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Carboxylate-Directed Highly Stereoselective Homogeneous Hydrogenation of Cyclic Olefins with Wilkinson's Catalyst

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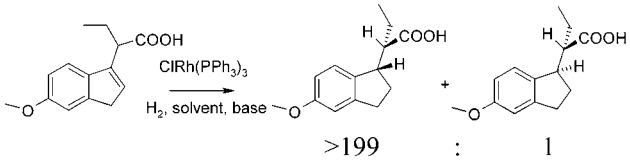
ABSTRACT



A highly efficient diastereoselective, carboxylate-directed homogeneous hydrogenation of cyclic olefins with use of Wilkinson's catalyst is described. Under the optimized reaction conditions, better than 99% de was achieved. The experimental protocol is very simple and readily amenable to scale-up.

Heteroatom-directed, homogeneous hydrogenation of olefins in the presence of a transition metal catalyst provides a powerful approach to regio- and stereochemical control in organic synthesis.[1] The directive effects arise when the directing heteroatom, hydrogen, and the alkene simultaneously bind to the transition metal, permitting exclusive syn delivery of hydrogen to the unsaturation site. The Wilkinson's catalyst $RhCl(PPh_3)_3$ worked successfully with olefins bearing an alkoxide directing group, providing the first example of stereoselective directed hydrogenation.[2] It unfortunately has failed to work with more commonly used directing groups such as hydroxyl, ethers, esters, and amides. For this reason, subsequent research in this area has been focused on cationic rhodium and iridium catalysts such as $[Rh(nbd)(diphos\text{-}4)]BF_4$[3] and $[Ir(cod)py(PCy_3)]PF_6$ (Crabtree's catalyst)[4] which work effectively with a variety of directing groups.[5] Recently, we had a need for a simple and scaleable diastereoselective hydrogenation method. We revisited Wilkinson's catalyst because it is air and water stable and readily commercially available.[6] We reasoned that, although hydroxyl and others such as esters, ethers, and amides cannot displace the chloride ligand of the Wilkinson's catalyst, a key requirement for effecting a directed hydrogenation,[7] the carboxylate, a better nucleophile,[8] may be able

(1) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307 and references therein.

(2) (a) Thompson, H. W.; Naipawer, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 6379. (b) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232. For applications of the Thompson method in the synthesis of complex organic molecules, see: (c) McCombie, S. W.; Cox, B.; Lin, Sue-Ing; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1990**, 2083. (d) Callam, C. S.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 167. (e) Preston, S. A.; Cupertino, D. C.; Palma-Ramirez, P.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 977.

(3) Brown, J. M.; Chaloner, P. A.; Kent, A. G.; Murrer, B. A.; Nicholson, P. N.; Parker, D.; Sidebottom, P. J. *J. Organomet. Chem.* **1981**, *216*, 263.

(4) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. (b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (c) Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994.

(5) (a) Stock, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (b) Schultz, A.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905. (c) Brown, J. M.; Hall, S. A. *Tetrahedron Lett.* **1984**, *25*, 1393. (d) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (e) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869.

(6) Price from 2002−2003 Aldrich catalog: Wilkinson's catalyst, $70 000/mol; Crabtree's catalyst, $700 000/mol.

(7) With Wilkinson's catalyst, displacement of the chloride ligand by the directing group is required for efficient stereoselective delivery of hydrogen. For more in-depth discussion on this point, see ref 1.

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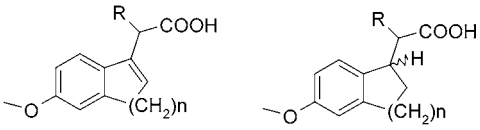
to do so, thus permitting stereochemical control.[9] In this letter, we wish to describe our findings of using the carboxylate group in directed stereoselective hydrogenation of cyclic olefins with Wilkinson's catalyst.

Olefinic substrates **1**−**3** (Figure 1) were readily obtained via Reformatsky reaction[10] from the appropriate ketones and



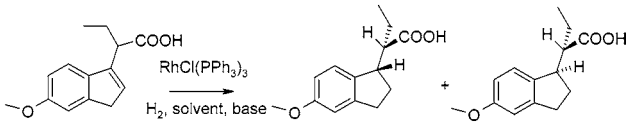
1: R = ethyl, n = 1
2: R = methyl, n = 1
3: R = methyl, n = 2

1a,b: R = ethyl, n = 1
2a,b: R = methyl, n = 1
3a,b: R = methyl, n = 2

Figure 1. Structures of olefinic substrates and their corresponding hydrogenation products.

