

# Mechanistic aspects of hydrogen addition during enantioselective rhodium-catalysed reduction of C=C double bonds with formic acid/triethylamine or molecular hydrogen†

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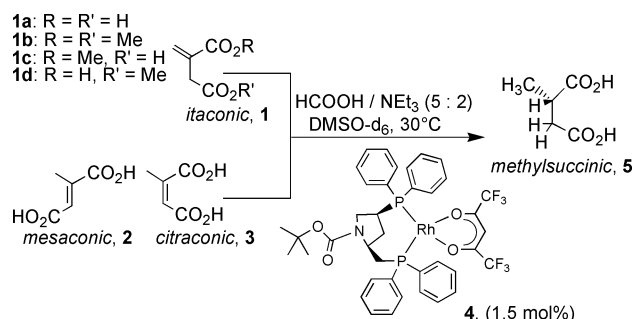
Deuterium labelling experiments reveal a remarkably different hydrogen addition mode during homogeneously catalysed C=C bond reduction of itaconic acid derivatives **1a–d** using molecular hydrogen (hydrogenation) or formic acid/triethylamine (transfer hydrogenation). The expected vicinal addition of two hydrogen atoms across the double bond prevails for all substrates in conventional hydrogenation, whereas the deuterium pattern depends largely on the nature of the carboxyl group in the  $\beta$  (or allylic) position during transfer hydrogenation. Vicinal addition is observed only in case of itaconic acid **1a** and  $\alpha$ -methylitaconate **1c**, while 1,3-addition is preferred with dimethylitaconate **1b** and  $\beta$ -methylitaconate **1d**. Significant amounts of polydeuterated products are formed also during hydrogenation and transfer hydrogenation. Monitoring the deuterium pattern as a function of time reveals that deuterium scrambling is responsible for polydeuteration, but not for the change of the addition mode. The use of monodeuterated formic acid isotopomers shows that the incorporation from the hydridic formyl position occurs preferentially at the terminal end of the double bond (C-3) whereas the protic hydrogen is directed either in the higher substituted olefinic (C-2) or the methylene (C-1) position. Control experiments using mesaconic (**2**) and citraconic (**3**) acids demonstrate that double bond migration in **1a–d** is negligible under the reaction conditions. These results are best rationalised on the basis of a common mechanism for hydrogenation and transfer hydrogenation that involves (i) the generation of Rh–H intermediates, (ii) reversible hydride transfer to coordinated substrate to form two isomeric  $\sigma$ -alkyl intermediates, and (iii) irreversible product liberation through protolytic Rh–C cleavage. The key intermediates are similar if not identical for hydrogenation and transfer hydrogenation. The change of the hydrogen transfer pattern can be explained on the basis of the relative rates of the individual steps within the catalytic cycle as compared to the rate of isomerisation of the  $\sigma$ -alkyl intermediates.

## Introduction

The reduction of C=C double bonds is one of the most fundamental synthetic transformations and plays a key role in the manufacturing of a wide variety of bulk and fine chemicals. Hydrogenation of olefinic substrates can be achieved readily with molecular hydrogen in many cases, but transfer hydrogenation methods using suitable donor molecules such as formic acid or alcohols are receiving increasing attention as possible synthetic alternatives.<sup>1</sup> Transfer hydrogenation is attractive especially for the small scale production of diverse products as it requires no special equipment and avoids the handling of potentially hazardous gaseous hydrogen. Highly stereoselective methods have emerged from transfer hydrogenation techniques based on the use of suitable chiral transition metal complexes in homogeneous solution.<sup>2</sup> Especially, chiral rhodium phosphine complexes have proven extremely effective for both hydrogenation and transfer hydrogenation of C=C double bonds.<sup>2b,3</sup> Although the mechanism of rhodium-catalysed homogeneous hydrogenation of C=C bonds with molecular hydrogen has been studied in great detail and all key intermediates have been identified by spectroscopic techniques,<sup>4</sup> much less is known about the corresponding transfer hydrogenation sequence.<sup>5–8</sup>

In the simplest case, transfer hydrogenation reactions with

formic acid can result from a tandem process comprising independent hydrogen donor decomposition and subsequent conventional hydrogenation using two different catalytic systems for the two half reactions.<sup>9</sup> The majority of efficient and especially enantioselective transfer hydrogenations seems to follow more complex pathways, however, where the same active centre is responsible for the cleavage of the hydrogen donor and the transfer of the hydrogen equivalents to the substrate.<sup>5–8</sup> The present study sheds some light on the intimate mechanistic details of the hydrogen addition step for rhodium-catalysed transfer hydrogenation using the formic acid/triethylamine azeotrope as the hydrogen source (HCO<sub>2</sub>H/NEt<sub>3</sub> 5 : 2) (Scheme 1). The isomeric unsaturated dicarboxylic acids **1a**, **2**, and **3**



**Scheme 1** Enantioselective rhodium-catalysed transfer hydrogenation of isomeric unsaturated acids and esters **1–3**. Initially formed esters are converted to the free acid **5** during hydrolytic work-up (see Experimental section).

