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Identification of new catalysts for the asymmetric reduction of imines into chiral amines with polymethylhydrosiloxane using high-throughput screening

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Abstract—The use of high-throughput techniques allowed the rapid identification of new catalysts for the enantioselective reduction of imines using polymethylhydrosiloxane (PMHS) as a reducing agent. By a simple modification of the chiral ligand structure that came out of the screening, the enantioselectivity of the reduction was increased from 40% ee to 60% ee.

The use of polymethylhydrosiloxane (PMHS) as a reducing agent is an interesting alternative to the use of hydrogen since no pressure reactor is required. Furthermore, PMHS is inexpensive, nontoxic and stable to air and moisture co-product of the silicon industry.[1] It has already been used in many applications like reduction of ketones, esters, imines, halogen or phosphine oxides but also asymmetric reductions.[1,2] For example ketones can be reduced into chiral alcohols with PMHS in the presence of zinc-chiral diamines,[3] cadmium/bis-oxazoline catalysts[4] or copper/chiral diphosphines.[5] We were interested in reducing imines into chiral amines using PMHS as a reducing agent.[6] Some catalysts are already described for this reaction, particularly the titanocene complex developed by Hansen and Buchwald that leads to chiral amines with very high enantioselectivities.[7] However this method requires a catalyst preactivation and the addition of an amine in the course of the reaction. Other examples of achiral imine reductions with PMHS have also been published. Thus $ZnCl_2$ (2 equiv)[8] and $Ti(OiPr)_4$ (1.25 equiv, in situ formation of imine)[9] were used as catalysts but in stoichiometric amount. A convenient method was published by Fu and Lopez that uses a catalytic amount of a tin^{IV} complex to perform the reaction.[10] Recently Mortreux and co-workers showed that a zinc–diamine complex could be used in a catalytic amount to reduce effectively ketones and imines.[11]

We wish to report herein the results obtained in a parallel screening of a large number of catalyst–chiral ligand combinations for the enantioselective reduction of imines into chiral amines using PMHS as a reducing agent. Since the numerous type of catalysts that have been described to activate PMHS, a diversified parallel library was prepared by combining commercially available catalysts and chiral ligands.[12] The chiral ligands were chosen among acids, alcohols, aminoalcohols, diamines or diphosphines in order to identify all types of structures that could be able to induce chirality (Scheme 1).

Two targets were identified as model substrates for the parallel library screening, the ketimine **1** and the cyclic imine **2** (Scheme 2).

The reactions were performed in 96-well microtiterplates using reagents in solution (imine/PMHS: 1/1,2 mol% of catalyst and 2 mol% of ligand in MeOH). The solutions were delivered using a Gilson 215 robot inside a glovebox. The reactions were quenched after 20 h with a solution of MeONa in MeOH. The crude reaction mixtures were directly analyzed by GC (conversion) and by HPLC analysis (enantioselectivity). The results obtained for the reduction of the ketimine **1** are shown in Scheme 3 and those for the reduction of the cyclic imine **2** in Scheme 4.

Keywords: Asymmetric imine reduction; PMHS; High-throughput screening.

