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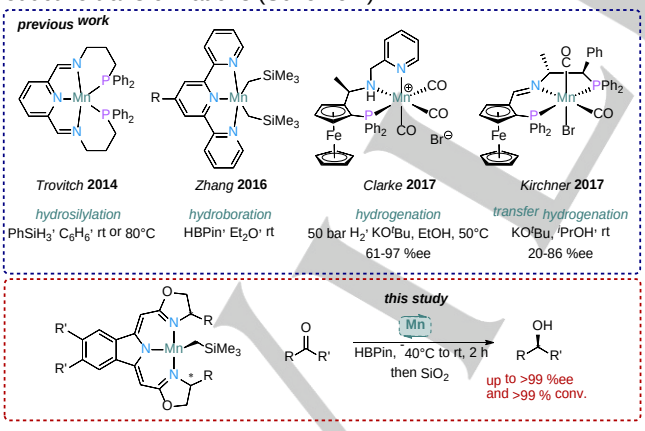
Mechanism-Based Enantiodivergence in Manganese Reduction Catalysis: A Chiral Pincer Complex for the Highly Enantioselective Hydroboration of Ketones

Vladislav Vasilenko, Clemens K. Blasius, Hubert Wadepohl and Lutz H. Gade*[a]

Abstract: A manganese alkyl complex containing a chiral "boxmi" pincer ligand is a precatalyst for a catalyst of unprecedented activity and selectivity in the enantioselective hydroboration of ketones producing preparatively useful chiral alcohols in excellent yields and up to >99 %ee. It is applicable for both aryl alkyl and dialkyl ketone reduction under mild conditions (TOF >450 h^{-1} at –40°C) and an earth-abundant base metal catalyst which operates at very low catalyst loadings (as low as 0.1 mol%) and with a high level of functional group tolerance. We provide evidence for the existence of two distinct mechanistic pathways for manganese-catalyzed hydride transfer and elaborate their role for enantiocontrol in the selectivity-determining step.

Nature's metalloenzymes, employing earth-abundant, non-toxic base metals, in particular iron and manganese,[1] allow for reactions that are usually considered to be the domain of noble metal catalysis – even more so when it comes to chiral building blocks.[2] Recent efforts to use 3d transition metals have produced highly active homogeneous iron catalysts for enantioselective oxidations[3] and reductions of a plethora of substrates.[4] In contrast, manganese complexes have mainly been employed in oxidation catalysis with reductive transformations remaining scarce.[5] Nevertheless, the excellent aptitude of manganese in this field has only just been demonstrated in seminal contributions by Trovitch,[6] Zhang,[7] Beller,[8] Kempe,[9] Kirchner,[10] Milstein,[11] and others.[12] Very recently, Kirchner and Clarke reported the first examples of the exploitation of chirality for Mn-catalyzed enantioselective reductive transformations (Scheme 1).[13]



Scheme 1. Selected example of previously reported manganese catalysts for ketone reduction and our approach for enantioselective hydroboration.

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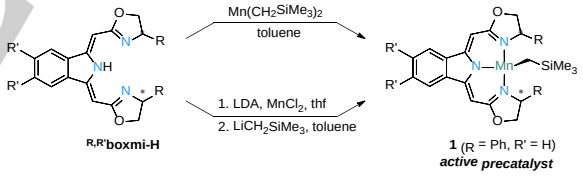
Recently,[14] we reported the potential of the chiral bis(oxazolinyl-methylidene)isoindoline ("boxmi")[15] pincers as ancillary ligands in iron-based catalysts for the enantioselective hydrosilylation of ketones. The stability of these chiral catalysts and the efficiency of the stereodirecting ligands indicated the possibility to employ the boxmi pincer systems in a more general way in enantioselective 3d metal reduction catalysis. We herein present the first manganese-based catalyst for enantioselective hydroboration of ketones,[16] providing excellent enantiomeric excess and high conversion efficiency, which renders the method an attractive alternative to the established stereoselective reductions. We will also provide evidence for the nature of the key reactive species in the catalytic hydroboration which appears to be notably different from that involved in the corresponding hydrosilylation.