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**Table 1** Conversion and enantioselectivity as a function of the reaction time for transfer hydrogenation under the conditions of Scheme 1

Substrate	Conversion (%)			ee ( <i>S</i> ) (%)		
	10 min	1 h	8 h	10 min	1 h	8 h
<b>1a</b>	8	28	100	80	78	73
<b>1b</b>	30	70	100	26	25	27
<b>1c</b>	100	—	—	63	—	—
<b>1d</b>	2	7	80	36	28	16
<b>2</b>	8	25	100	2	4	3
<b>3</b>	n.d. <sup>a</sup>	n.d. <sup>a</sup>	8	n.d. <sup>a</sup>	n.d. <sup>a</sup>	8

<sup>a</sup> n.d. = not detectable.

and the esters **1b–d** were chosen as substrates to study the effects of systematic structural variation. Methylsuccinic acid **5** is obtained as the only product from all these substrates after hydrolytic work-up. The chiral complex [(bppm)Rh(hfacac)] **4** (bppm = (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-(diphenylphosphino)methyl)pyrrolidine; hfacac = 1,1,1,5,5,5-hexafluoroacetylacetonate) was used as catalyst precursor for transfer hydrogenation as well as for control experiments using molecular hydrogen or deuterium. (*S*)-**5** was formed as the preferred enantiomer from all substrates regardless of the reaction conditions.

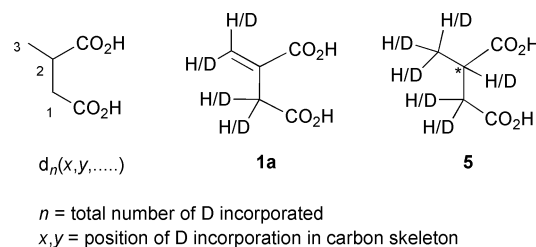
## Results and discussion

The reaction rates and enantioselectivities observed for the transfer hydrogenation of substrates **1a–d** vary considerably under identical reaction conditions, but there is no direct correlation between rate and selectivity (Table 1). With  $\alpha$ -methylitaconate **1c** quantitative conversion is achieved within less than 10 min, while the reduction of  $\beta$ -methylitaconate **1d** requires more than 24 h to reach completion. The highest enantioselectivity of 73% at complete conversion is obtained with itaconic acid **1a** and the enantioselectivity of **1c** is only slightly lower with 63%.<sup>10</sup> The acid group in the  $\beta$ -position (or allylic position) seems to be necessary for high selectivity, as the enantioselectivities of **1b** and **1d** are much lower with 27% and 16%, respectively. The two acids **2** and **3** lacking an allylic carboxyl group give an almost racemic product. (*Z*)-Configured **3** is reduced at an extremely low rate and only 75% conversion could be reached even after further treatment with excess formic acid and an extended reaction time of five days. Only a small decrease of the enantioselectivity during the reaction is observed with **1a**, but it is more significant in the case of **1d**.

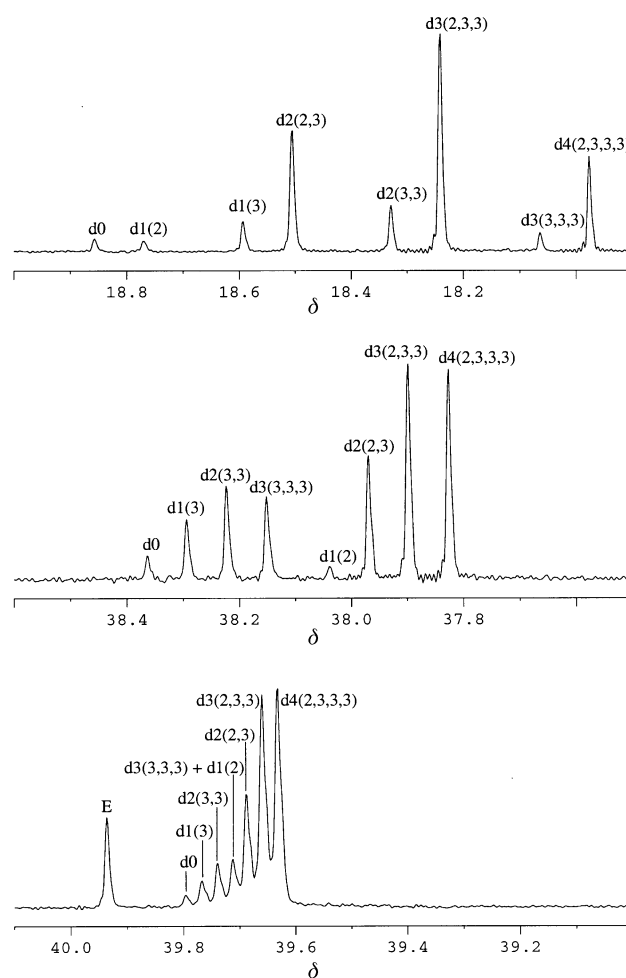
Labelling experiments were carried out as described in detail in the Experimental section. The acidic positions of the carboxylic acids were exchanged for deuterium when D<sub>2</sub>, DCOOD or HCOOD were used as reducing agents. No exchange with the H/D-groups of the solvent or triethylamine was observed by direct NMR analysis of reaction mixtures in selected experiments. Similarly, no H/D exchange was observed for isolated **5** under either transfer hydrogenation or hydrogenation conditions. Therefore, all incorporation and scrambling processes discussed below must occur before the irreversible liberation of the product from the catalyst.