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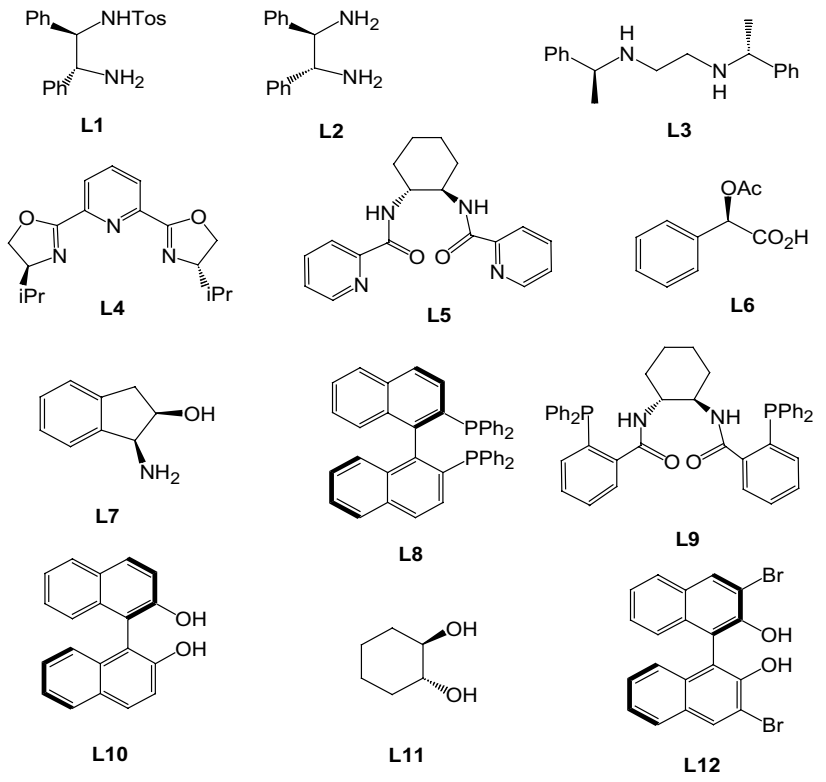
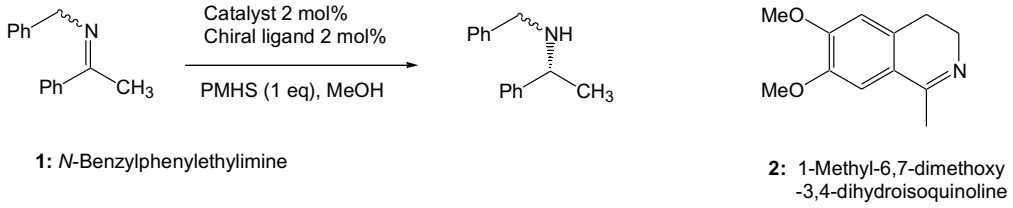


Scheme 1.



Scheme 2. Asymmetric reduction of imines with PMHS.

