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An Unexpected Directing Effect in the Asymmetric Transfer Hydrogenation of α,α-Disubstituted Ketones

Rina Soni, John-Michael Collinson, Guy C. Clarkson, and Martin Wills*

Department of Chemistry, The University of Warwick, Coventry CV4 7AL, U.K.

m.wills@warwick.ac.uk

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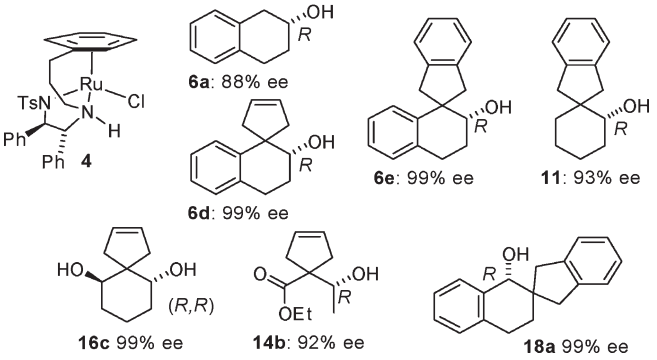
ABSTRACT

Enantioselectivities of asymmetric transfer hydrogenation of α,α-disubstituted ketones using catalyst **4**.



α,α-Disubstituted ketones containing an aromatic ring or alkene are reduced in high enantiomeric excess using an asymmetric transfer hydrogenation catalyst. The sense of reduction indicates that the unsaturated region of the ketone adopts a position adjacent to the Ru-bound η^6-arene ring in the reduction transition state.

Asymmetric transfer hydrogenation (ATH) of ketones represents a valuable method for the formation of enantiomerically pure alcohols.[1−4] The catalyst system **1** based on Ru(II) η^6-benzene complexes of the readily available diamine ligand TsDPEN has proven to be particularly versatile.[2] The mechanism of action of these catalysts is believed to involve the formation of an enantiomerically pure precatalyst **1** which is then converted to hydride **2** via unsaturated complex **3**.[3] Hydride **2** transfers two hydrogen atoms to the substrate via the cyclic six-membered transition state shown in Figure 1.[3]

The enantioselectivity depends on an edge-face CH/π interaction which stabilizes the electron-rich (usually aromatic) ring of a substrate in a specific orientation relative to the Ru η^6-arene. Excellent ee's are thus observed for acetophenone derivatives. For substrates not fitting this model, ee's are frequently lower and unpredictable, although there are examples of alternative ATH catalysts which have a broad substrate range.[5]

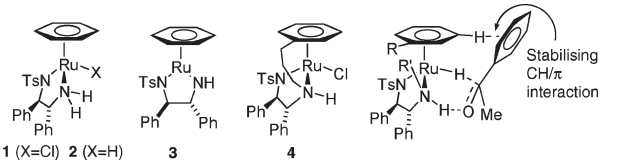


Figure 1. Complexes **1**−**4** and involvement of *N*-H and CH/π interaction in ATH transition state using hydride derived from **1** (R = R′ = H) and **4** (R−R′ = $(CH_2)_3$).

(1) (a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406. (b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *36*, 226–236. (c) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300–1308. (d) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237. (e) Hashiguchi, S.; Noyori, R. *Acc. Chem. Res.* **1997**, *30*, 97–102. (f) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750–1770.

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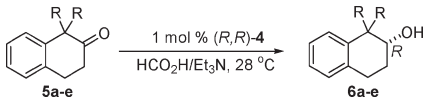
We are interested in extending the range of substrates to which ATH catalysts, notably those derived from Ru(II)/TsDPEN combinations, can be successfully applied in the formic acid/triethylamine (FA/TEA) reduction system.[6] One challenging group of ketones is the one which contains an adjacent quaternary center.[2f,g,7] Some notable successes have been reported, for example, the use of a Ru(II)/amino alcohol catalyst in the ATH of cyclic ketones containing α,α-dimethyl substituents,[2f] and Ru(II)/oxazoline catalysts capable of ATH of both pinacolone and 2,2-dimethylcyclohexanone in ee's of >99%.[2g] In contrast, Ru(II)/TsDPEN complexes, and their close analogues, appear to be less efficient in the reduction of such substrates. Tethered catalyst **4**[6] has proved to benefit from an increased level of activity and, therefore, seemed appropriate for use in tests on hindered substrates. The reduction of pinacolone gave, in our hands, a product of only 10% ee (*S*, 56% isolated yield) after 24 h at 30 °C using 1 mol % of catalyst (*R,R*)-**4**.[6a] This is in contrast to the reduction of PhCO^{t}Bu which with 0.5 mol % of (*R,R*)-**4** is reduced in 77% ee (*R*, 95% conversion) after 32 h.[6b] In the latter case, the sense of reduction is directed by the established CH/π interaction. Given the challenge presented by sterically hindered substrates, and the potential for the generation of novel homochiral alcohols, we undertook an investigation into the ATH of a range of α,α-disubstituted ketones.