Mechanistic conclusions from deuterium labelling studies require a reliable and efficient method for the analysis of all possible isotopomers, which can evolve in a rather complex task even for seemingly simple molecules. For methylsuccinic acid **5** there is a total of 32 isotopomers considering the three positions in the carbon skeleton and including possible diastereomeric substitutions. Up to 12 isotopomers are possible for itaconic acid **1a**. The numbering scheme and nomenclature used to distinguish these isotopomers in the present paper is given in Fig. 1.

The concerted use of <sup>1</sup>H, <sup>2</sup>D, and <sup>13</sup>C-NMR spectroscopy together with two dimensional high resolution HSQC-experi-

**Fig. 1** Numbering scheme and nomenclature of isotopomers exemplified for **1a** and **5**. Stereochemically distinct positions at C-3 (**1a**) and C-1 (**5**) are indicated as 3/3' and 1/1', respectively.

ments allows the unambiguous assignment of all possible isotopomers of **5** and **1a**.<sup>11</sup> The additive shifts of the carbon resonances by substitution of deuterium for hydrogen in the simultaneously proton and deuterium decoupled {<sup>1</sup>H,<sup>2</sup>D}-<sup>13</sup>C-NMR spectra is particularly useful for qualitative and quantitative analysis of such isotopomeric mixtures.<sup>5,12</sup> As a representative example, Fig. 2 shows the relevant parts of the

**Fig. 2** Methyl (top trace), methylene (middle trace) and methine region (lower trace) of the <sup>13</sup>C{<sup>1</sup>H,<sup>2</sup>D}-NMR-spectrum of an isotopomeric mixture of **5** obtained from deuteration of **1a** with D<sub>2</sub> after 92% conversion (E = starting material).

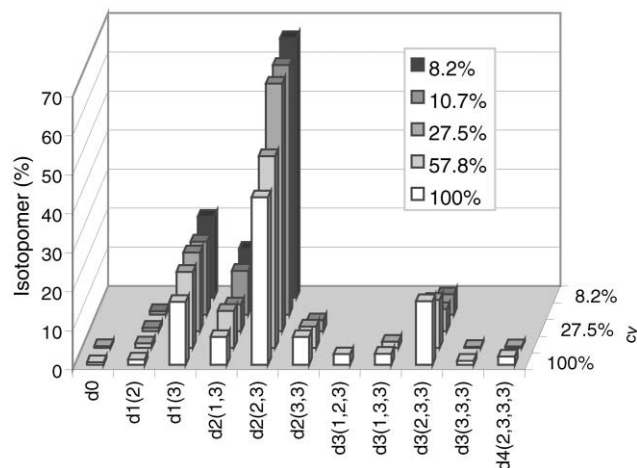
{<sup>1</sup>H,<sup>2</sup>D}-<sup>13</sup>C-NMR spectrum of a mixture of **1a** and **5** obtained from deuteration with D<sub>2</sub> at 92% conversion. All signals are clearly separated and quantitative analysis of the isotopomers of **5** is possible by integration of the signals arising from C-1, because there is no deuterium incorporation at this position under the given conditions. Similar sets of comparable signals with no significant distortion of signal intensities from differences in relaxation times can be identified also in other cases. To substantiate the high accuracy of this technique, Table 2 shows

**Table 2** Comparison of deuterium distribution as determined from mass spectroscopy and  $\{^1\text{H}, ^2\text{D}\}^{13}\text{C}$ -NMR spectroscopy for representative transfer deuterations of **1c** and **1d** with DCOOD

Deuterium content of <b>5</b>	<b>1c</b>		<b>1d</b>	
	MS (%)	NMR (%)	MS (%)	NMR (%)
d <sub>0</sub>	13	14.5	6	6.7
d <sub>1</sub>	43	40.2	38	37.9
d <sub>2</sub>	33	33.8	39	37.4
d <sub>3</sub>	9	9.6	14	14.8
d <sub>4</sub>	2	1.9	3	3.2

the excellent agreement of the total deuterium incorporation obtained from the sum of the individual isomers in the NMR spectra with results from mass spectrometry for two typical transfer hydrogenation experiments using **1c** and **1d** as substrates. There are only minor deviations even for highly deuterated isotopomers, where low concentrations and weak signal intensities would exclude conventional  $^{13}\text{C}$ -NMR spectroscopic analysis. Up to eighteen different isotopomers of **5** were unambiguously identified and quantified with these techniques in some of the samples resulting from transfer deuteriation in the present study.

The reduction of itaconic acid **1a** with DCOOD/ $\text{NEt}_3$  using catalyst **4** in  $\text{DMSO-d}_6$  results in a complex mixture of at least eleven isotopomers of **5** after full conversion (Fig. 3). There is a

**Fig. 3** Distribution of isotopomers of **5** obtained from transfer deuteriation of **1a** with DCOOD at different conversions.

significant amount of isotopomers containing more than two deuterium atoms. The overall deuterium incorporation corresponds to 2.08 equivalents, which is a low estimate, however, as the protic positions of commercial DCOOD and the deuterium exchanged substrate are far from 100% deuterium content. The deuterium scrambling may be associated with the reversibility of the initial hydrogen transfer from the metal to the coordinated substrate.<sup>6</sup> If the substrate has time to leave the metal center before it is reduced completely, a reversible first transfer is expected to lead to detectable amounts of deuterated starting material in the reaction mixture. Indeed, significant amounts of deuterium incorporation in the starting material **1a** can be detected during the intermediate stages of transfer deuteriation. Under the conditions of Fig. 3, there is already deuterium incorporation in 5.4% of the starting material **1a** after 8.2% conversion. After 58% conversion nearly 45% of **1a** contains deuterium mainly located at the C-3 position (35.7% of d<sub>1</sub>(3)-**1a** and 7.9% of d<sub>2</sub>(3,3)-**1a**) with no significant preference for the (*E*) or (*Z*) position.

