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Shvo's catalyst in chemoenzymatic dynamic kinetic resolution of amines – inner or outer sphere mechanism?†

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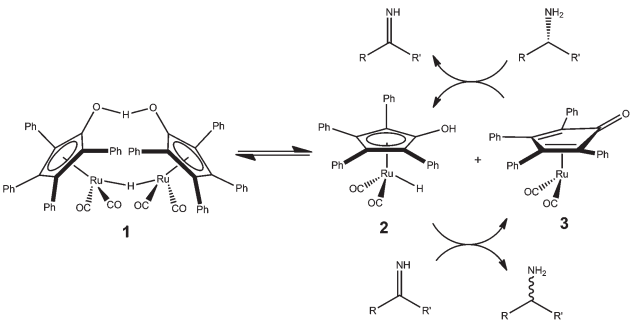
Boniek G. Vaz,[a] Cintia D. F. Milagre,[b] Marcos N. Eberlin*[c] and Humberto M. S. Milagre*[b]

Evidence is provided for the inner-sphere mechanism with actual metal coordination of the racemic amine in the crucial hydrogen transfer step promoted by Shvo's catalyst of the chemoenzymatic dynamic kinetic resolution (DKR) of amines. Key intermediates involved in this H-transfer step were intercepted and continuously monitored by electrospray ionization mass spectrometry (ESI-MS) and characterized by their dissociation chemistries *via* ESI-MS/MS.

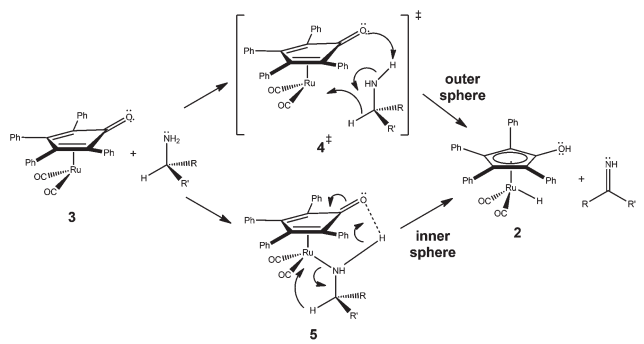
Dynamic kinetic resolution (DKR)[1] combines enzymatic resolution with metal-catalyzed racemization. This elegant and efficient strategy fully converts a racemic substrate, such as chiral amines, into a single enantiomeric product. DKR has been therefore widely used in synthetic organic chemistry to obtain economically important building blocks. Various metal complexes such as those of ruthenium, rhodium and iridium are known to catalyze the racemization of amines, but only a few of them are compatible with enzymatic resolution. A pivotal example is Shvo's catalyst[2] **1**, a cyclopentadienone-ligated diruthenium complex which efficiently promotes fast racemization of amines[1c,3] under mild conditions (Scheme 1).

Shvo proposed, however, that intact **1** is not directly involved[4] but thermally dissociates into two mono-ruthenium active species, 16-electron and 18-electron Ru complexes (**3** and **2**, Scheme 1). Evidence for **2** has been obtained by NMR and IR spectroscopy,[5a] but **3** has remained elusive. Although H-transfer is a key step in the amine racemization, another important open question regarding H-transfer is the nature of substrate coordination to the metal center. For this key step, two main propositions have been offered:[5–7] (i) the outer-sphere mechanism in which H-transfer occurs in a concerted fashion outside the coordination sphere of the metal *via* transition state $\mathbf{4}^{\ddagger}$ or (ii) the inner-sphere mechanism in which H-transfer occurs in a stepwise fashion inside the coordination sphere *via* **5** (Scheme 2). Hydrogenation is a canonical reaction in homogeneous catalysis with metal-hydride intermediates playing the central role; hence, a fundamental understanding of the actual mechanism is crucial for further development of more efficient catalysts.

We report herein an investigation, *via* electrospray ionization mass spectrometry (ESI-MS) and its tandem version ESI-MS/MS, of the mechanism of the chemoenzymatic DKR



Scheme 1 Shvo's catalyst **1** and its thermal dissociation products **2** and **3** and a mechanistic view of their role in amine racemization.



Scheme 2 Alternative mechanisms of amine dehydrogenation.

