Stereocontrol in Homogeneous Catalytic Hydrogenation via Hydroxyl Group Coordination

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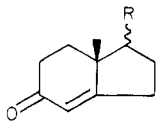
The control of stereochemistry in catalytic hydrogenation reactions has been a desirable but elusive goal. In many instances, the stereochemical result cannot even be *anticipated* unless extremely close analogy is available.

We have been interested for a number of years in finding means to remedy this situation in the hope that some form of attraction to a preexisting, easily introduced center might lead to the desired stereochemical control. The hydroxyl group has often served well in directing reactions other than hydrogenation (peroxy acid oxidations, Simmons-Smith cyclopropanation, etc.) but only scattered reports[1] have appeared that suggest the possibility of this type of stereocontrol in a hydrogenation reaction.

In any event, none of these isolated observations have led to a generally useful or predictable solution to the problem. After some unsuccessful experiments with Wilkinson's rhodium catalyst,[2] we turned to the iridium catalyst $Ir(cod)py(PCy_3)PF_6$[3,4] introduced by Crabtree et al.[5] because it has two sites that would be available for coordination with a bidentate substrate and because its ability to reduce trisubstituted double bonds made possible the study of a considerable range of structural types. The report[6] that alcohols deactivate this catalyst was somewhat disturbing but did suggest that the alcohol function might be a very effective ligand.

We now show that a high degree of stereocontrol can indeed be achieved in the hydrogenation of a variety of cyclohexenols. Perhaps the most striking case we have uncovered involves indenones of type **1**.



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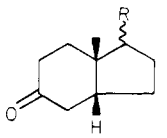

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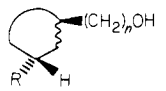
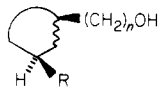
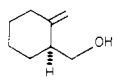
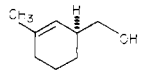
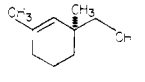
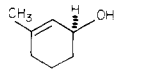
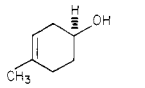
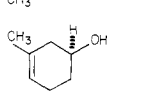
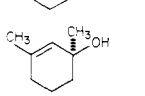
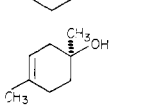
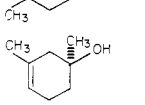
Table I



A, $n = 0, 1$



B, $n = 0, 1$

entry	substrate[a]	ratio A/B[b]	yield,[c] %
1		1:1 (1:2)	86
2		6:1 (1:3)	78
3		9:1 (1:1)	82
4		74:1 (1:3)	48
5		33:1 (1:3)	85
6		27:1 (1:5)	76
7		>100:1 (1:1)	64
8		>100:1 (1:1)	87
9		>100:1 (1:1)	74

[a] The usual conditions for the above reductions, carried out on 35-200 mg of the cyclohexenol, consisted in adding, under argon, degassed, calcium hydride-distilled methylene chloride (to produce a 0.025 M solution) to 20 mol % of the catalyst. This was followed by the substrate. The solution was stirred at room temperature under hydrogen until TLC on silica gel indicated completion (usually less than 2 h). [b] The ratios were determined by capillary GC (25-m SE-30 column). The ratios in parentheses refer to reduction with 5% palladium-charcoal in methanol. [c] Yields refer to the reduced isomeric mixture isolated after purification by silica gel chromatography. In some cases, the apparent yield was undoubtedly lowered because of product volatility.

When R is either a carbonyl or a β-hydroxyl group, the iridium homogeneous hydrogenation system gave essentially exclusive *cis*-indanone **2** formation, the same well-known result of heterogeneous hydrogenation of that system.[7] In the case of **3** (**1**, R

(1) Inter alia: Eisenbraun, E. J.; George, T.; Riniker, B.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 3648. Thompson, H. W.; Naipawer, R. E. *Ibid.* **1973**, *95*, 6379. Thompson, H. W.; McPherson, E. *Ibid.* **1974**, *96*, 6232. Fujimoto, R.; Kishi, Y.; Blount, J. *Ibid.* **1980**, *102*, 7154.