The quantitative distribution of isotopomers of product **5** during the course of the transfer deuteriation of **1a** shows that three isotopomers d<sub>1</sub>(3)-**5**, d<sub>2</sub>(1,3)-**5**, and d<sub>2</sub>(2,3)-**5** are already

present at low conversion where deuterium incorporation into the substrate is still negligible (Fig. 3). The relative ratio of these three main isotopomers remains fairly constant throughout the reaction, whereas their contribution to the total number of isotopomers decreases with conversion owing to deuterium scrambling. This clearly indicates that two distinct processes are operating: The intrinsic selectivity of the hydrogen addition leads to a given distribution of hydrogen/deuterium at positions C-1, C-2 and C-3, whereas scrambling leads to the formation of more and less highly deuterated species through a separate exchange processes. The relative distribution of the major isotopomers is largely determined by the intrinsic selectivity and therefore allows conclusions about the hydrogen addition step with different substrates.

The major isotopomer d<sub>2</sub>(2,3)-**5** obtained during transfer deuteriation of **1a** is formed *via* the expected vicinal addition of two deuterium equivalents across the C=C double bond. The d<sub>1</sub>(3) congener can result at least partly from incomplete deuteriation of the protic positions in the substrate *via* the same addition mode. From the beginning, there is also a noticeable incorporation in position C-1, but it remains very small as compared to the main vicinal 2,3-addition mode. This situation changes completely when the corresponding dimethyl ester **1b** is used as substrate. In contrast to **1a**, the diester **1b** is reduced by DCOOD/ $\text{NEt}_3$  almost exclusively *via* deuterium addition at C-1 and C-3, with very little incorporation at C-2 after full conversion (Fig. 4). The isotopomer d<sub>2</sub>(1,3)-**5** is formed with 57% selectivity at 30% conversion, as compared to only 9% d<sub>2</sub>(2,3)-**5** at this stage. Again, the ratio of about 8 : 1 remains constant up to complete conversion, even though scrambling takes place also in this case (total deuterium incorporation is 1.81). There is no preference for the incorporation into either of the two diastereomeric positions at C-1.

This remarkable switch of the hydrogen addition mode can be directly associated with the nature of the carboxylic group in  $\beta$ -position (or allylic position). Substrate **1c** contains a free carboxylic acid group in this position and is reduced preferentially *via* the 2,3-addition mode. Although the distinction of the two sites is less pronounced for substrate **1d**, the deuterium pattern clearly indicates that the esterification of the  $\beta$ -position significantly favours 1,3-incorporation. Fig. 5 summarises the distribution of the d<sub>2</sub> isotopomers for the four substrates **1a–d**.

As most hydrogenation catalysts are effective also for double bond isomerisation, it is important to assess the reduction and deuterium addition for the carbon skeletons of mesaconic acid (**2**) and citraconic acid (**3**), which are isomeric to those of the itaconates **1**. Neither **2** nor **3** were ever observed in the products or mixtures during any of the experiments described here. This rules out the formation of **3** as it would accumulate in the reaction mixture owing to its extremely slow rate of reduction. The reduction of **2** with DCOOD/ $\text{NEt}_3$  results in the formation of only three significant isotopomers after full conversion. The two monodeuterated species d<sub>1</sub>(1) and d<sub>1</sub>(2) sum to 20%, reflecting mainly the incomplete deuteriation of the protic positions of DCOOD and **2**. No significant amounts of products with more than two deuteriums are detected. The isotopomer d<sub>2</sub>(1,2)-**5**, which is expected from vicinal addition at the internal double bond, is formed with a high selectivity of approximately 80% throughout the course of the reaction. The same isotopomer is also the major product from the transfer deuteriation of **3**, albeit extreme scrambling and a very broad distribution of isotopomers is observed during the sluggish reduction of this compound. Most notably, the d<sub>2</sub>(1,2) isotopomer of **5** is not formed in appreciable amounts from any of the itaconates **1a–d** (Fig. 5). This demonstrates unambiguously that double bond isomerisation to form the carbon skeletons of either **2** or **3** does not contribute to product formation during transfer hydrogenation of **1a–d**.

Most notably, the change of the deuterium addition mode upon esterification is unique for the transfer hydrogenation method-

ology and is not observed during deuteration of itaconic acid derivatives **1a** and **1b**. As seen from Fig. 6, almost identical distributions of isotopomers are obtained with both substrates from deuteration with D<sub>2</sub>.<sup>13</sup> It is also interesting to note that *polydeuteration is much more pronounced under hydrogenation conditions* than in transfer hydrogenation (compare Fig. 6 and Fig. 4). The total amount of deuterium incorporation corresponds to 4.63 and 2.85 equivalents for **1a** and **1b**, respectively. Nevertheless, only traces of deuterated starting materials are observed during the intermediate stages of the deuteration experiments, indicating that scrambling and polydeuteration occurs almost exclusively while the substrate is bound to the rhodium center.

