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) 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 therefore been 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, a cyclopentadienone-ligated diruthenium complex which efficiently promotes fast racemization of amines under mild conditions (Scheme 1).

Shvo proposed, however, that intact is not directly involved 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, 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: (i) the outer-sphere mechanism in which H-transfer occurs in a concerted fashion outside the coordination sphere of the metal via transition state 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...
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.6,9 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
amine substrate (±)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 co-
ordinated 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) chem-
istry in ESI(+)-MS/MS experiments (Fig. S2–S10) corroborate
these assignments. The resulting ESI-MS/MS data of the frag-
ment ion of m/z 664 (Fig. S7) support its structural assign-
ment 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(CH3)NH2 yielding
[2 + H'] of m/z 543. The minor ions of m/z 515 and 487 are sec-
ondary 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 4‡, which should be too short-lived to allow for its
accumulation in solution and so prompt its detection via
ESI

via ESI(−)-MS in slightly alkaline media (0.1% NH4OH 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
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The alternative outer-sphere mechanism would proceed via
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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 4‡ 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. 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 4‡ 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).

**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).

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Notes and references