(2) For some interesting examples of moderate asymmetric induction in acyclic unsaturated alcohols, using a rhodium catalyst, see, however: Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348.

(3) cod = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine.

(4) We thank Dr. H. Felkin of the CNRS Laboratories in Gif-sur-Yvette (France) for his kindness in making available to us the preparation of this catalyst, which as Prof. Crabtree informed us, is described in the doctoral thesis of G. E. Morris, University of Paris, 1976. Because the details of the preparation of Crabtree's catalyst are not easily available, we are detailing them here (all manipulations were carried out in an inert atmosphere until the final recrystallization). To a degassed mixture of 3 mL of pyridine, 20 mL of acetone, 10 mL of ethanol and 2 mL of water were added 1.4 g of $[IrCl(cod)]_2$, available from Strem Chemicals, and 0.8 g of KPF_6. After stirring for half an hour, the solvent was removed, finally under high vacuum, and the resulting yellow crystals of $[Ir(cod)\ Py_2]PF_6$ were washed with degassed water to remove KCl and dried (96%). The above dipyridyl complex was stirred to room temperature in dry CH_2Cl_2 for 10 min with a slight excess over 1 equiv of PCy_3. Removal of solvent, recrystallization from CH_2Cl_2-ether, and pumping overnight gave $[Ir(cod)py(PCy_3)]PF_6$ in 92% yield.

(5) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E.; *J. Organomet. Chem.* **1979**, *168*, 183.

(6) Suggs, J. W.; Cox, S. D.; Crabtree, R. H.; Quirk, J. M. *Tetrahedron Lett.* **1981**, 303. After completion of the work in this paper, we learned that Crabtree et al. have begun to look at directing effects in hydrogenation with the iridium catalyst and that they have observed such an effect in the case of terpinen-4-ol.

(7) (a) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 4547. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239. (c) Baggaley, K. H.; Brooks, S. G.; Green, J.; Redman, B. T. *J. Chem. Soc. C* **1971**, 2671. Stork, G.; Shiner, C.; Winkler, J. *J. Am. Chem. Soc.* **1982**, *104*, 310. (d) For conditions, see table, footnote a. Reduction of these enones was much slower (24 h or more) than with the unconjugated olefins in the table, but the yields of saturated ketones were nevertheless >90%. The hydroxyindenone **3** was made by Mitsunobu inversion of **1**, R = β-OH. The identities of the cis and trans compounds were established by direct comparison with authentic samples and by oxidation of **4** to the known *trans*-7a-methyl-1,5-indandione, mp 52-52.5 °C, as reported[7c] and by the characteristic NMR signal of the angular methyl groups at δ 1.22 and 1.09, respectively, for the cis and trans indandiones (cf. a and b above).

(8) The stereochemistry of these compounds was assigned by comparison (NMR, GC) with authentic compounds made from the Diels-Alder adducts of methyl acrylate and 1,3-pentadiene (prepared in this laboratory by Dr. K. Atwal; cf.: Nakagawa, K.; Sawai, M.; Iishi, Y.; Ogawa, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2487), followed by Pd-charcoal hydrogenation and lithium aluminum hydride reduction.

(9) Correlated by comparison (mp, NMR, IR) of the carboxylic acids obtained by Jones oxidation of the alcohol mixture from the hydrogenations with authentic materials: Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1973**, *38*, 1694.

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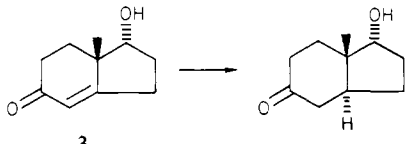
= α-hydroxyl) the result of heterogeneous hydrogenation (5% palladium on charcoal) was still the almost exclusive formation of the *cis*-indanone **2**, R = α-hydroxyl.