The most significant and obvious difference between the hydrogen transfer from H<sub>2</sub> and HCOOH is the intrinsic dis-

tingtion of a hydridic hydrogen in the formyl position and a protic hydrogen at the carboxylic position. Experiments using HCOOH and DCOOH were carried out to examine a possible preference for the incorporation from these to positions during transfer hydrogenation. Earlier experiments with phenylitaconic acid as the substrate have shown that there is a rapid scrambling of the isotopes at the formyl and the protic position during transfer hydrogenation with monodeuterated formic acids.<sup>5,14,15</sup> Fortunately, the much faster reduction rate of the unsubstituted itaconates **1a** and **1b** prevented this scrambling from being complete in the present case, revealing a clear preference for the hydrogen isotope from the formyl position to be incorporated into the C-3 position. The d<sub>1</sub>(3) isotopomer of **5** was formed from DCOOH/NEt<sub>3</sub> with 67% and 72% selectivity for **1a** and **1b**, respectively. Most significantly, the experiments

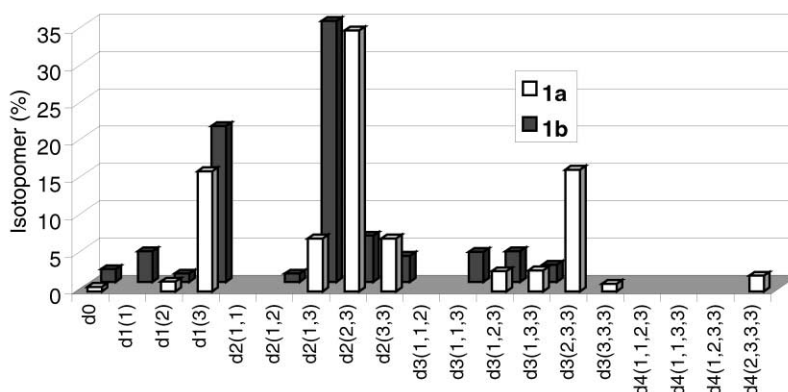


Fig. 4 Isotopomer distribution of **5** obtained by transfer deuteration of **1a** and **1b** with DCOOD after full conversion.

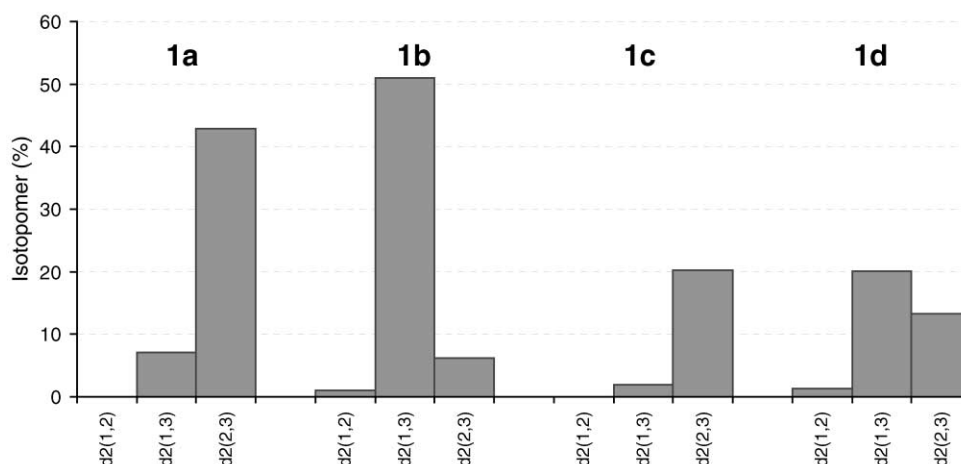


Fig. 5 Distribution of the double deuterated isotopomers d<sub>2</sub> of **5** obtained by transfer deuteration of **1a–1d** with DCOOD after full conversion.