Scheme 1. Reduction of β-Tetralone Derivatives



We prepared ketones **5a**−**e**, which represent a series in which steric bulk adjacent to the ketone is systematically varied. The reduction of β-tetralone is reported to proceed in 82% ee (*R*) in FA/TEA using catalyst (*R,R*)-**1**,[2b] although methoxy-substituted β-tetralones have been reported to be reduced with higher enantioselectivity.[2e] The product is of a configuration which indicates that a CH/π edge/face interaction determines the enantiocontrol of the reaction (Figure 3a).[2b] Similarly, β-tetralone **5a** was reduced in 88% ee (*R*) using catalyst (*R,R*)-**4** (Scheme 1, Figure 2). In previous work in our group, we have demonstrated that α-substituted β-tetralones are also reduced in high ee under the control of the key CH/π edge/face interaction (Figure 3a).[8] By placing large substituents between the aryl ring of the substrate and its ketone, we hoped that the effect would be to disrupt this interaction and provide a means for correlation of the steric bulk with the enantioselectivity of reduction.

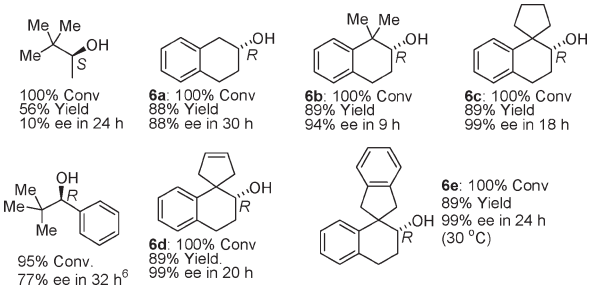


Figure 2. Alcohols formed by reduction of hindered β-tetralones using catalyst (*R,R*)-**4**.

In the event, the results were surprising. All of compounds **5b**−**e** were reduced in high enantiomeric excess, higher than for β-tetralone **5a** and with the same absolute configuration (Scheme 1, Figure 2). This indicates that, in this series, despite their high steric bulk, the substituents *reinforce* the enantiocontrol of the reaction by the catalyst. Indeed, as the group gets larger, the ee increases and remains high even for **5c** possessing a saturated spiro cycle. For substrates **5d** and **5e**, an additional CH/π effect may

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also be operating between the Ru(II) η^6-arene and the alkene or second aromatic ring respectively (Figure 3b). The reason for the increased enantioselectivity for the reduction of **5b** and **5c** is less clear, however there has been speculation that hydrophobic (dispersion) effects can contribute to the control of ATH reductions.[3f]

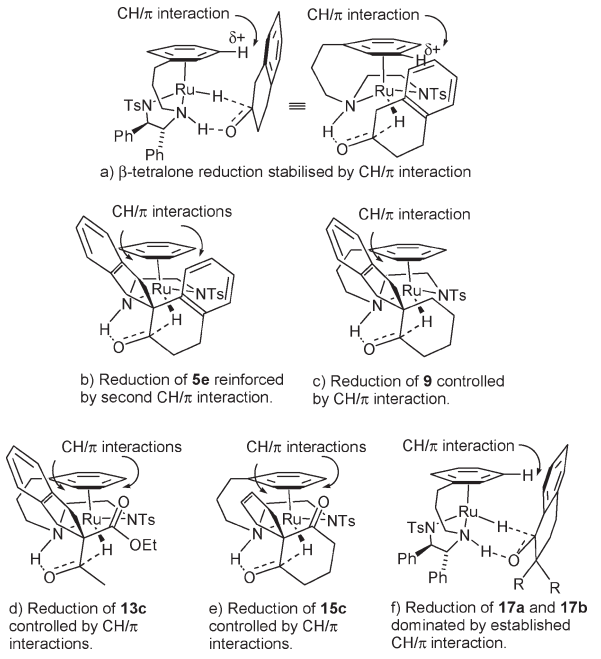


Figure 3. Proposed stabilizing interactions in transition states of reduction of hindered ketones and tetralones with (*R,R*)-**4**. For clarity, the C−H bond on the arene is omitted in b−f.

In the case of **6e**, an X-ray crystallographic structure of the (1*S*)-(+)-10-camphorsulfonic acid derivative **7** was obtained (Figure 4a) in order to establish the absolute configuration.[9] For **6d** the Mosher derivative was prepared and the configuration was assigned by reference to shifts in the ^{1}H NMR spectrum (see the Supporting Information).[10] The reduction of the enantiomerically enriched sample of compound **6d** gave **6c** with identical configuration to that obtained by direct reduction of **5c**, confirming the same sense of reduction of both the saturated and unsaturated ketones **5c** and **5d** respectively. The configuration of **6b** was also assigned using the Mosher derivative method (see the Supporting Information).

