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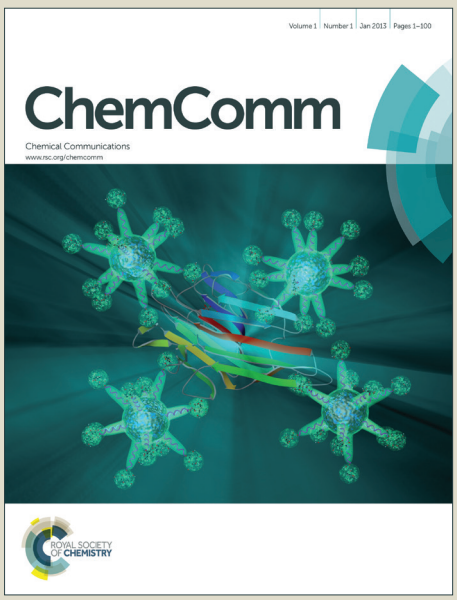

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Diastereomeric Control of Enantioselectivity: Evidence for Metal Cluster Catalysis†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

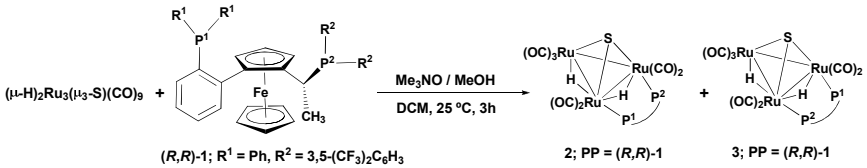
DOI: 10.1039/b000000x

Enantioselective hydrogenation of tiglic acid effected by diastereomers of the general formula [(μ-H)$_2$Ru$_3$(μ$_3$-S)(CO)$_7$(μ-P-P*)] (P-P* = chiral Walphos diphosphine ligand) strongly supports catalysis by intact Ru$_3$ clusters. A catalytic mechanism involving Ru$_3$ clusters has been established by DFT calculations.

A number of homogeneous catalytic systems that are based on dimetallic 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.[1] It is however difficult to clearly identify clusters as homogeneous catalysts.[2] Duckett, Dyson and coworkers[3] have demonstrated that the clusters [H$_2$Ru$_3$(CO)$_{10}$(L)$_2$] (L=phosphine) function as homogeneous catalysts for the hydrogenation of alkynes (diphenylacetylene), although a competing catalytic pathway involving fragmentation to form the mononuclear species [Ru(H)$_2$(CO)$_2$(L)(alkyne)] as active catalysts is also observed. Norton[4] 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 chiral tetrahedrane clusters, but cluster racemization was found to occur faster than productive catalysis.[5] The generation of a chiral cluster framework through the coordination of a suitable chiral ligand allows the above criterion to be modified such that if asymmetric induction in a catalytic system is observed, and if the enantioselectivity of the catalytic reaction is reversed by using another diastereomer of the cluster, where the chirality of the ligand remains the same but the chirality of the cluster framework has been changed, then this would constitute prima facie evidence for cluster-promoted asymmetric induction. Here we wish to present such a catalytic system that is based on two diastereomeric cluster complexes, where an unprecedented reversal of the enantioselectivity of a catalytic asymmetric reaction occurs upon reversal of the chirality of the cluster framework.

