# Diastereoselective homogeneous hydrogenations without direction by substituents

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**The Rh complex catalysed hydrogenation of an α-(hydroxyalkyl)-*N*-methoxyacrylamide and the Ru complex catalysed hydrogenation of an α-(fluoroalkyl)acrylate both proceed with ⩾90% selectivity to give the *syn*-isomer.**

In the directed hydrogenation of alkenes, coordination of a polar functionality to the catalyst leads to enhanced diastereoselectivity in the reduced product. Stereochemical control may arise by complexation of an alcohol, amide, ester or sulfoxide group.[1] The vast majority of substituent-directed diastereoselective reactions follow similar principles.[2] For the common case of an acyclic alkene with an allylic stereogenic centre, a simple model based on the constrained conformation of the complexed alkene **1a** suffices [Fig. 1(*a*)]. This model, for which the torsional angle H–C—**C**=C is 180°, is calculated to be 5 kJ mol$^{-1}$ higher in enthalpy than the rotamer (H–C–C=C = 0°).[3] In the absence of complexation by a polar functional group, diastereoselectivity will be controlled by steric factors. An alternative mode of complexation, shown in Fig. 1(*b*), was required to test this prediction. In practice this was realised by synthesis of the corresponding *N*-methyl-*N*-methoxyamide according to Nahm and Weinreb.[4] In a related unsaturated amide, the preferred conformation of the amide side-chain has N–O *anti* to C=O, thus permitting the desired complexation.[5]

The synthetic route[6] from compound **1a** provides access to both alcohol **2a** and its Bu$^t$Me$_2$Si ether **2b**. Hydrogenation of **2a** was carried out with the Rh complex **3** as previously described[1] in either MeOH or ClCH$_2$CH$_2$Cl and gave a near-equal mixture of *syn*- and *anti*-diastereomers **4a** and **5a** (Scheme 1). This is in contrast to the results observed for hydrogenation of all other α-(hydroxyalkyl)acrylates under related conditions, where the *anti*-isomer predominates. The contrasting result obtained here suggests that there are two competing pathways in hydrogenation which operate in opposite senses, one involving N–O participation, the other O–H participation. Support for this proposal stems from hydrogenation of silyl ether **2b**, which gives 92% of the corresponding *syn*-product **4b**. In separate experiments it was verified that the α-silyloxyalkyl acrylates **1b**–**d** gave mixtures of both *syn*-**6b**–**d** and *anti*-**7b**–**d** on hydrogenation, confirming that the reduced basicity and increased bulk of the silyl ethers attenuates their complexation to rhodium relative to OH. Both the selectivity and the rate depend on the size of the siloxy group in the manner expected if the stereoselectivity is controlled by the relative steric bulk of the substituents at the α-stereogenic centre.

The hydrogenation of compound **2b** can be interpreted in accord with the model in Fig. 1(*b*). It is assumed that the side-chain can adopt its minimum energy conformation with α-C–H eclipsing C=C, and there are then two diastereomeric sets of intermediates which lead on to the diastereomeric products **4b** and **5b**. The proportions will be determined primarily by the perceived bulk of the two non-hydrogen substituents at the stereogenic centre. As would be expected on the basis of relative *A* values (1.79 for Et *vs.* 0.74 for OSiMe$_3$),[7] the ethyl group prefers to be remote from the metal complex (Scheme 2), leading to the observed preference for *syn* hydrogenation.

A further example of *syn*-directed hydrogenation was discovered adventitiously, in a search for fluorine participation in catalysis. There are precedents for C–F activation by several transition metal complexes, but none which demand C–F