[a]*Institute of Chemistry, Federal University of Goiás, Campus Samambaia, Caixa Postal 131, Goiânia, Goiás CEP 74001-970, Brazil*
[b]*Department of Organic Chemistry, Institute of Chemistry, Univ. Estadual Paulista UNESP, 14800-060 Araraquara, SP, Brazil. E-mail: humbertomilagre@iq.unesp.br*
[c]*ThoMSon Mass Spectrometry Laboratory – Institute of Chemistry, University of Campinas UNICAMP, 13084-971 Campinas, SP, Brazil. E-mail: eberlin@iq.unicamp.br*

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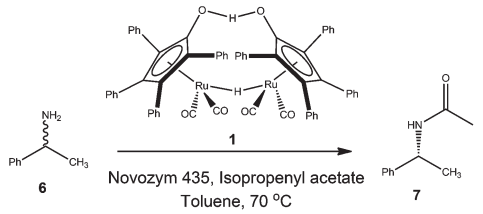


Scheme 3 DKR of **6** catalyzed by Shvo's catalyst **1**.

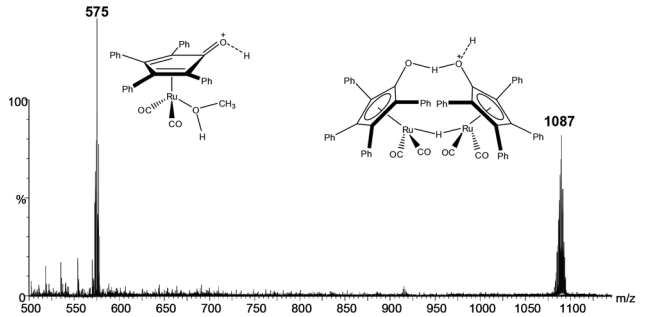


Fig. 1 ESI(+)-MS of a toluene solution of Shvo's catalyst **1** after 20 min from its dilution with methanol.

with Shvo's catalyst **1** using the model reaction of racemic (±)1-phenylethylamine **6** promoted by lipase Novozym® 435 (Scheme 3).

ESI-MS(/MS) has been established as a major technique for mechanistic studies.[8,9] The technique is used to "fish" out, with high sensitivity, speed and gentleness, ionic or ionized intermediates directly from reaction solutions into the gas phase, in which proper characterization by a variety of MS techniques can be performed.

To probe whether indeed the Shvo's catalyst **1** dissociates in solution to **2** and **3** (Scheme 1), we first monitored by ESI(+)-MS the thermal dissociation of Shvo's catalyst **1** (0.02 mmol) in toluene (10 mL) at 70 °C. For proper ESI(+), the catalyst solution was diluted either with acetonitrile (Fig. S1†) or methanol (Fig. 1) and slightly acidified with formic acid (0.1%). In all the spectra collected, two abundant ions could be easily and directly intercepted: the protonated forms of the intact Shvo's catalyst **1** (*m*/*z* 1087) and its mono-Ru species **3** coordinated either with acetonitrile (*m*/*z* 584) or methanol (*m*/*z* 575). The ions of *m*/*z* 1087, *m*/*z* 584 and *m*/*z* 575 were further characterized by ESI(+)-MS/MS (Fig. S1–S2†).

Fortunately therefore, the so far elusive species **3** could be intercepted and properly characterized by MS and MS/MS data. The failure of ESI(+)-MS to detect **2** can be rationalized by its high reactivity in acidic methanol or acetonitrile, in which the nascent **2** may rapidly suffer H-abstraction from Ru by H^+ followed by ring slippage (η^5 to η^4) yielding H_2 and **3** (Scheme S1†). It is likely therefore that **3** predominates in solutions of **1** and is formed both directly from **1** and from its counterpart **2**. In an effort to detect traces of **2**, due to the high sensitivity of ESI-MS, spectra were collected under a number of different conditions such as with no addition of acids and also