The manganese precatalyst **1** was obtained directly from the corresponding boxmi-H protioligand and the readily available dialkylmanganese precursor $Mn(CH_2SiMe_3)_2$.[17] Alternatively, complex **1** could be synthesized by alkylation of manganese chlorido complexes with $LiCH_2SiMe_3$ (Scheme 2). In a first assay we found that the hydroboration of the test substrate **2a** at room temperature with 5 mol% of **1** (R = Ph, R' = H) reached completion within minutes, furnishing the chiral alcohol (*S*)-**3a** after workup with 92 %ee (Table 1, entry 1).



Scheme 2. One- and two-step access to the active precatalyst **1** (for variation of R, R', see Table 1).

The rapid conversion in the catalytic reaction at room temperature led us to investigate the hydroboration of acetophenone at reduced temperature. The addition of neat pinacolborane to a substrate/catalyst mixture at –40°C gave the secondary alcohol in 96 %ee and full conversion after 2 h (Table 1, entry 2). Following the same protocol, we then varied the substitution pattern of the boxmi ligand. Whilst alteration of the backbone moiety R' had no significant impact on the selectivity of the catalyst, only modest enantiomeric excess was detected upon exchange of the oxazoline R groups from phenyl to isopropyl, *tert*-butyl or benzyl. Moreover, these derivatives led to the formation of the (*R*)-enantiomer as the major product, indicating the presence of two distinct, enantiodivergent mechanistic pathways (*vide infra*). Notably, the activity of the catalyst was mostly unaffected by these ligand variations, with full conversions observed in all cases (see SI for a complete list of ligands).

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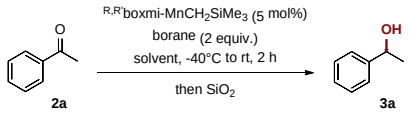
Table 1. Screening of reaction conditions for the enantioselective hydroboration of ketones.



#	R'	R[a]	borane	solvent	conv. (%)[b]	%ee[b]
1[c]	H	Ph	HBPin	toluene	>99	92 (*S*)
2	H	Ph	HBPin	toluene	>99	96 (*S*)
3	Me	Ph	HBPin	toluene	>99	96 (*S*)
4	Ph	Ph	HBPin	toluene	>99	96 (*S*)
5	H	^{i}Pr	HBPin	toluene	>99	22 (*R*)
6	H	^{t}Bu	HBPin	toluene	>99	12 (*R*)
7	Me	Bn	HBPin	toluene	>99	14 (*R*)
8	H	Ph	HBCat	toluene	45	6 (*R*)
9	H	Ph	9-BBN	toluene	97	10 (*R*)
10	H	Ph	BH_3·THF	toluene	78	0
11	H	Ph	HBPin	THF	>99	84 (*S*)
12	H	Ph	HBPin	Et_2O	>99	95 (*S*)
13	H	Ph	HBPin	CH_2Cl_2	>99	85 (*S*)
14	H	Ph	HBPin	MeCN	>99	70 (*S*)
15	H	Ph	HBPin	Hexane	>99	94 (*S*)

[a] (*S*)-enantiomers of all ligands were employed. [b] Determined by HPLC or GC analysis. [c] Performed at rt. Identical results were obtained for isolated and *in situ* generated precatalysts.

Attempts to arrive at similar results with commercially available ligands such as pybox remained unsuccessful, producing exclusively racemic or poorly enantioenriched mixtures of **3a** (see SI). A further study of the reaction conditions revealed that the selectivity of the reduction is strongly affected by the reducing agent. In fact, boranes other than HBPin (Table 1, entries 8-10) gave lower conversions and unsatisfactory enantioselectivities. Solvent screening revealed excellent enantiodiscrimination for low polarity solvents such as toluene, Et_2O and hexane. Slightly lower selectivities were observed for THF, MeCN, and CH_2Cl_2.

