pure form figure 2.

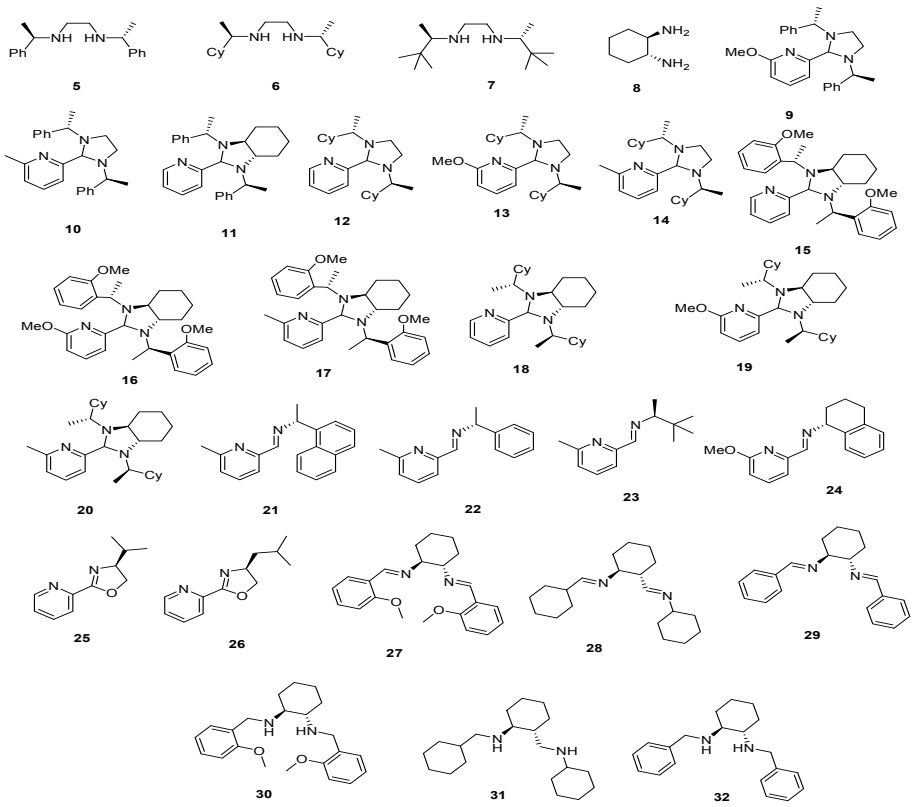
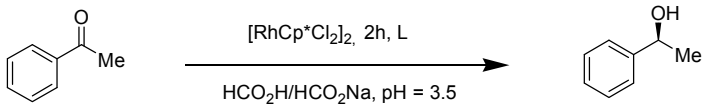


Fig. 2: Ligands employed in this study.

At first we compare the results of ligands prepared in situ with that of purified one and found almost same results, 42% vs 43% ee and 71% vs 73% conversion for 3 (entry 1, table 1) which encouraged us to proceed further for the evaluation of other ligands by using one pot synthesis without the need of purification. Oxazoline ligands were both used in situ and in the purified form and maximum ee 45% and conversion 70% (entry 27, table 1) were recorded for 25. With encouraging results we made a small library and tested it in a reaction (Table 1, figure 2). Such ligands could be carried out in parallel and could easily be produced in a day. Substituents on the aldehyd had positive effect on both the conversion and selectivity (3 versus 10, 12 versus 14 and 18 versus 20) due to presence of methyl group aiding the availability to metal atom while bisimine having the methoxy and phenyl group give positive effect due to resonance (27 versus 28).

Table 1: Asymmetric transfer hydrogenation in water



Entry	Ligand	Conversion %	ee%	config.
1	**3**	71	42	R
2	***3**	73	43	R
3	**4**	33	25	S
4	***4**	34	25	S
5	***5**	40	30	S
6	***6**	20	15	S
7	***7**	55	40	R
8	***8**	25	21	R
9	**9**	80	52	S
10	**10**	95	70	S
11	**11**	80	48	R
12	**12**	56	35	R
13	**13**	78	52	R
14	**14**	78	54	R
15	**15**	57	45	S
16	**16**	65	45	S
17	**17**	78	52	S
18	**18**	52	30	S
19	**19**	70	41	R
20	**20**	77	45	R
21	**21**	90	66	R
22	**22**	70	53	R
23	***22**	75	54	S
24	**23**	80	51	S
25	**24**	70	45	S
26	**25**	65	39	S
27	***25**	65	40	S
28	**26**	50	35	R
29	***26**	52	36	R
30	**27**	68	53	R
31	***27**	70	54	S
32	**28**	44	47	S
33	***28**	45	48	S
34	**29**	62	52	S
35	***29**	64	53	S
36	***30**	25	21	S
37	***31**	20	15	S
38	***32**	15	10	S

* Ligands isolated and purified prior to use

Steric effect played an important role in complex formation and achieving good ees as the enantiomeric excess of 1-phenylethanol obtained was maximum 70% for 10 (Entry 10 table 1), which helped us to access structure of the ligands in easy way. Honestly speaking none of our ligand is able to give product with exemplary conversion and ee, but we were able to improve the literature by combining easily available raw materials for synthesizing a small library of three classes of ligands and such lignads can directly be used for asymmetric catalysis. Furthermore, it is not necessary to synthesize ligands in large scale and through purification but can easily be tested in microlitre quantities of the two fragments and thus by reducing cost, waste and time. Once finding a clue for the best ligand it can be synthesized and purified easily. Studies to find optimum conditions for the successful ligands are underway in our group.

3. Conclusions

In conclusion we have applied the library to the transfer hydrogenation of acetophenone with rhodium in water. After the comparison of results obtained from purified vs. in-situ ligands it was found that the technique is suitable for rapid recognition of best catalytic system. Three different types of ligands were tested and the ee > 60% was easily identified. The positive trend of the results was explained due to presence of substituents on aldehyde moiety.

4. Acknowledgements

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