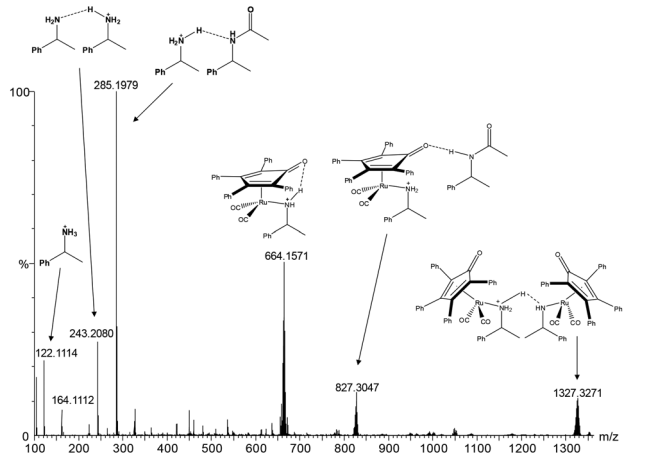
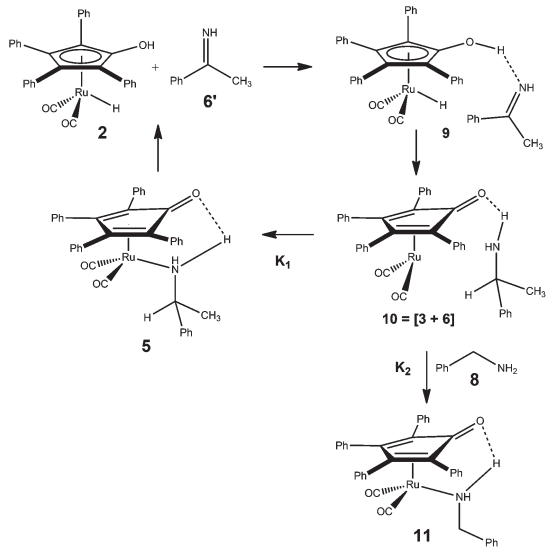


Fig. 2 ESI(+)-MS after 30 min of the model DKR reaction.

via ESI(−)-MS in slightly alkaline media (0.1% NH_4OH solution as the additive), but no Ru-containing anions related to **2** could be detected.

Next, ESI(+)-MS monitoring was performed for the model reaction (Scheme 3), *i.e.*, the one-pot chemoenzymatic DKR of (±)1-phenylethylamine **6** (0.50 mmol), **1** (0.02 mmol), lipase Novozym® 435 (20 mg), and isopropenyl acetate (2.00 mmol) in toluene (10 mL) at 70 °C under magnetic stirring. Prior to the acquisition of all ESI(+)-MS, samples from the reaction solution were diluted with methanol and slightly acidified with formic acid (0.1%). Fortunately, ESI(+)-MS was able to detect a comprehensive set of six major ions most typically after 30 min of reaction (Fig. 2). These ions were identified as protonated forms of the amine **6** of *m*/*z* 122 and its dimer of *m*/*z* 243, **7** of *m*/*z* 164, the [**6** + **7**] adduct of *m*/*z* 285, **3** coordinated with **6**, that is, the key intermediate **5** of *m*/*z* 664, as well as [**5** + **5**] of *m*/*z* 1327 and [**5** + **7**] of *m*/*z* 827. Accurate mass measurements, the characteristic pattern of Ru isotopologue ions, and their collision-induced dissociation (CID) chemistries in ESI(+)-MS/MS experiments (Fig. S2–S10†) corroborate these assignments. The resulting ESI-MS/MS data of the fragment ion of *m*/*z* 664 (Fig. S7†) support its structural assignment as **5** since the ion, upon collision activation, shows mainly two consecutive losses of CO that yield fragments of *m*/*z* 636 and *m*/*z* 608 and a loss of the $PhCH(CH_3)NH_2$ yielding [**2** + H^+] of *m*/*z* 543. The minor ions of *m*/*z* 515 and 487 are secondary fragments formed by two subsequent CO losses from the ion of *m*/*z* 543. The dissociation of **5** preferentially by two consecutive losses of CO (and not by amine loss) indicates that the amine substrate (**6**) is strongly bound to **1** *via* Ru coordination.

Note that the clear interception of abundant forms of the long-lived, relatively stable and abundant **5** seems to shed light on the mechanistic views for the H-transfer step (Scheme 2) supporting the prevalence of the inner-sphere mechanism. The alternative outer-sphere mechanism would proceed *via* transient $\mathbf{4}^{\ddagger}$, which should be too short-lived to allow for its accumulation in solution and so prompt its detection *via* ESI



Scheme 4 Intermediates **5** and **11** expected in the Casey-like trapping experiment using the achiral benzylamine (**8**).