The "spiro" CH/π effect can alone direct enantioselective reductions, as illustrated by the contrasting results obtained for reduction of compounds **8** and **9**. Reduction of **8** under the same conditions as shown in Scheme 1

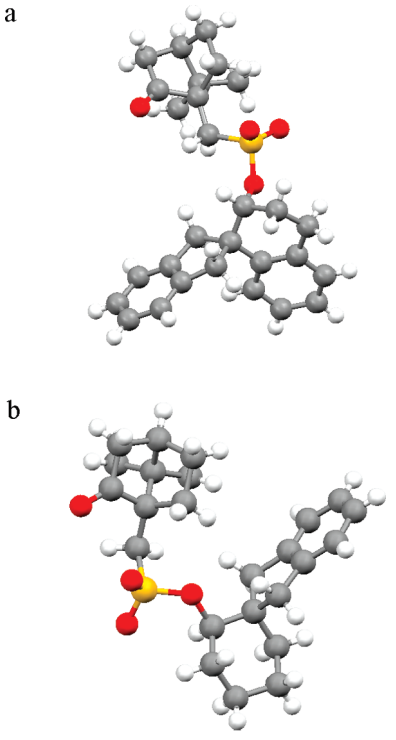


Figure 4. X-ray crystallographic structures of camphorsulfonic acid derivatives (a) (*R*)-**7**[9] and (b) (*R*)-**12**.[11]

resulted in formation of **10** in 71% ee (*S* configuration assigned by analogy with pinacolone reduction), whereas **9** gave **11** in 93% ee (1 mol % catalyst, 28 °C). The absolute configuration of **11** was determined by an X-ray crystallographic study of the (1*S*)-(+)-10-camphorsulfonic acid derivative **12** (Figure 4b).[11] The sense of reduction of **9** must arise through a transition state in which the quaternary center is orientated in the position proximal to the Ru(II) η^6-arene (Figure 3c). In the comparison between **8** and **9**, the aromatic ring of the substrate clearly results in an improvement of the ee, over that of a similar substrate lacking this group.

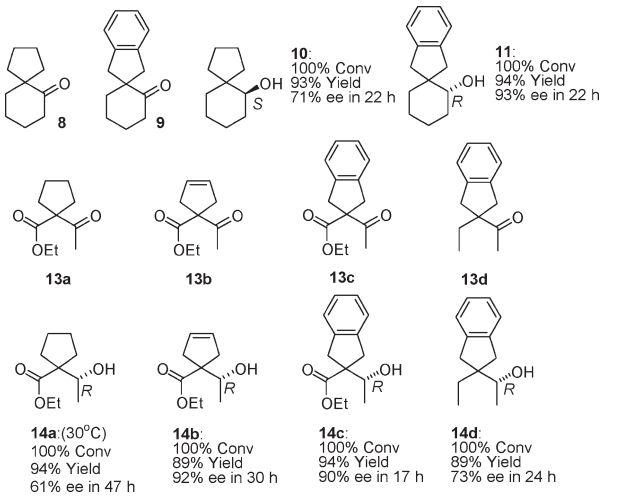
The speculated importance of an unsaturated function in directing the ATH of α,α-disubstituted ketones was further substantiated by a study of the asymmetric transfer hydrogenation of the acyclic ketones **13a**−**c** using the tethered catalyst (*R,R*)-**4**. The enantiomeric excesses of the products **14a**−**c** were 61%, 92%, and 90% respectively. The configurations of the chiral centers in **14a** and **14c** were assigned by ^{1}H NMR analysis of the Mosher derivatives (see the Supporting Information).[10] The configuration of **14b** was assigned by hydrogenation to give **14a** of identical configuration to that generated using the same enantiomer of catalyst.

(9) X-ray data for (*R*)-**7** (CCDC no. 817154), $C_{28}H_{32}O_4S$, M = 464.60, orthorhombic, space group $P2(1)2(1)2(1)$, a = 7.43712(9) Å, b = 8.62914(9) Å, c = 36.4793(4) Å, α = 90°, β = 90°, γ = 90°, U = 2341.09(5) Å^3, T = 100(2) K, λ = 1.54184 Å, Z = 4, D(calc) = 1.318 Mg/m^3, F(000) = 992. μ(Mo Kα) = 1.491 mm^{-1}. Crystal character: colorless block. Crystal dimensions 0.20 × 0.16 × 0.08 mm.