In previous studies, we have obtained excellent conversion and good enantioselectivity in asymmetric hydrogenation of α-unsaturated carboxylic acids, effected by catalytic systems based on [(μ-H)$_4$Ru$_4$(CO)$_{10}$(L)] clusters (L=bulky chiral ferrocene-based diphosphine).[6] 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 [(μ-H)$_2$Ru$_3$(μ$_3$-E)(CO)$_{9-2x}$(dppm)$_x$] (E = O, x=2; E = S, x=1,2) have been shown to be efficient precursors for catalytic olefin hydrogenation reactions.[7,8] Reaction of [(μ-H)$_2$Ru$_3$(μ$_3$-S)(CO)$_9$] with the Walphos diphosphine R,R-**1** in the presence of Me$_3$NO results in the formation of clusters **2** and **3** with the common empirical formula [(μ-H)$_2$Ru$_3$(μ$_3$-S)(CO)$_7$(μ-**1**)] (Scheme 1). The bridging of adjacent metals by the heterobidentate ligand leads to an intrinsically chiral metallic framework unless there is complete planarity,[9] and the coordination of the enantiomerically pure diphosphine ligand **1** thus yields a mixture of diastereomers **2** and **3** due to different connectivities of the heterobidentate ligand (cf. Scheme 1). Clusters **2** and **3** could be isolated and were characterized by comparing their IR and ^{1}H/^{31}P NMR spectral data with those of [(μ-H)$_2$Ru$_3$(μ$_3$-S)(CO)$_7$(dppm)][7] (*cf.* ESI†). The ^{31}P NMR data confirmed the difference in the bridging mode of the diphosphine ligand in **2** and **3**. For **2**, the P^1 signal (cf. Scheme 1) appears as a triplet, indicating coupling to both hydrides, while the signal for P^2 is a doublet. In contrast, the signal for P^1 in **3** appears as a doublet while that of P^2 is a doublet of doublets. The identities of the two diastereomers were further confirmed by the determination of their crystal structures (Figs 1 and 2).

The catalytic activities of **2** and **3** were examined in asymmetric hydrogenation of tiglic acid.[6,10] Spectroscopic measurements (IR, ^{1}H/^{31}P NMR, *cf.* ESI†) 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



Scheme 1. The synthesis of clusters **2** and **3**.

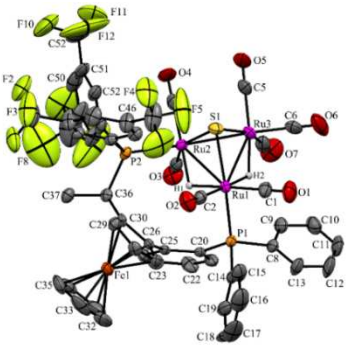


Fig. 1 Molecular structure of $[(\mu\text{-H})_2Ru_3(\mu_3\text{-S})(CO)_7(\mu\text{-}\mathbf{1})]$ **2** with thermal ellipsoids drawn at the 50% probability level. C-H hydrogen atoms have been omitted for clarity. Selected bond distances [Å] and angles [°]: Ru1-Ru 2 2.8951(7), Ru1-Ru3 2.9023(6), Ru2-Ru3 2.7536(6), Ru1-P1 2.359(2), Ru2-P2 2.333(1), Ru1-S1 2.368(2), Ru2-S1 2.375(2), Ru3-S1 2.346(2), Ru1-H1 1.75(5), Ru1-H2 1.69(5), Ru2-H2 1.76(4), Ru3-H1 1.76(5).

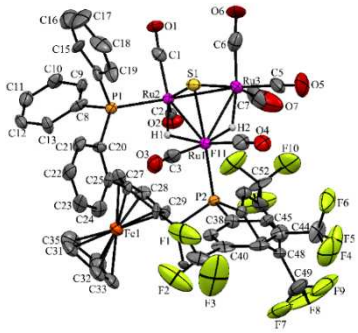


Fig. 2 Molecular structure of $[(\mu\text{-H})_2Ru_3(\mu_3\text{-S})(CO)_7(\mu\text{-}\mathbf{1})]$ **3** with thermal ellipsoids drawn at the 50% probability level. C-H hydrogen atoms have been omitted for clarity. Selected bond distances [Å] and angles [°]: Ru1-Ru2 2.915(2), Ru1-Ru3 2.894(2), Ru2-Ru3 2.746(2), Ru1-P2 2.335(4), Ru2-P1 2.348(5), Ru1-S1 2.361(5), Ru2-S1 2.358(5), Ru3-S1 2.351(5). Ru1-H1 1.53, Ru1-H2 1.57, Ru2-H2 1.90, Ru3-H1 1.67 (riding on Ru atoms).