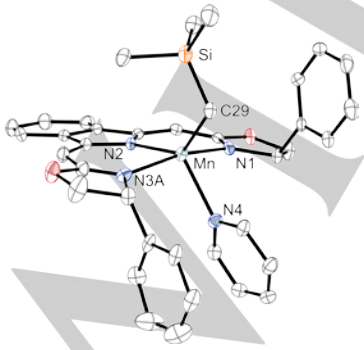
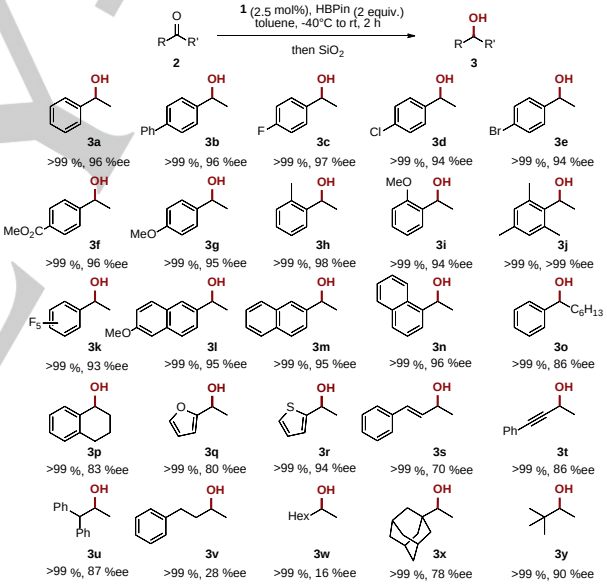


Figure 1. Molecular structure of the precatalyst pyridine adduct **1·(py)**, determined by X-ray diffraction (disorder involving part of one oxazoline ring and attached phenyl group not shown). Displacement ellipsoids set at 30 % probability level, hydrogen atoms omitted for clarity. Selected bond lengths (Å): Mn-C29 2.158(5), Mn-N1 2.293(3), Mn-N2 2.185(4), Mn-N3 2.285(13)/2.294(14), Mn-N4 2.245(4).

Despite their highly active nature, the *in situ* generated pre-catalysts were found to be readily accessible in pure form and could be stored as such, so that isolated complex **1** was used in all further studies. In addition, we were able to obtain X-ray quality crystals of the pyridine adduct **1·(py)**, featuring a trigonal-bipyramidal coordination environment with a meridionally-coordinating pincer attached to the manganese center (Figure 1). The observed Mn-N bond lengths are all within the expected range for 3d metal boxmi complexes, and the Mn-C bond distance is similar to other Mn(II) alkyl compounds with tridentate nitrogen ligands.[7,14,18]

In order to evaluate the general applicability of the novel catalyst platform, we subjected a wide range of substrates to our standard protocol at 2.5 mol% catalyst loading. Excellent conversions and enantioselectivities were obtained for all aryl methyl ketones (up to >99 %ee) with only subtle changes in enantiodiscrimination depending on the substitution pattern (Scheme 3, **3a**–**k**). Polycycles were found to be equally suitable, whereas replacement of the methyl group by longer alkyl chains gave slightly diminished enantiomeric excess (**3l**–**n** and **3o**,**p**, respectively). Similarly, heterocyclic ketones were reduced with good to excellent enantiodiscrimination (**3q**,**r**).



Scheme 3. Substrate scope of the manganese-catalyzed hydroboration of ketones.

Notably, we observed that direct attachment of the aryl group to the carbonyl function was no prerequisite for a high selectivity. In fact, vinyl and alkynyl ketones (**3s**,**t**) were converted to the corresponding alcohols with respectable enantiomeric excess and excellent chemoselectivity, *i.e.* no detectable hydroboration of the unsaturated carbon-carbon bond. Additionally, 1,1-diphenylacetone was reduced with good stereodiscrimination, whilst an increased linker length only produced modest selectivity (**3u**,**v**). Likewise, 2-octanone (**3w**) was reduced with a high activity but only poor stereoselectivity, regardless of the boxmi derivative employed as the stereodirecting ligand. Importantly, good to excellent stereodiscrimination was observed for dialkyl ketones with