We are pleased to report, however, that the homogeneous iridium reduction in methylene chloride now gave very largely the *trans*-indanone **4** (ratio of trans to cis ~96:4).[7] This rather



3 4

dramatic result of stereochemical control by an appositely placed hydroxyl led us to examine a considerable number of other unsaturated alcohol systems. The results are shown in Table I.

It is apparent that cyclohexenols with allylic or homoallylic double bonds are reduced with high selectivity (~97:3) for secondary alcohols and more than 99:1 for the tertiary analogues. It is interesting that the primary cyclohexenylcarbinols give only fair (entries 2 and 3) or no selectivity (entry 1). Whether this results from less favorable equilibria with unsaturated primary alcohols, or from a certain ambiguity regarding the preferred stereochemistry of these particular hydroxy olefin complexes, or yet some other cause, is at present unknown.

It is worth noting that all these reductions are catalytic and usually proceed rapidly and in high yield. The previously mentioned deactivation of the catalyst by alcohols[6] could easily have led to the conclusion that any successful hydrogenation of an olefinic alcohol would be noncatalytic, but it is clear that rapid ligand equilibration on the catalyst must take place between the initially formed saturated alcohol and its unsaturated precursor.

In all the above cases, essentially no stereoselectivity was observed under heterogeneous conditions, with 5% palladium on charcoal. Similarly, and in keeping with the directing influence of the hydroxyl group, the acetates that were examined (from entries 1 through 6) gave essentially no selectivity under the homogeneous iridium conditions.

It is too early to tell the range of reactions of olefins that might be controlled, stereochemistry and regiochemically, by the coordination of homogeneous transition-metal catalysts with hydroxyls or other ligating functions. It is already clear, however, that hydroxyl-directed hydrogenation is a reaction of considerable generality.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

Registry No. 3, 84367-54-4; *trans*-**4**, 84367-55-5; *cis*-**4**, 84367-56-6; $[Ir(cod)Py(PCy_3)]PF_6$, 64536-78-3; 2-methylenecyclohexylmethanol, 78426-32-1; 3-methylcyclohex-2-en-1-ylmethanol, 80729-05-1; 1,3-dimethylcyclohex-2-en-1-ylmethanol, 84281-25-4; 3-methylcyclohex-2-en-1-ol, 21378-21-2; 4-methylcyclohex-3-en-1-ol, 51422-70-9; 3-methylcyclohex-3-en-1-ol, 53783-91-8; 1,3-dimethylcyclohex-2-en-1-ol, 29481-98-9; 1,4-dimethylcyclohex-3-en-1-ol, 70837-28-4; 1,3-dimethylcyclohex-3-en-1-ol, 71933-07-8; *trans*-2-methylcyclohexylmethanol, 3937-46-0; *cis*-2-methylcyclohexylmethanol, 3937-45-9; *trans*-3-methylcyclohexylmethanol, 84281-26-5; *cis*-3-methylcyclohexylmethanol, 24453-33-6; *trans*-1,3-dimethylcyclohexylmethanol, 84281-27-6; *cis*-1,3-dimethylcyclohexylmethanol, 84281-28-7; *trans*-3-methylcyclohexanol, 7443-55-2; *cis*-3-methylcyclohexanol, 5454-79-5; *trans*-4-methylcyclohexanol, 7731-29-5; *cis*-4-methylcyclohexanol, 7731-28-4; *trans*-1,4-dimethylcyclohexanol, 16980-60-2; *cis*-1,4-dimethylcyclohexanol, 16980-61-3; *trans*-1,3-dimethylcyclohexanol, 15466-93-0; *cis*-1,3-dimethylcyclohexanol, 15466-94-1.

(10) The stereochemistry was established by comparison (NMR, GC) with authentic substances made by hydride reduction of the related ketones: Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *Ibid.* **1956**, *78*, 2579.