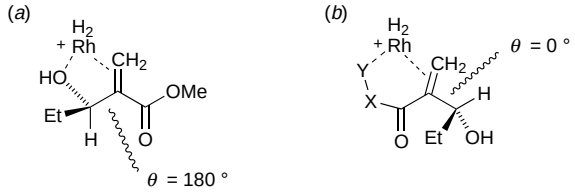
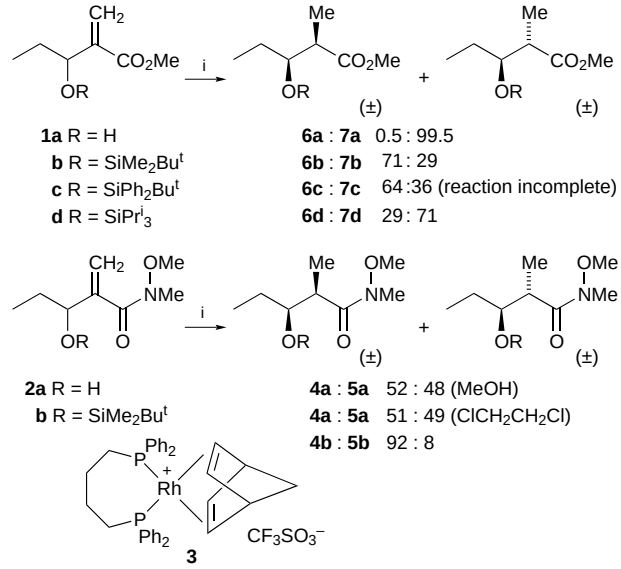
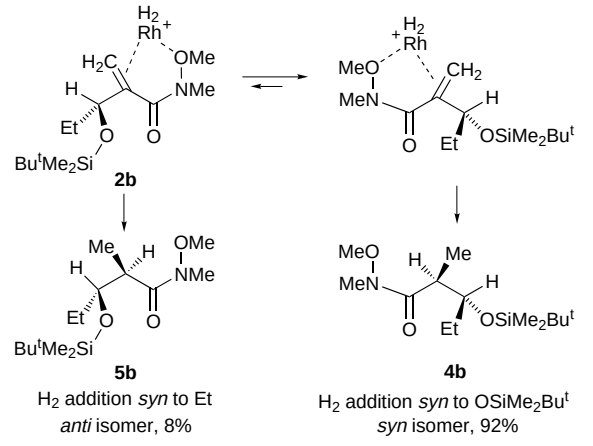


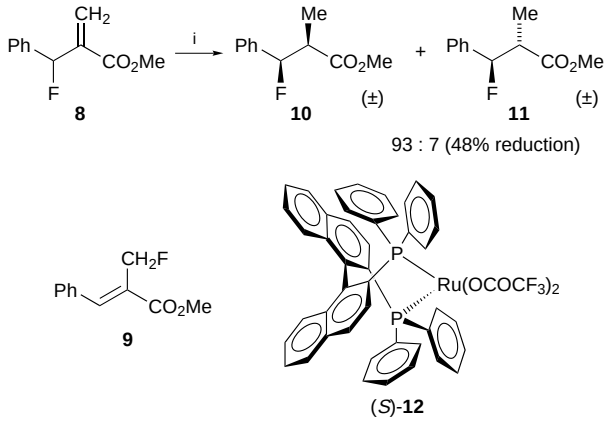

**Fig. 1** Alternative reactant chelates in hydrogenation




**Scheme 1** *Reagents and conditions*: i, **3** (1–4 mol%), $H_2$ (1.5 atm)




**Scheme 2**




**Scheme 3** *Reagents and conditions*: i, **12** (4 mol%), $H_2$ (3 atm), $ClH_2CCH_2Cl$, 40 h

participation to augment the selectivity of a catalytic process. Some examples of C–F···M interactions in organometallic crystal structures, and indeed the only two derived from late transition metals, involve Ru;[8] the Ru···F bond lengths are 2.366 and 2.489 Å, much longer than other bonds from Ru to second-row elements. These observations guided our approach.

The phenyl analogue of compound **1a** reacted with diethylaminosulfur trifluoride (DAST)[9] to produce the corresponding allyl fluoride **8** with *ca.* 5–10% competing allylic isomerisation to the primary fluoride (*Z*)-**9** (Scheme 3). In initial studies it was found that hydrogenation of compound **8** with Crabtree's catalyst[10] (25 °C, 2 atm, $CH_2Cl_2$) occurred cleanly with low diastereoselectivity. The diastereomers *syn*-**10** and *anti*-**11** were separately identified from independent synthesis of the *anti*-isomer **11** by DAST fluorodehydroxylation of its *anti*- alcohol precursor, which occurred with 75% retention of configuration,[11] verified by spectral comparison with literature assignments which are based on an X-ray analysis.[12] When hydrogenation of the allyl fluoride **8** was carried out with (*S*)- or *rac*-BINAP–Ru complexes **12**, the *syn*-diastereomer **10** was formed as 90% of the reduced product, but in a slow reaction sustained for up to 20 turnovers. The ee of recovered allyl fluoride was low when enantiomerically pure catalyst was employed. Since Ru and Rh give parallel stereoselectivity in directed hydrogenation,[13] this result cannot be the consequence of a fluorine-directed hydrogenation but rather reflects the preferred coordination of the reactant in the C=C–C–H = 0° conformation,[14] and the relative steric size of fluoro and phenyl substituents. The failure to observe clear-cut evidence for C–F participation at a potentially fluorophilic metal site has origins related to the reluctance of C–F to act as an hydrogen-bond acceptor.[15]

It has been a general rule that diastereoselectivity in organometallic catalysis requires substituent participation through complexation.[1,2] Although modest specificity has been obtained here, it is useful to realise that significant stereocontrol in homogeneous hydrogenation can arise from the intrinsic conformational preferences of the reactant.

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## Footnote and References

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