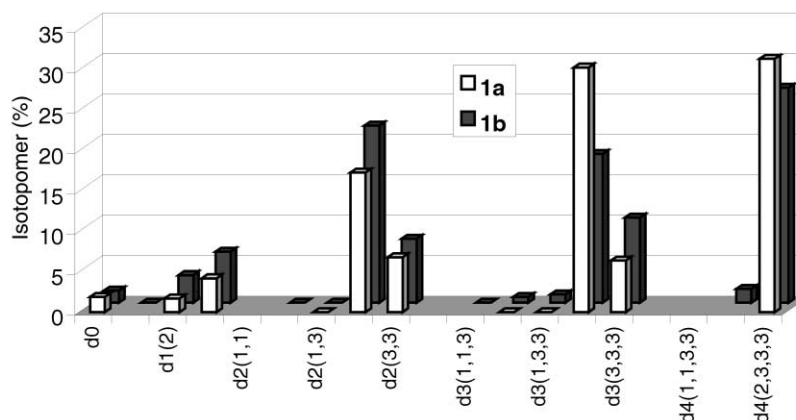


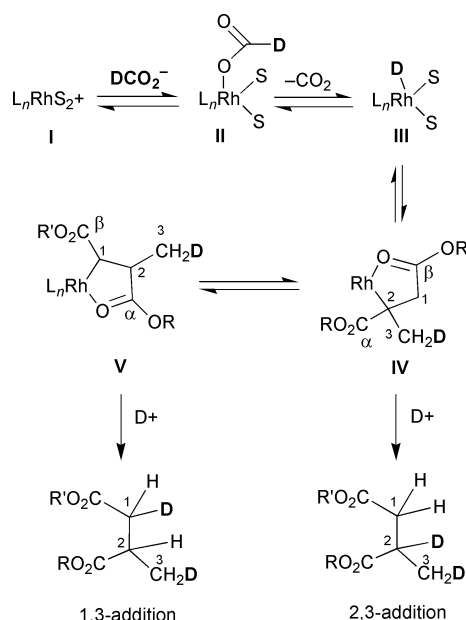
Fig. 6 Isotopomer distribution of **5** obtained by deuteration of **1a** and **1b** using D<sub>2</sub> after full conversion.



using HCOOD revealed that the change of the 2,3 vs. the 1,3 addition mode is directly associated with the delivery of the protic hydrogen: the relative ratio of the two monodeuterated isotopomers  $d_1(1)\text{-5}$  and  $d_1(2)\text{-5}$  was 1 : 5 when **1a** was reduced with HCOOD/ $\text{NEt}_3$ , whereas it changed to 7 : 1 for **1b**.

## Mechanistic conclusion

The enantioselective reduction of C=C double bonds in unsaturated carboxylic acids and esters can be achieved using either molecular hydrogen (hydrogenation) or a mixture of formic acid and triethylamine (transfer hydrogenation). For a wide range of substrates and catalysts, there are striking similarities in reactivity and stereoselectivity for both techniques when chiral rhodium phosphine complexes are used as catalysts.<sup>3,16</sup> Together with the results of a previous mechanistic study,<sup>5</sup> this strongly suggests that the major reaction paths and the key intermediates during the hydrogen addition step are largely similar in both processes. Scheme 2 depicts a mechanistic



**Scheme 2** Mechanistic rationale for the change from vicinal 2,3-addition to 1,3-addition during transfer deuteration of itaconates **1a–d** ( $\text{R}, \text{R}' = \text{D}, \text{Me}, \text{S}_2 = \text{solvent or substrate}$ ).

scenario for the transfer deuteration of itaconates **1a–d** that allows the rationalisation of all the findings of the present study on the basis of such a common catalytic pathway.

The transfer hydrogenation of **1a** using rhodium bis(phosphine) catalysts exhibits a primary kinetic isotope effect  $k_{\text{H}}/k_{\text{D}} = 3.2$  when the formyl hydrogen is replaced with deuterium.<sup>5</sup> This is in excellent agreement with other isotopic effects for the decarboxylation of formic acid or formates to give  $\text{CO}_2$  and metal hydrides. The scrambling of the isotopes of the formyl position and the protic position during hydrogen transfer is also best rationalised on the basis of the formation of rhodium hydride intermediates. Although other hydrogen transfer mechanisms may be possible with heterogeneous catalysts,<sup>8</sup> it seems therefore most appropriate to identify the first step of the catalytic cycle of the homogeneously rhodium phosphine catalysed transfer hydrogenation with the decarboxylation of coordinated formate to yield a rhodium hydride intermediate such as **III**.

Just like **III**, all intermediates in Scheme 2 are drawn as neutral species for simplicity. Obviously, the rhodium hydride complexes can be subject to protonation under transfer hydrogenation conditions. Similarly, they will exist in part as cationic dihydrides under hydrogenation conditions. The exchange of rhodium bound hydrides with protons in solution can be

expected to be the major pathway for isotope scrambling from the formyl and protic position and for the incorporation of more than one deuterium into substrates and product. In order to account for the formation of polydeuterated compounds, the insertion of the olefinic bond into the  $\text{Rh-H}$  bond to form the chelated  $\sigma$ -alkyl intermediate **IV** must be reversible.<sup>6,13</sup> This must hold for both the hydrogenation and transfer hydrogenation sequence. The insertion is of course equivalent to H migration from rhodium to C-3, and the reverse  $\beta$ -hydrogen abstraction from the same position readily explains why C-3 is the major position for polydeuteration. The larger amount of polydeuteration with molecular deuterium reflects at least partly the much higher D/H-ratio under 20 bar of  $\text{D}_2$  as compared to transfer deuteration with five equivalents of DCOOD.

Irreversible liberation of the product from the rhodium center through protolytic cleavage of the metal alkyl bond in **IV** leads finally to the vicinal 2,3-addition product in transfer deuteration. In hydrogenation, the  $\text{Rh-C}$  bond can be cleaved by direct protolysis,<sup>17</sup> via a classical oxidative addition/reductive elimination pathway, or via base-assisted  $\sigma$ -bond metathesis reaction with  $\text{H}_2$ .<sup>18</sup> The relative amount of polydeuteration/scrambling to vicinal 2,3-addition is determined by the relative ratios of the reversible insertion and the irreversible product formation step. It is important to note that this is not necessarily related to the amount of detectable deuterated starting material, as this requires the additional step of de-coordination of the substrate from the metal center in **III** ( $\text{S}_2 = \text{substrate}$ ). This complexation/de-complexation equilibrium depends strongly on the substrate, but is also largely influenced by reaction conditions such as solvent, pH, etc. Indeed, a qualitative correlation of the amount of scrambling in the product **5** and the deuterium incorporation in the substrates **1–3** is observed within the series of transfer deuteration experiments, but not for the comparison of transfer hydrogenation and hydrogenation.