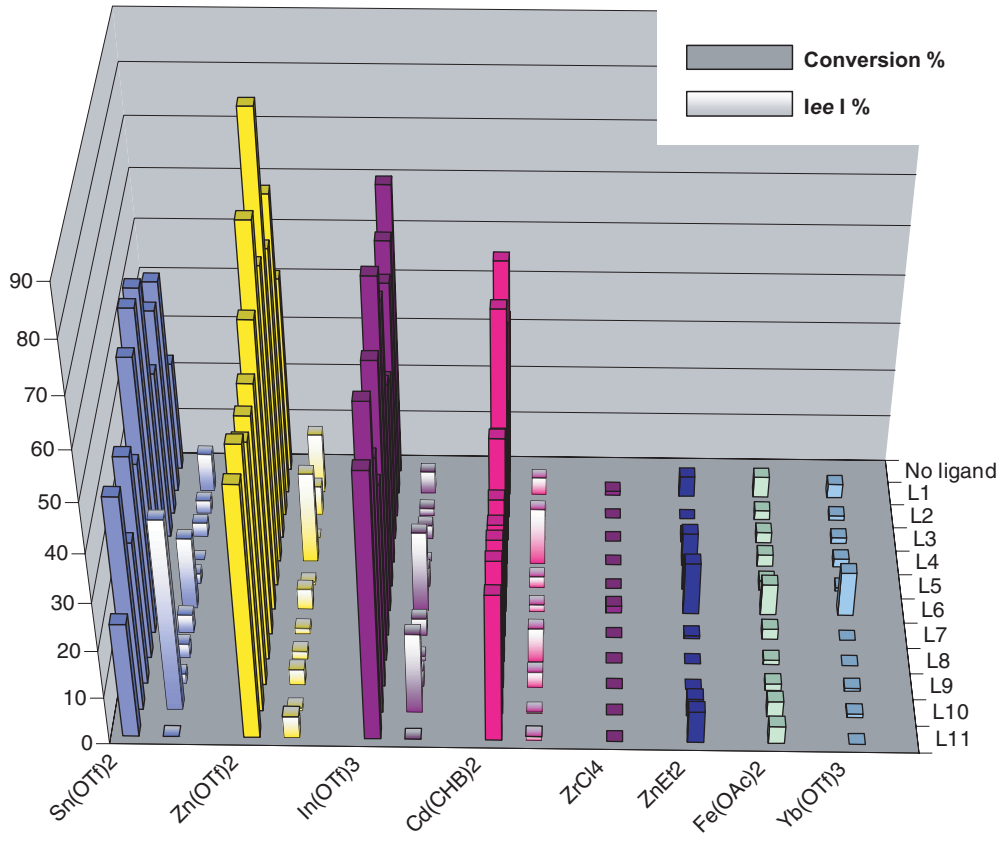
Among the catalysts screened, $Sn(OTf)_2$, $Zn(OTf)_2$, $In(OTf)_3$, $Cd(CHB)_2$[†] turned out to be active even in 2 mol% amount. Although different tin and zinc catalysts were already known to perform the reaction catalytically,[10,11] indium and cadmium catalysts were not yet described. Interestingly the addition of a ligand led in most cases to an increase of the catalyst activity. The best enantioselectivity was obtained with $Sn(OTf)_2$/binaphthol (**L10**) leading to the *N*-benzylphenylethylamine with up to 40% ee. Chiral induction (up to 20% ee) was also observed with binaphthol (**L10**) in combination with $In(OTf)_3$ and with PyBox (**L4**) in combination with $Zn(OTf)_2$ or $Cd(CHB)_2$. Although Zn/**L3** complex is known for the enantioselective reduction of ketones,[3] no enantioselectivity was observed for the reduction of imine **1** in our screening conditions using this catalyst. Surprisingly, even simple chiral carboxylic acid like O-acetylmandelic acid (**L6**) led to some chiral induction (up to 16% ee) in combination with $Sn(OTf)_2$ or $In(OTf)_3$.

The substrate specificity often observed for enantioselective reactions was confirmed by performing a similar screening for the enantioselective reduction of imine **2**. The results are shown in Scheme 4.

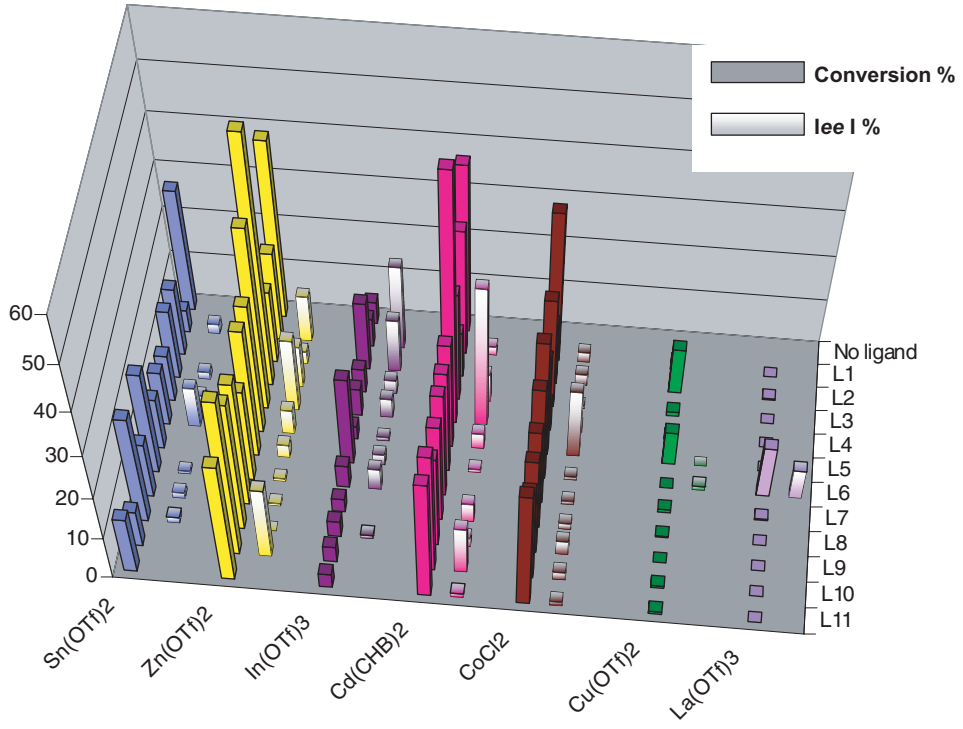
The best result for the reduction of the cyclic imine **2** was obtained with $Cd(CHB)_2$/PyBox (**L4**) leading to the corresponding amine with 32% ee. Furthermore $In(OTf)_3$ that was active for the reduction of imine **1** turned out to be much less efficient for the reduction of imine **2**. $CoCl_2$ showed some activity for the reduction but no chiral induction was observed. Similar activities were observed with $ZnBr_2$ instead of $Zn(OTf)_2$.

