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Diastereomeric Control of Enantioselectivity: Evidence for Metal Cluster Catalysis†

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Enantioselective hydrogenation of tiglic acid effected by diastereomers of the general formula 
\[([\mu-H_2]Ru_3(\mu_2-S)(CO)_2(\mu-P-P^*)])\] (P-P* = chiral Walphos diphosphine ligand) strongly supports catalysis by intact Ru3 clusters. A catalytic mechanism involving Ru3 clusters has been established by DFT calculations.

A number of homogeneous catalytic systems that are based on dimetallacene complexes and/or clusters have been developed. In several of these systems, the polynuclear complexes have been implicated as the active catalysts, or direct precursors to polynuclear catalysts. It is however difficult to clearly identify clusters as homogeneous catalysts. Duckett, Dyson, and coworkers have demonstrated that the clusters [H2Ru3(CO)6(L)2] (L=phosphine) function as homogeneous catalysts for the hydrogenation of alkenes (diphenylacetylene), although a competing catalytic pathway involving fragmentation to form the mononuclear species [RuH2(CO)4(alkyne)] as active catalysts is also observed. Norton has defined an irrefutable criterion that identifies a cluster species as an active catalyst, viz. the observation of asymmetric induction in a reaction that is catalysed by a cluster that is chiral by virtue of the cluster framework only (i.e. excluding chiral ligands). This concept has been probed in the silylation of acetophenone using a chiral catalyst.

Diastereomeric reversal of the enantioselectivity of a catalytic symmetric ligand remains the same but the chirality of the cluster framework only (i.e. excluding chiral ligands). This concept has been probed in the silylation of acetophenone using a chiral catalyst.

In previous studies, we have obtained excellent conversion and very good enantioselectivity in asymmetric hydrogenation of unsaturated carboxylic acids, effected by catalytic systems based on [H2Ru3(CO)6(L)] clusters (L=bulky chiral ferrocene-based diphosphine). In continuation of this research, we have focused our attention on triruthenium hydrido clusters containing triply bridging chalcogenide ligands that may function as “clamps” to maintain an intact cluster framework. The trinuclear clusters [(\mu-H)Ru3(\mu-L)(E)(CO)5] (E = O, x=2; E = S, x=1,2) have been shown to be efficient precursors for catalytic olefin hydrogenation reactions. Reaction of [(\mu-H)Ru3(\mu-L)(S)(CO)5] with the Walphos diphosphine R,R-1 in the presence of Me2NO results in the formation of clusters 2 and 3 with the common empirical formula [(\mu-H)Ru3(\mu-S)(CO)7(\mu-1)] (Scheme 1). The bridging of adjacent metal centers by the heterobidentate ligand leads to an intrinsically chiral metallic framework. In continuation of this research, we have obtained excellent conversion and very good enantioselectivity in asymmetric hydrogenation of unsaturated carboxylic acids, effected by catalytic systems based on [H2Ru3(CO)6(L)] clusters (L=bulky chiral ferrocene-based diphosphine). In continuation of this research, we have focused our attention on triruthenium hydrido clusters containing triply bridging chalcogenide ligands that may function as “clamps” to maintain an intact cluster framework.

The catalytic activities of 2 and 3 were examined in asymmetric hydrogenation of tiglic acid. Spectroscopic measurements (IR, 1H/13C NMR, and mass spectrometry) showed no signs of changes in the clusters after catalytic runs. The catalysis results are summarized in Table 1. The enantioselectivities are low in comparison to mononuclear catalysts, but relatively high by the standards of cluster-based systems. This reflects an inherent preference for the cluster framework.

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weakness in the chiral induction effected by clusters – the substrate is likely to bind at a metal site with minimum steric hindrance (vide infra) and the chiral induction effected by bulky chiral ligands is thus diminished. However, we have observed significantly higher enantioselectivities in other cluster-based systems. The reversal in enantioselectivity in experiments where 2 and 3 were used as catalysts indicates that it is indeed the clusters that are the active catalysts, or closely related triruthenium species. Further, a mechanism involving cluster decomposition during catalysis and regeneration of intact cluster at the end of the catalytic cycle would be accompanied by formation of both diastereomers, even if only one form of the cluster was used initially. However, no trace of the other diastereomer was observed at the end of catalytic cycles employing 2 or 3.

In previous studies, we have shown that strong chiral induction by chiral phosphine can be achieved in cluster-based hydrogenations and, as a consequence, that reversal of enantioselectivity can be effected by reversal of phosphine chirality. In order to further investigate the enantioselectivity observed for the sulfide-capped clusters 2 and 3, the analogous diastereomeric pair based on S,S-1, viz. 4 (with diphosphine connectivity corresponding to 2) and 5 (connectivity corresponding to 3) were prepared, and characterized by comparing spectroscopic data with those of 2 and 3 (cf. ESI†).

Again, a reversal of enantioselectivity with reversal in diphosphine connectivity was observed when 4 and 5 were used as hydrogenation catalysts (Table 1). Furthermore, the chiral induction by the diphosphine ligand is confirmed, as the enantioselectivity is reversed with reversal in diphosphine chirality (2 vs 4, and 3 vs 5).

### Table 1 Summary of catalytic asymmetric hydrogenation reactions

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>R,R-1</td>
<td>2</td>
<td>49</td>
<td>23</td>
<td>R</td>
</tr>
<tr>
<td>R,R-1</td>
<td>3</td>
<td>79</td>
<td>56</td>
<td>S</td>
</tr>
<tr>
<td>S,S-1</td>
<td>4</td>
<td>55</td>
<td>24</td>
<td>S</td>
</tr>
<tr>
<td>S,S-1</td>
<td>5</td>
<td>64</td>
<td>52</td>
<td>R</td>
</tr>
</tbody>
</table>

[a] The amount of substrate consumed in the catalytic experiments, assessed by NMR spectroscopy. [b] Favoured enantiomer.