An important contribution to the stability of **IV** results from the formation of a five-membered chelating ring with coordination of C-3 and the carboxyl group in the  $\beta$ -position (allylic position) of the substrate. It is important to note that an isomeric  $\sigma$ -alkyl complex **V** exists that contains a similar five-membered chelating ring with an almost identical coordination mode. In this structure, C-1 is bound directly to the metal center and stabilisation occurs through the  $\alpha$ -carboxyl group. Protolytic cleavage of the  $\text{Rh-C}$  bond from intermediate **V** corresponds to an overall 1,3-addition of two deuterium (or hydrogen) atoms.

A possible pathway for the interconversion of **IV** and **V** must involve the breaking of the  $\text{sp}^3$ -hybridised C–H bond at C-1. This process is equivalent to the  $\beta$ -hydride elimination that leads to the polydeuteration at C-3. Although the latter is likely to be preferred for statistical and stereo-electronic reasons, an isomerisation pathway involving the scission of the C–H bond at C-1 is clearly a viable process. The ratio of vicinal to 1,3-addition depends in this scenario on the relative reaction rates of  $\text{Rh-C}$  cleavage and interconversion as well as on the stability difference between **IV** and **V**. Under the conditions of hydrogenation, the product liberating step occurs always from intermediate **IV**, regardless of the substitution pattern of itaconates **1a–d**. Under transfer hydrogenation conditions, intermediate **V** becomes kinetically accessible for the compounds **1b** and **1d** bearing an ester group in the  $\beta$ -position. The stability of the five membered ring in **IV** will be drastically reduced by esterification of the carboxylic group in the  $\beta$ -position, thus favouring both the rate of isomerisation and the relative stability of **V**. The additional shift towards 1,3-addition by esterification of both carboxylic groups is less obvious, but might be related to possible assistance of the free ester group in the protolysis of the  $\text{Rh-C}$  bond.

In summary, the network of isomerisation and product forming steps shown in Scheme 2 provides a plausible explanation

for the key experimental facts of the present detailed study of the hydrogen addition step in hydrogenation and transfer hydrogenation. It is based on the assumption that the mechanistic pathways of both reactions involve closely related intermediates.<sup>19</sup> The results presented here provide therefore important insight not only into the transfer hydrogenation pathway, but also into asymmetric hydrogenation in general. Recently, the competition of 2,3- vs. 1,3-addition was used as a mechanistic probe to assess the hydrogen addition pathway during hydrogenation in supercritical CO<sub>2</sub> as solvent.<sup>20</sup> The reversibility of the olefin insertion and the potential influence of the isomerisation on the stereoselectivity of the overall reduction in both hydrogenation and transfer hydrogenation is another intriguing aspect that emerges from this study.

## Experimental

All catalytic reactions and manipulations of air-sensitive materials were carried out under argon atmosphere. Solvents were purified, dried and degassed according to standard procedures and stored under argon. The deuterium content in the protic position of the formic acid isotopomers was found to decrease upon prolonged storage in standard glassware even under an argon atmosphere. Silylation of the glassware by treatment with Me<sub>3</sub>SiCl and subsequent flame drying prior to use ameliorated these problems to a certain extent. The following commercially available compounds were used: (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-(diphenylphosphinomethyl)pyrrolidine (bppm) (>98%, Fluka), citraconic acid **3** (98%, Aldrich), D<sub>2</sub> (MG: 2.7), dimethylitaconate **1b** (>97%, Fluka), d<sub>2</sub>-formic acid (CD: D > 99%, OD: D = 90%, Aldrich), d<sub>1</sub>-formic acid (DCO<sub>2</sub>H, D = 98%, CIL), d<sub>1</sub>-formic acid (HCO<sub>2</sub>D, D = 98%, CIL), itaconic acid **1a** (>99%, Fluka), mesaconic acid **2** (99%, Aldrich).  $\alpha$ -Methylitaconate **1c** and  $\beta$ -methylitaconate **1d** were synthesised according to literature procedures.<sup>21,22</sup> NMR spectra were recorded on Bruker AMX-300 for routine analysis and on a DMX600 spectrometer for the analysis of isotopomeric mixtures. Chemical shifts  $\delta$  are reported in ppm relative to external H<sub>3</sub>PO<sub>4</sub> for <sup>31</sup>P and to SiMe<sub>4</sub> for <sup>1</sup>H and <sup>13</sup>C, using the solvent resonance as internal standard if possible. The enantiomeric excess was determined by HPLC (instrument: MDLC-1; stationary. phase: 250 mm Chiralcel OD-H, 4.6 mm i. d.; mobile phase: n-heptane, 2-propanol, formic acid = 90 : 10 : 1; *T/p/F*: 308 K/2.5 Mpa/0.5 ml min<sup>-1</sup>; detector: RI, E = 32) or GC (HP 5890/531; column: 30 m G-TA gamma CD; G/228; temperature: 180/60 0.8/min 87 5/min 180/300; gas: 0.9 bar H<sub>2</sub>). Mass spectroscopic analysis of the deuterium content was carried out on a Finnigan MAT95 in DE mode using CA ionization (gas: NH<sub>3</sub>).