To confirm the results obtained from parallel screening the most promising catalysts were tested for the reduction of imine **1** and imine **2** on a lab scale. The results are summarized in Table 1.

[†] OTf: triflate; CHB: cyclohexanebutyrate.



Scheme 3. Screening of catalysts for the asymmetric reduction of the ketimine **1** with PMHS.



Scheme 4. Screening of catalysts for the asymmetric reduction of the cyclic imine **2** with PMHS.

Table 1. Enantioselective reduction of imines with PMHS[a]

Entry	Imine	Catalyst	Catalyst amount (mol%)	Ligand	Time (h)	Conversion (%)[b]	Ee (%)[c]
1	**1**	$Sn(OTf)_2$	10	—	4.5	82	—
2	**1**	$In(OTf)_3$	10	—	22	67	—
3	**1**[d]	$Zn(OTf)_2$	2	—	6	87	—
4	**1**	$Cd(CHB)_2$	10	—	22	62	—
5	**1**	$Sn(OTf)_2$	2	**L10**	2	98 (90)[e]	40 (*R*)
6	**1**	$Zn(OTf)_2$	2	**L10**	6	>99	30 (*R*)
7	**1**	$In(OTf)_3$	2	**L10**	6	56	29 (*R*)
8	**2**[f]	$Cd(CHB)_2$	2	**L4**	20	60	33
9	**1**	$Sn(OTf)_2$	2	**L12**	6	85	60 (*R*)
10	**1**	$Zn(OTf)_2$	2	**L12**	6	87	33 (*R*)
11	**1**	$In(OTf)_3$	2	**L12**	6	50	36 (*R*)

[a] Reactions were performed at room temperature with imine (1.0 mmol), PMHS (1.2 equiv), ligand (× mol%), catalyst (× mol%) in MeOH.
[b] Determined by GC using a γ-DEX225 Supelco column.
[c] Determined by HPLC using a Daicel OD-H column.
[d] 2 equiv of PMHS was used.
[e] Isolated yield%.
[f] Toluene was added to solubilize the amine.

The catalytic activity of $Sn(OTf)_2$, $In(OTf)_3$, $Zn(OTf)_2$ and $Cd(CHB)_2$ was confirmed. Thus $Zn(OTf)_2$ can be used in catalytic amount as low as 2 mol% but the use of 10 mol% of $Sn(OTf)_2$, $In(OTf)_3$ or $Cd(CHB)_2$ is necessary to obtain a good conversion (Table 1, entries 1–4).