(10) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

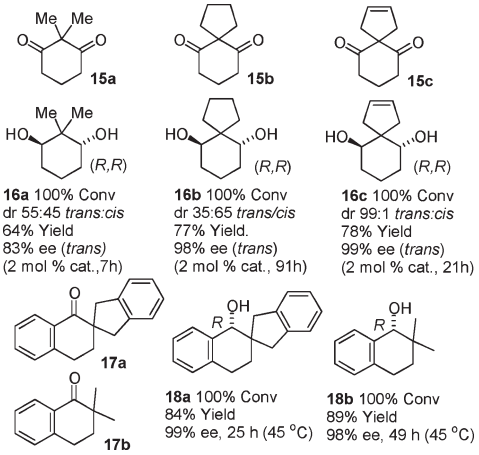
(11) X-ray data for (*R*)-**12** (CCDC no. 817152), $C_{24}H_{32}O_4S$, M = 416.56, monoclinic, space group $P2(1)$, a = 9.9752(2) Å, b = 10.52392(16) Å, c = 11.2107(2) Å, α = 90°, β = 116.107(3)°, γ = 90°, U = 1056.81(3) Å^3, T = 100(2) K, λ = 0.71073 Å, Z = 2, D(calc) = 1.309 Mg/m^3, F(000) = 448. μ(Mo Kα) = 0.181 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.50 × 0.30 × 0.30 mm.

These results again indicate that an element of unsaturation in the cyclic part of the substrate is beneficial for high enantioselectivity in the ATH reaction. However, the ATH of substrate **13d** to **14d** of just 73% ee also indicates that the ester has an additional directing effect—possibly a further CH/π interaction with the Ru(II) η^6-arene—and that both are required for high ee's to be obtained with these substrates (Figure 3d).



The effect can also be extended to the enantioselective reduction of 1,3-diketones.[12] Diketone **15c** was reduced in 99% ee with an almost complete selectivity for the *trans* product **16c**, the configuration of which was assigned using the Mosher ester method.[10] In contrast, the saturated derivative **15b** was reduced in low diastereoselectivity, with an unexpected preference for the *cis* isomer but still with a high enantioselectivity for the chiral *trans* product **16b**. 2,2-Dimethylcyclohexa-1,3-dione **15a** was reduced in only 55:45 dr (*trans* isomer of 83% ee). These results again underline the capacity of a unsaturated functionality, together with an additional carbonyl group to direct highly enantioselective reductions of ketones which do not contain directly adjacent aromatic rings (Figure 3e). In the case of **15c**, this CH/π interaction is sufficient to also direct the second ketone reduction. In the case of **15b**, it cannot, and the *cis* product is predominantly formed, possibly via a noncatalyst-directed diastereoselective reduction.

Finally, we wished to establish whether this directing effect was more or less effective than the well-established CH/π interaction (Figure 1). This required the preparation of **17a** and **17b**, which was achieved in one step from α-tetralone by alkylation with 1,2-di(bromomethyl)benzene and methyl iodide respectively. Reduction with catalyst (*R,R*)-**4** proceeded in quantitative yield to give products **18a** (99%ee) and **18b** (98% ee) respectively. Alcohol **18b** is known[13] and was shown to be the *R*-enantiomer by comparison of its optical rotation to that reported (see the Supporting Information). The additional rigidity of **17b** clearly has an important influence on the selectivity, given that the closely analogous PhCO^{t}Bu was reduced in significantly lower ee (77%). An attempt to form the (1*S*)-(+)-10-camphorsulfonic acid derivative of **18a** led to the isolation of a racemic ether (see the Supporting Information). However, the Mosher ester derivative was formed and isolated, analysis of which indicated that the configuration was *R* (see the Supporting Information).[10,14] This result indicates that the CH/π directing effect of an aromatic ring *directly* adjacent to the ketone with the Ru(II) η^6-arene remains the dominant one (Figure 3f). The same reactions, in similar ee but at lower rates, could be also achieved for certain substrates using catalyst **1** (see the Supporting Information).



In summary, although not as strong a directing effect as the established CH/π interaction with an aromatic ring directly adjacent to the ketone, the interaction of an unsaturated carbocyclic group of the substrate with the Ru(II) η^6-arene appears to be a constructive one which can alone direct the asymmetric reduction of ketones in high ee. This directing effect provides a means for the highly enantioselective reduction of hindered ketones and may prove useful in the design of future catalysts for use in asymmetric synthesis. The enantiopure alcohols prepared may also form the basis of novel ligands for extended applications and new structural motifs.

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Supporting Information Available. Full experimental procedures for synthesis of ketones and their reductions, X-ray crystallographic data, ^{1}H and ^{13}C NMR spectra, and ee determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For assignment of configuration, in all cases we have followed the IUPAC convention in giving a phenyl ring priority over a tBu group: Cross, L. C.; Klyne, W. *Pure Appl. Chem.* **1976**, *45*, 11–30.