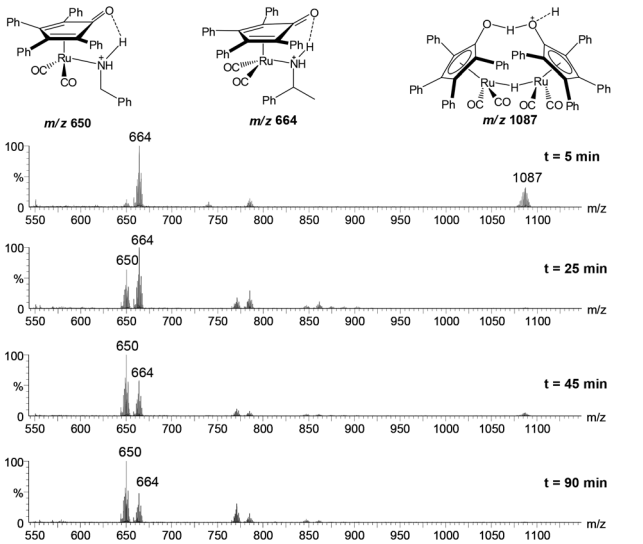
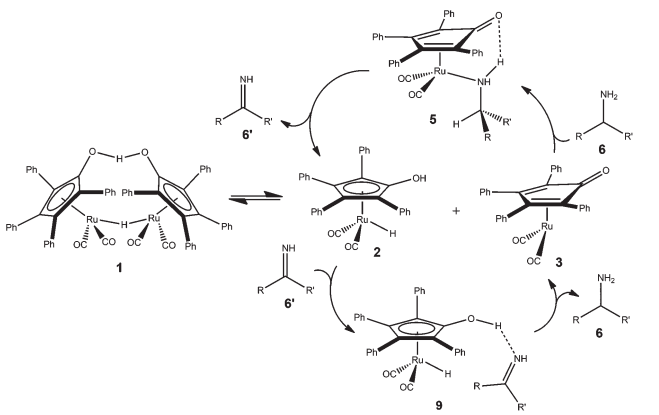


Fig. 3 Temporal ESI(+)-MS monitoring of the Casey-like trapping experiment.

(+)-MS. The long-lived nature of **5** is also demonstrated by its survival in the gas phase and its considerable resistance towards collision dissociation. In contrast, efficient interception of the short-lived $\mathbf{4}^{\ddagger}$ by ESI(+)-MS would therefore not be expected.

Looking for additional ways to probe the DKR mechanism, we noted that Casey proposed an interesting experiment to probe the nature of the H-transfer intermediate. Casey's idea was to add a second, similar achiral amine (benzylamine **8**) as a trapping nucleophile.[6] If the inner-sphere mechanism occurs, **3** would therefore competitively coordinate with either **6** or **8** to form the long-lived intermediates **5** and **11** (Scheme 4) in a stepwise fashion following slightly different kinetics. Since the reaction proceeds *via* exclusive enzymatic transformation of **6**, intermediate **5** should be consumed while **11** accumulates. In contrast, the outer-sphere mechanism would lead to a failure to detect $\mathbf{4}^{\ddagger}$ with the sole accumulation of **11**. Considering therefore the interception of **5** by ESI(+)-MS, a Casey-like trapping experiment using the achiral benzylamine (**8**) in the racemization of (*S*)-phenylethylamine **6** with **1** was therefore monitored up to 90 min of reaction (Fig. 3).

After 5 min of reaction, **1** of *m*/*z* 1087 and **5** of *m*/*z* 664 (Fig. 3) were detected but a new ion of *m*/*z* 650, likely intermediate **11** (Fig. S9†), began to appear. As the reaction proceeded, indeed as expected assuming the inner-sphere mechanism, **1** was continuously consumed and **11** of *m*/*z* 650 became more and more abundant and eventually predominant. The initial predominance of **5** of *m*/*z* 664 over **11** of *m*/*z* 650 indicates that $k_1 > k_2$ (Scheme 4).



Scheme 5 Shvo's catalyst **1** and its thermal dissociation products **2** and **3** and major intermediates **5** and **9** for amine racemization as revealed by ESI-MS monitoring.

Conclusions

The ESI fishing of both **3** and **5** directly from the reaction solution and their MS detection and MS/MS characterization as abundant long-lived key intermediates as well as the temporal accumulation of **11** to the detriment of **5** in the Casey-like trapping reaction provided evidence for the inner-sphere H-transfer mechanism. ESI-MS monitoring has also been able to probe the formation of the elusive **3** due to thermal dissociation of Shvo's catalyst **1** in solution. A more comprehensive view of the mechanism of the chemoenzymatic DKR of amines using Shvo's catalyst **1** could therefore be presented (Scheme 5).

Acknowledgements

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