The use of an excess of alcohol is critical to run the reaction catalytically. In the absence of methanol no conversion was observed whereas the use of only 2 equiv led to a very sluggish reaction. Interestingly the reduction could be performed under an air atmosphere.

The addition of a ligand led in all cases to a catalyst activation and 2 mol% of catalyst is then enough to get a high conversion (Table 1, entries 5 and 6). The best enantioselectivity observed in microtiterplate for the reduction of imine **1** and **2** were confirmed (Table 1, entries 5 and 8).

Since the binaphthol ligand (**L10**) led to the best chiral induction we tried to modify its structure. Thus the enantioselectivity was increased to 60% ee for the reduction of imine **1** simply by adding two bromo substituents in 3 and 3′ positions of the binaphthol (see ligand **L12**, Scheme 1 and Table 1, entry 9). However this substituent effect was not as strong with $Zn(OTf)_2$ and $In(OTf)_3$ (Table 1, entries 10 and 11).

In summary we have successfully used high throughput techniques in order to identify new catalysts like $In(OTf)_3$ and $Cd(CHB)_2$ for the reduction of imines into amines using PMHS as a reducing agent. Chiral induction was observed by simple combinations of catalysts such as $Sn(OTf)_2$, $Zn(OTf)_2$, $In(OTf)_3$ and $Cd(CHB)_2$ with chiral ligands. The screening of various type of chiral ligands allowed us to identify active structures. Then a more focused ligand design strategy allowed us to increase our best enantiomeric excess from 40% to 60% ee. The advantage of using high-throughput screening was again demonstrated since the most efficient catalyst was substrate depending. Further optimizations of the chiral ligand structures in order to increase the enantioselectivity of the reaction are in progress in our laboratory.

Acknowledgements

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References and notes

1. For a review on PMHS chemistry see: Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381–3391.
2. Recent applications of PMHS in enantioselective reductions of conjugated double bonds: (a) Lipshutz, B. H.; Servesko, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789–4792; (b) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793–4795.
3. Mimoun, H.; de Saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158–6166.
4. Lawrence, N. J.; Bushell, S. M. *Tetrahedron Lett.* **2000**, *41*, 4507–4512.
5. (a) Courmarcel, J.; Mostefaï, N.; Sirol, S.; Choppin, S.; Riant, O. *Isr. J. Chem.* **2001**, *41*, 231; (b) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917; (c) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779–9789.
6. For reviews on enantioselective imine reduction see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; (b) Spindler, F.; Blaser, H.-U. In *Transition Metals For Organic Synthesis*; Belle, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; pp 69–80.
7. (a) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*(5), 713–715; (b) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103–1107.
8. Chandrasekhar, S.; Venkat Reddy, M.; Chandraiah, L. *Synth. Commun.* **1999**, *29*(22), 3981–3987.
9. Chandrasekhar, S.; Raji Reddy, Ch.; Moinuddin Ahmed *Synlett* **2000**, *11*, 1655–1657.
10. Lopez, R. M.; Fu, G. C. *Tetrahedron* **1997**, *53*, 16349–16354.
11. Bette, V.; Mortreux, A.; Lehmann, C. W.; Carpentier, J. F. *Chem. Commun.* **2003**, 332–333.
12. For reviews on high-throughput screening in catalysis see: (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284–310; (b) Maier, W. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1216–1223; (c) Jandeleit, B.; Shaefer, D. J.; Powers, T. S.;

Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494–2532; (d) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885–1889; see also (e) Taran, F.; Gauchet, C.; Mohar, B.; Meunier, S.; Valleix, A.; Renard, P. Y.; Créminon, C.; Grassi, J.; Wagner, A.; Miokowski, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 124–127; (f) Hoogenraag, M.; Klaus, G. M.; Elders, N.; Hooijschuur, S. M.; McKay, B.; Smith, A. A.; Damen, E. W. P. *Tetrahedron: Asymmetry* **2004**, *15*, 519, and references cited therein.