bromoesters followed by saponification. The carboxylates were generated in situ via addition of an appropriate base. We initially examined the hydrogenation of the sodium carboxylate of the indene substrate **1** generated in situ by sodium bicarbonate in an ethanol/water (2:1) mixture. With 2 equiv of sodium bicarbonate, the hydrogenation proceeded cleanly at 60 psi with 5 mol % catalyst loading to produce both diastereomers **1a** and **1b** with a ratio of 98:2 in favor of **1a** (Scheme 1). The diastereomeric ratio was determined

Scheme 1



by both ^{1}H NMR (δ values for the peri-ArH in **1a** and **1b** are 7.03 and 7.10, respectively, in DMSO-d_6) and chiral HPLC, which allowed baseline separation of all four diastereomers.[11]

The stereochemistry of **1a** was determined by single-crystal X-ray crystallography. The racemate of **1a** was readily resolved by (*R*)-α-methyl benzylamine. The X-ray of the less soluble salt showed an (*SS*)-configuration for the indane acid.

The observed stereochemical outcome of the hydrogenation can be readily rationalized by using the concept of directed hydrogenation. The two faces of the olefin in these substrates are diastereotopic due to the preferred orientation of the allylic proton, as shown for the indene substrate **1** (Figure 2) that minimizes interactions with the peri-ArH

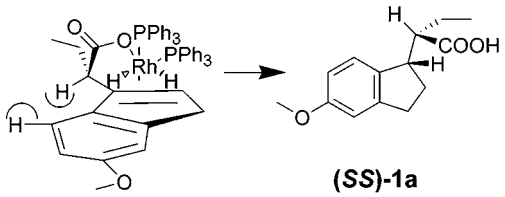


Figure 2. Proposed origin of stereoselectivity of the carboxylate-directed olefin hydrogenation.

proton. The carboxylate anion enters the coordination sphere of the rhodium complex by displacing the chloride ligand. The net effect of such coordination is that delivery of hydrogen atoms from the catalyst to the double bond takes place preferentially from the same side as the carboxylate group, leading to predominate formation of **1a**.

Further optimization of the reaction conditions to increase throughput led to the identification of the amine salts as better counterions than the sodium salts. The amine salts generally are more soluble in organic solvents, which permits hydrogenation to proceed at higher concentrations. The results are summarized in Table 1. We began by hydrogenating a

Table 1. Diastereoselective Hydrogenation of **1** with Use of Wilkinson's Catalyst

runs	cat., mol %	solvents	base/equiv	time (h)	de	yield (%)
1	5	EtOH/H_2O	$NaHCO_3$/2.0	36	96	90[a]
2	5	THF/EtOH	quinine/1.0	5	>99	30[b]
3	5	THF/EtOH	TEA/1.5	12	99	98[a]
4	1	THF/EtOH	TEA/1.5	24	90	90[b]
5	5	THF/EtOH	none	18	88	95[b]
6	5	THF	TEA/1.5	12	>99	20[b]
7[c]	5	THF/EtOH	TEA/1.5	36	>99	40[b]
				72	>99	50[b]
8[d]	5	THF/EtOH	TEA/1.5	24	>99	95[a]

[a] Isolated yield. [b] Conversion of substrate based on ^{1}H NMR. [c] 1 atm of H_2. [d] 30 psi of H_2.

diastereomerically pure quinine salt from the resolution of **1**.[12] The reaction proceeded very cleanly at 60 psi in EtOH/THF (9:1) with 5 mol % of Wilkinson's catalyst to yield the *S*,*S*-enantiomer in >99% de. When a racemate of **1** was hydrogenated in the presence of 1.0 equiv of quinine under the same conditions, >99% de was observed (entry 2, Table 1). While quinine is not the most preferred base for our purposes (high molecular weight and double bond), these results clearly demonstrated the superior performance of an amine as the base due to better solubility. We examined

(8) Nucleophilic constants for CH_3OH 0.0, CH_3COO^- 4.3, Cl^- 4.37, CH_3O^- 6.29. Data from: Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

(9) Base-promoted coordination of the carboxyl to Rh via the carboxylate anion has been indicated to be responsible for enhancing enatioselectivity and catalyst turnovers in enatioselective hydrogenations catalyzed by rhodium complexes of chiral ligands. See: (a) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (b) Valentine, D., Jr.; Sun, R. C.; Toth, K. *J. Org. Chem.* **1980**, *45*, 3703.