### Synthesis of [(bppm)Rh(hfacac)] **4**<sup>23</sup>

673 mg (1.62 mmol) [(cod)Rh(hfacac)] and 891 mg (1.61 mmol) bppm were each dissolved in 5 ml THF. Both solutions were cooled to -78 °C and the bppm solution was slowly added to the solution of the rhodium complex *via* a cannula. While warming to room temperature over night the orange color of the solution changed to brown. The solvent was removed *in vacuo* and the glassy residue dried at 50 °C under high vacuum for four days to give 1.16 g (1.34 mmol, 83%) of **4** as a brown solid. <sup>1</sup>H-NMR (300.1 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  1.40 (s, 9H; (CH<sub>3</sub>)<sub>3</sub>C), 2.26–3.76 (m, 6H; CH<sub>2</sub>), 4.57 (m, 1H; NCH), 4.67 (m, 1H, PCH), 5.95 (s, 1H, CF<sub>3</sub>CCH), 7.70–8.23 (m, 20H; arom. CH). <sup>13</sup>C{<sup>1</sup>H}-NMR (50.3 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  28.64 (s, (CH<sub>3</sub>)<sub>3</sub>C), 34.5 (s, NCHCH<sub>2</sub>), 37.9 (s, NCH<sub>2</sub>), 38.3 (s, NCH), 49.6 (d, <sup>1</sup>J<sub>CP</sub> = 62 Hz, PCH<sub>2</sub>), 55.0 (d, under CD<sub>2</sub>Cl<sub>2</sub>, PCH), 79.9 (s, (CH<sub>3</sub>)<sub>3</sub>C), 90.8 (s, CF<sub>3</sub>CCH), 127.4–135.6 (m, arom. CH), 157.7 (s, NCO), 171.6 (q, <sup>2</sup>J<sub>CF</sub> = 33 Hz, CF<sub>3</sub>C), CF<sub>3</sub> not detected. <sup>31</sup>P{<sup>1</sup>H}-NMR (121.5 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  39.5 (d, d, P1, <sup>1</sup>J<sub>RhP1</sub> = 185 Hz, <sup>2</sup>J<sub>P1P2</sub> = <sup>2</sup>J<sub>P1P2'</sub> = 62 Hz), 65.8 (d, d, P2, <sup>1</sup>J<sub>RhP2</sub> = 191 Hz, <sup>2</sup>J<sub>P1P2</sub> = 62 Hz), 66.1 (d, d, P2', <sup>1</sup>J<sub>RhP2'</sub> = 193 Hz, <sup>2</sup>J<sub>P1P2'</sub> = 62 Hz). MS: *m/z* = 863

(M<sup>+</sup>), 763 (M<sup>+</sup> – C<sub>5</sub>O<sub>2</sub>H<sub>8</sub>) high resolution MS: found: min. 863.117, max. 863.127; calc: 863.122.

### General procedure for the H/D exchange of the protic positions in substrates **1a**, **1c** and **1d**

3 g of substrate were dissolved in 10 ml d<sub>1</sub>-methanol, the solution stirred for 10 min and the solvent then removed *in vacuo*. The procedure was repeated three times to achieve an H/D-exchange of  $\geq 90\%$

### General procedure for transfer deuteration

The following procedure is representative for a reaction with monitoring of conversion. Smaller scale reactions (1.5 mmol substrate) were carried out in cases where only the final distribution was analysed. The appropriately O-deuterated substrate **1–3** (22.5 mmol) and [(bppm)Rh(hfacac)] **4** (0.336 mmol, 1.5 mol% Rh) were dissolved in 15 ml d<sub>6</sub>-DMSO and triethylamine (45.0 mmol) followed by the desired isotopomer of formic acid (112.5 mmol) were added. The reaction was stirred at 30 °C and up to eight samples of 1.6 mL were withdrawn over a period of 8 h and quenched with 10 ml 5% HCl. For substrates **1a**, **2**, and **3** the aqueous solution was extracted five times with a total of approximately 40 ml diethyl ether. The combined organic phases were washed with 5 ml 10% HCl, dried over MgSO<sub>4</sub>, and evaporated to leave **5** as a white solid in >85% yield. For substrates **1b**, **1c** and **1d**, the aqueous solution obtained after quenching was rendered basic by addition of sodium hydroxide and stirred for two weeks at room temperature to ensure complete hydrolysis of the ester groups.<sup>24</sup> Compound **5** was isolated from these solutions after acidification as described for the other substrates.

### General procedure for deuteration reaction

A stainless steel pressure vessel was charged with substrate **1a** or **1b** (2.0 mmol), catalyst **4** (30.0  $\mu$ mol, 1.5 mol% Rh), methanol-d<sub>1</sub> (3 ml) and NEt<sub>3</sub> (4.0 mmol). The solution was pressurised with D<sub>2</sub> (20 bar) at 30 °C and stirred for 2–20 h. The reactor was cooled to room temperature, vented, and the solution quenched and worked up as described above.

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