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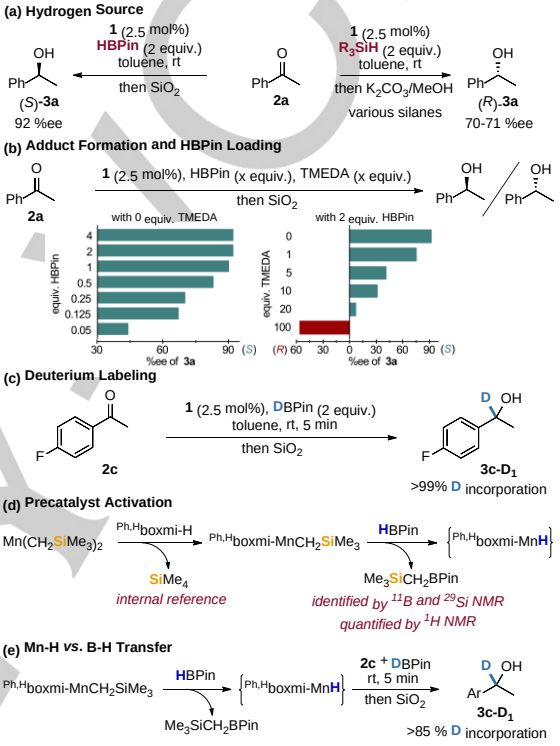
sterically sufficiently dissimilar substituents (**3x**,**y**), highlighting the role of steric effects for enantiocontrol.

To further assess the catalytic activity of the hydroboration, we gradually lowered catalyst loadings (down to 0.1 mol%, for details see SI). At room temperature, concentrations as low as 0.25 mol% facilitated a smooth conversion of **2c** within less than 5 minutes, indicating a lower limit for the turnover frequency of 4800 h^{-1}. For the standard conditions (2.5 mol% catalyst loading and -40°C) TOF values of at least 450 h^{-1} were achieved. The excellent scalability of our protocol was further corroborated by applying it to a gram scale synthesis of 1-phenylethanol. Using 1 mol% of precatalyst **1**, 1 g of acetophenone **2a** was reduced in quantitative yield and 95 %ee.

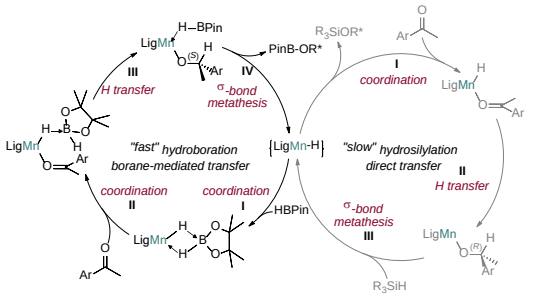
The remarkable performance of the manganese catalyst directed our attention toward the mechanism of the hydroboration. Notably, neither the activity nor the selectivity of the catalyst were affected by the presence of the common radical traps triphenylmethane and 9,10-dihydroanthracene (0.1 and 1.0 equiv.), rendering radical processes unlikely. In order to gain more detailed insights into the catalytic cycle and precatalyst activation pathways, we performed a range of control experiments (see Scheme 4, and SI). In view of the strong influence of the borane on the reduction process (*vide supra*), we hypothesized that HBPin is involved in the stereodescriminating step of the catalytic cycle. In order to probe the existence of a common manganese hydride intermediate as the hydrogen transfer agent, we performed the reduction with a range of other reductants (see SI for further details). Surprisingly, the corresponding hydrosilylation produced an inverted stereoinduction in favor of the (*R*)-alcohol while the observed enantioselectivity proved to be independent of the silane employed (Scheme 4a). This finding indicates that a hydride transfer from the reducing agent might be a critical step in manganese-catalyzed reductions, and strongly contrasts with the behavior of the related iron catalysts, where the same enantiomer is formed preferentially, irrespective of the reducing agent employed.[14] This discovery lead us to the assumption that the boxmi manganese catalyst can operate *via* two distinct pathways, *i.e.* involving a direct hydrogen transfer for the hydrosilylation or *via* a borane-mediated reduction for the hydroboration. As expected for a competition between these enantiodivergent pathways, we observed a strong correlation of the product enantioselectivity with the amount of HBPin added – with an increasing fraction of (*R*)-enantiomer formed at low pinacol borane concentrations (Scheme 4b). Importantly, an inversion of the stereochemistry of the manganese-catalyzed hydroboration was also observed, when the reaction was carried out in the presence of TMEDA, providing an additional indication of the occurrence of a catalyst-borane adduct in the stereoselectivity determining step of the hydroboration.