(11) The stereochemistry was established by use of the ^1H and ^{13}C NMR data reported in the following: Grenier-Coustalot, M. F.; Zahidi, A.; Bonastre, J.; Grenier, P. *Bull. Soc. Chim. Fr.* **1979**, 229. Rei, M.-H. *J. Org. Chem.* **1979**, *44*, 2760.

2-Substituted Tetrahydrofurans of Known Absolute Stereochemistry by S_cN' Chirality Transfer

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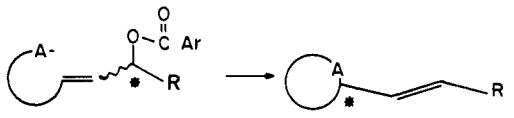
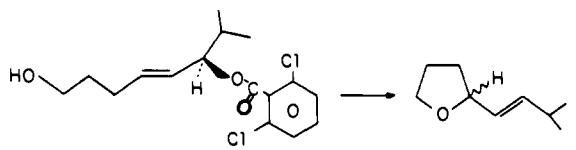
To the extent that it leads to a predictable stereochemical result, the SN_2-like cyclization of esters of optically active allylic alcohols (**1** → **2**) holds considerable interest since such a process results



1 2

in the transfer of the carbon–oxygen chirality to that of a carbon atom of the newly formed ring. We have previously shown that when A in **1** above is either a sulfur[1] or a carbon atom,[2] the S_cN' reaction takes place with a high degree of concertedness to give entry of the A group anti to the departing ester, thus leading to tetrahydrothiophene and cyclopentane systems of known absolute stereochemistry.

The poor nucleophilic properties of an alkoxide ion did not augur well for the possibility of extending the process to the synthesis of optically active tetrahydrofurans or pyrrolidines (cf. **1**, A = O or N). The problem, of course, is that hard anions like alkoxide ions are not very suitable for the S_cN' reaction involving departing benzoates. In fact, clean cyclization to the 2-alkenylfuran **4** could



E-3 4

be achieved by starting with the 2,6-dichlorobenzoate of the (*R*)-*trans*-diol **3** (80% optical purity; for preparation, see below) in the polar solvent 2,2,2-trifluoroethanol (2 h reflux with 2.2 equiv of potassium *tert*-butoxide; 69% yield), but under these conditions the product (**4**) was almost entirely racemized.[3]

This type of cyclization also did not prove useful as a route to chiral pyrrolidines. When in **3** above the cyclizing hydroxyl was replaced by a methylamino group, cyclization in refluxing trifluoroethanol, in the presence of triethylamine, gave very considerable racemization. It is worthy of note, however, that to the very small extent that chirality was transferred, the same anti relationship of the entering and departing groups was found that we had previously demonstrated for thio and carbon anions.

The difficulty attending simple base-catalyzed formation of a tetrahydrofuran ring led us to consider the applicability of the Pd-assisted SN′ reaction.[4] In considering this possibility, we were conscious of two problems. Intermolecular alkylations to form ethers have been shown to be quite efficient with aryl ethers of allylic alcohols[5] but are often poor with their esters. A second

(1) Stork, G.; Kreft, A. F. *J. Am. Chem. Soc.* **1977**, *99*, 3851.
(2) Stork, G.; Schoofs, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 5081.
(3) All compounds were purified by "flash" chromatography on silica, generally with a pentane–ether elution. Satisfactory spectral data were obtained for all compounds.
(4) For a recent review, see: Trost, B. *Acc. Chem. Res.* **1980**, *13*, 385. The pioneering work of Trost in establishing the stereochemistry of palladium-mediated displacement by carbanions in allylic systems is reviewed in that reference. See also: Trost, B.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559.
(5) The formation of ethers by palladium-assisted intermolecular displacement, starting with allylic alcohol derivatives, was first demonstrated by Hata et al.: Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392. Cf.: Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. A referee has brought to our attention an unpublished paper reporting the formation, with fair to good stereoselectivity, of spirotetrahydrofurans by palladium-catalyzed S_cN' processes (Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.*, in press.

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