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.[6b] 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.[11] 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,[12] 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[6b] and, as a consequence, that reversal of enantioselectivity can be effected by reversal of phosphine chirality.[13] In order to further investigate the reversal in 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

Ligand	Catalyst	Conversion[a] (%)	ee (%)	Configuration[b]
R,R-**1**	2	49	23	*R*
R,R-**1**	3	79	56	*S*
S,S-**1**	4	55	24	*S*
S,S-**1**	5	64	52	*R*

[a] The amount of substrate consumed in the catalytic experiments, assessed by ^{1}H NMR spectroscopy. [b] Favoured enantiomer.

From Table 1, it is evident that in these catalytic systems the stereochemistry, 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.[14-15] 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 $Ru(CO)_3$ center, as shown in Fig 3.[16]

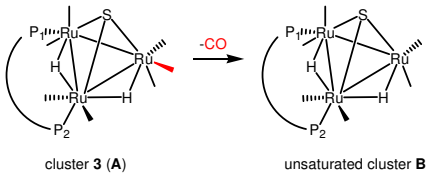
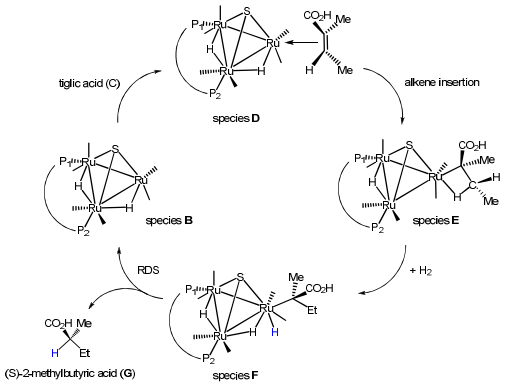


Fig. 3 Site-selective loss of CO from the $Ru(CO)_3$ center in cluster **3** (see text).

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 H_2 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 stereochemistry 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 Ru_3 clusters as the active hydrogenation catalysts.



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

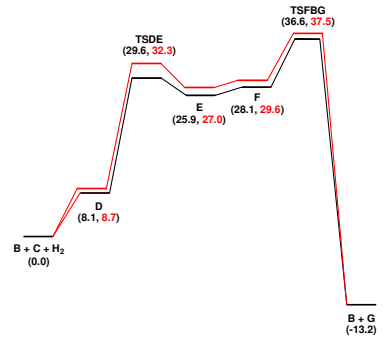


Fig. 3 Free energy profiles for the hydrogenation of tiglic acid catalysed by cluster **3**. Black and red profiles are for the si- and re-face alkene coordination routes, respectively.

In conclusion, we have prepared four diastereomers of the cluster $[(\mu\text{-H})_2Ru_3(\mu_3\text{-S})(CO)_7(\mu\text{-}\mathbf{1})]$, containing chiral cluster frameworks and chiral diphosphine 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 Ru_3 clusters as the active hydrogenation catalysts. While the (transient) formation of mononuclear chiral catalysts may be envisaged,[11] 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.

AFA thanks the EU Erasmus Mundus program for a predoctoral fellowship. AKS thanks the Carl Trygger Foundation for a postdoctoral fellowship. MGR thanks the Robert A. Welch Foundation (grant B-1093) for financial support; NSF support of the computational facilities at the University of North Texas through grant CHE-0741936 is acknowledged. We thank Dr. David Hrovat and Prof. Xinzheng Yang for many helpful ONIOM-based discussions.

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/

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11 Formation of a Noyori-type catalyst of the general formula $[Ru(\mathbf{1})(O_2CR)_2]$ is in principle possible but cannot explain a reversal of enantioselectivity. Formation of a $[Ru(\mathbf{1})_2X_2]$ (X=arbitrary monodentate anion) complex is even less likely, but could in principle form Λ and Δ-isomers; however, a racemic mixture would then expected to be formed, and the reversal of enantioselectivty would not be effected.

12 This is especially true with cluster **3**, whose DFT-computed ΔG° lies 2.0 kcal/mol above that of cluster **2**. Any fragmentation of **3** during catalysis, followed by cluster reassembly, would thermodynamically afford **2**.

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15 The DFT calculations were performed using a two-layered ONIOM (B3LYP/genecp: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 **B** and free CO lie 23.0 kcal/mol (ΔG) above cluster **3**.