We then set out to determine the origin of the C-1 hydrogen atom: The reaction of deuterated pinacol borane DBPin with ketone **2c** led to the exclusive formation of the C1-labelled alcohol **3c-D$_1$** after silica work-up – evidence for the role of the borane as the sole hydrogen source (Scheme 4c). However, the precatalyst instantly reacts with HBPin to form Me_3SiCH_2BPin and, presumably, a transient manganese hydride species, which is a potent hydrogen transfer agent in its own right (Scheme 4d). To discriminate between the manganese- and the boron-mediated hydrogen addition, we pre-generated the manganese hydride and added a mixture of the substrate and DBPin. Since the resulting product featured a high deuterium incorporation, a direct hydride migration from the boron rather than the metal atom appears to be favored in the hydroboration pathway (Scheme 4e). This is reminiscent of Guan's mechanism for the iron-catalyzed hydrogenation, in which the hydride exerts the role of a directing spectator ligand.[19]



Scheme 4. Mechanistic control experiments.

Based on these findings, we propose for the hydroboration a catalytic cycle similar to the hydrosilylation catalyzed by weak Lewis acids (Scheme 5, left).[20] After coordination of HBPin and the substrate (steps I and II), hydrogen transfer takes place (step III), a process that is critical to the stereoselectivity of the reaction. Elimination of the boronic ester finally regenerates the catalyst (step IV). The tendency of manganese borane adducts to undergo bridging is well-documented for carbonyl and cyclopentadienyl complexes,[21] as is the analogous affinity of the low-coordinate highly thermally unstable π-acceptor free manganese hydrides to undergo dimerization.[22] Therefore, we expect the borane-manganese adduct to be a key intermediate in the hydroboration cycle. This pathway is significantly faster than the corresponding direct migration of the hydrogen from the manganese hydride (Scheme 5, right), allowing for an excellent enantiocontrol in the hydroboration at sufficiently high pinacol borane loadings and in the absence of strongly coordinating co-ligands. However, our results also indicate that the direct hydride transfer is favored for manganese-catalyzed hydrosilylations, thus following a catalytic cycle similar to the iron-catalyzed process.[14]



Scheme 5. Tentative mechanistic proposal for the manganese-catalyzed hydroboration and hydcrosilylation of ketones.

In conclusion, we have developed a manganese(II)-based molecular catalyst for the stereoselective reduction of a broad range of ketone substrates under very mild conditions. In contrast to other active Mn catalysts that most likely operate through a radical mechanism,[6] preliminary experiments indicate that boxmi manganese complexes are expected to facilitate a heterolytic rather than a homolytic bond activation. Our system provides an example of the potential of enantioselective base metal catalysis and, in particular, the applicability of manganese catalysts in organic synthesis. It also highlights the role of enantiodivergent mechanistic pathways for enantioselective 3d metal catalysis.

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Keywords: enantioselective catalysis • hydroboration • reduction • manganese • enantiodivergence

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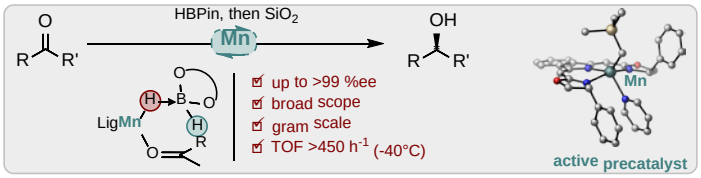

Direct or indirect: Two distinct mechanistic pathways are operative for manganese-catalyzed hydride transfer in the selectivity-determining step in the enantioselective hydroboration of ketones producing preparatively useful chiral alcohols in excellent yields and enantioselectivity (up to >99 %ee) with very low catalyst loadings and a high level of functional group tolerance.

*Vladislav Vasilenko, Clemens K. Blasius, Hubert Wadepohl, Lutz H. Gade**

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Mechanism-Based Enantiodivergence in Manganese Reduction Catalysis: A Chiral Pincer Complex for the Mild and Highly Enantioselective Hydroboration of Ketones