From Table 1, it is evident that in these catalytic systems the stereochimistry, as well as the bridging mode of the coordinated chiral ligand, strongly affects the outcome of hydrogenation in terms of both conversion and enantioselectivity. Use of cluster 3 yields an impressive 56% ee for (S)-2-methylbutyric acid. The mechanism responsible for the observed catalysis and details concerning the enantioselectivity were computationally investigated by electronic structure calculations. Scheme 2 shows the computed catalytic cycle for the hydrogenation of tiglic acid to (S)-2-methylbutyric acid employing cluster 3 (species A), where catalysis is initiated by the site-selective loss of CO from the Ru(CO)₅ center, as shown in Fig. 3.

Cluster B serves as the entry point into the catalytic cycle, and the free energy profile associated with this reaction is depicted in Fig 4. Si-face coordination of tiglic acid to B affords the alkene-substituted cluster D. Regiospecific insertion of the alkene into the proximal bridging hydride occurs via transition structure TSDE, whose energy is 29.6 kcal/mol uphill relative to B and C. The alternative alkene insertion route, which involves hydride transfer to the ester-substituted alkene carbon and the creation of the (S) stereogenic center, lies 6.6 kcal/mol above TSDE. The resulting agostic alkyl cluster E reacts with H₂ to furnish the transient trihydride cluster F. Reductive elimination in F gives (S)-2-methylbutyric acid (G) and regenerates cluster B, completing the catalytic cycle with a net release of 13.2 kcal/mol. Coordination of the re face of the prochiral substrate proceeds through a series of identical steps, all of which lie higher in energy than the si-face route. The energetics computed for the reaction profiles depicted in Fig 4 are in concert with the observed preference for the (S) enantiomer when cluster 3 is employed as the catalyst precursor. The mechanistic steps computed involve a fixed stereochimistry at the cluster, whose chirality directly influences the asymmetric induction observed in the hydrogenation product. The observed reversal in enantioselectivity with the different cluster diastereomers...
containing either \(R,R-1\) or \(S,S-1\) strongly support the involvement of intact \(\text{Ru}_3\) clusters as the active hydrogenation catalysts.

![Scheme 2](image)

**Scheme 2** Catalytic cycle for the hydrogenation of tiglic acid to (S)-2-methylbutyric acid by cluster 3.

**Fig. 3** Free energy profiles for the hydrogenation of tiglic acid catalysed by cluster 3. Black and red profiles are for the si- and re-face alkene coordination routes, respectively.

In conclusion, we have prepared four diastereomers of the cluster \([\mu-\text{H}]_2\text{Ru}_3(\mu_2-S)(\text{CO})_2(\mu-1)\], containing chiral cluster frameworks and chiral diphosine ligands. All diastereomers display different catalytic behaviour in the enantioselective hydrogenation of tiglic acid. The enantioselectivity is not only reversed with reversal in ligand chirality, but also with reversal in Cluster chirality. The latter observed reversal in enantioselectivity with the different cluster diastereomers containing either \(R,R-1\) or \(S,S-1\) strongly supports the involvement of intact \(\text{Ru}_3\) clusters as the active hydrogenation catalysts. While the (transient) formation of mononuclear chiral catalysts may be envisaged, such reactivity can neither explain the observed enantioselectivities for the diastereomeric pairs 2 and 3, and 4 and 5, nor the isolation of pure cluster diastereomers after catalysis. Application of Occam’s razor implicates cluster catalysis.

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### Notes and references

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- Electronic Supplementary Information (ESI) available: Experimental details, Crystallographic details, FTIR and NMR spectra. Complete ref 14, computational details, and atomic coordinates of optimized ground-state and transition-state structures. CCDC 993899 (2) and 993900 (3). See DOI: 10.1039/b000000x/

11. Formation of a Noyori-type catalyst of the general formula \([\text{Ru}(\text{L})_2(\text{CO})_2]_2\) is in principle possible but cannot explain a reversal of enantioselectivity. Formation of a \([\text{Ru}(\text{L})_2(\text{X})_2]_2\) (\(\text{X}=\text{arbitrary monodentate anion}\)) complex is even less likely, but could in principle form \(\Lambda\) and \(\Delta\)-isomers; however, a racemic mixture would then be expected to form, and the reversal of enantioselectivity would not be effected.
12. This is especially true with cluster 3, whose DFT-computed \(\Delta G^\ddagger\) lies 2.0 kcal/mol above that of cluster 2. Any fragmentation of 3 during catalysis, followed by cluster reassembly, would thermodynamically afford 2.
14. M.J. Frisch et al., Gaussian 09, revision B.01; Gaussian, Inc.; Wallingford, CT, 2010.
15. The DFT calculations were performed using a two-layered ONIOM (B3LYP/genrecp:PM6) approach, where the Walphos ligand, except for the phosphorus and iron atoms, was confined to the lower layer. The Ru and Fe atoms were treated using SDD effective core potential (ecp) basis sets, and all of the other high level atoms were described by a 6-31G(d) basis set. Standard-state corrections have been applied to all species to convert concentrations from 1 atm to 1 M.
16. The unsaturated cluster 2 and free CO lie 23.0 kcal/mol (\(\Delta G\)) above cluster 3.