(10) (a) Shriner, R. L. *Org. React.* **1942**, *1*, 1. (b) Rathke, M. W. *Org. React.* **1975**, *22*, 423.

triethylamine (TEA) as a lightweight and more economical alternative base. With 1.5 equiv of TEA, >99% de was obtained with 5 mol % of Wilkinson's catalyst at 60 psi hydrogen pressure in ethanol/THF (9:1) (entry 3). Better than 90% de could be achieved even with 1 mol % of the catalyst under these conditions (entry 4). With the free acid, only 88% de was observed in the ethanol/THF system (entry 5). This result is not surprising, since the COOH group must undergo dissociation to generate the COO^- before it can bind to the rhodium catalyst. This hypothesis is further supported by the following observation: when the corresponding methyl ester of **1** was subjected to hydrogenation under these conditions (with no base present), no de was observed. Obviously, the ester group is not capable of any significant coordination to the transition metal in this case, and therefore the hydrogenation was nonselective. The ethanol/THF ratio has a very noticeable effect on the reaction rates, and the optimized ethanol/THF ratio is 9:1 (v/v). When pure THF was used, the hydrogenation proceeded very slowly although with similarly high diastereoselectivity (entry 6). Addition of ethanol dramatically increased the reaction rate. This observation can be easily explained by the high solubility of hydrogen in ethanol.[13] Yet, THF is still needed in our system because it appears to offer better solubility for the catalyst and substrates, thus permitting the reaction to proceed at high concentrations. It is significant that these optimized conditions also permit the hydrogenation to proceed smoothly at a much lower hydrogen pressure (entries 7 and 8). The simplicity of the procedure has enabled us to conduct the hydrogenation on greater than 100-g scale.

For comparison, we also examined the heterogeneous hydrogenation of **1**. It proceeded smoothly in ethanol (Pearlman's catalyst, ammonium formate as the hydrogen source) to afford a mixture of diastereomers **1a** and **1b** in a ratio of 1:2. The hydrogenation of the methyl ester of **1** also showed similar stereoselectivity (1:3).

We also examined the homogeneous hydrogenation of the substrates **2** and **3** using our optimized conditions. Under these conditions, both substrates afforded the desired hydrogenation products (**2a** and **3a**, respectively) with better than 99% de.[14]

In summary, we have found that carboxylate group is a very effective directing group for directed homogeneous hydrogenation with Wilkinson's catalyst. Under our reaction conditions, indene and 3,4-dihydronaphthalene acids are hydrogenated smoothly via their amine carboxylates in a highly stereoselective manner. The ease of handling and relatively low cost of the catalyst make this methodology a very practical one. Furthermore, since carboxyl group is readily interconvertable with a variety of functional groups such as esters, amides, hydroxyl, etc., this methodology thus constitutes a very practical alternative to the cationic catalyst-based directed stereoselective hydrogenation.[5]

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Supporting Information Available: Complete experimental details and X-ray crystal structure (ORTEP representation) of the (*R*)-α-methyl benzylanine salt of (*SS*)-**1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Column, Chiracel AD, 4.6 (i.d.) × 250 mm; mobile phase A, 0.1% TFA (trifluoroacetic acid) in hexanes, mobile phase B, 0.1% TFA in IPA (isopropyl alcohol); method, isocratic 95% A (5%B), 20 min; flow rate, 1.5 mL/min; detector (UV), 284 nm. Retention times for the four diastereomers are 5.163 (*SR*), 6.255 (*RS*), 10.262 (*RR*), and 14.399 min (*SS*); the first letter denotes the absolute configuration of the carbon adjacent to the carboxyl group. The stereochemistry assignment for each peak is described as the following: a nonequal racemic diastereomeric mixture was analyzed by chiral HPLC to obtain 4 baseline-resolved peaks. Peaks 3 and 4, 1 and 2 are enantiomer pairs based on UV integration. The absolute configuration of peak 4 is determined to be *SS* by X-ray structural analysis. Peak 3 can then be assigned a *RR* configuration with certainty. The absolute configurations of peaks 1 and 2 were determined by another experiment. Optically active (*S*)-indene acid (96% ee) from the chemical resolution was subjected to diastereoselective hydrogenation. The indane acid obtained was then analyzed by chiral HPLC. Due to high diastereoselectivity of the hydrogenation (>99% de), only the (*SR*)-diastereomer peak should be detectable by HPLC (retention time 5.363 min, ca. 0.97% area) in addition to the desired *SS* diastereomer (major) and its enantiomer *RR*. The 2nd peak from the 1st experiment (6.255 min) can then be assigned an *RS* configuration with certainty.

(12) The racemate of the indene substrate (**1**) can be resolved chemically with quinine prior to the stereoselective hydrogenation. The resolution yielded the (*S*)-enantiomer as the less soluble diastereomeric salt in acetonitrile (34%yield, 96−97% ee). The free acid was liberated by dissolving the salt in 2 N aqueous HCl followed by extraction into methylene chloride. The (*SS*)-enantiomer of **1a** was then readily obtained in high ee after hydrogenation.

(13) *CRC Handbook of Chemistry and Physics*; Weast, R., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1969; p B-114.

(14) The stereochemistry assignments of **2a** and **3a** are based on analogy to that of **1a** and are consistent with nOe and coupling constants data. The de measurements are based on ^{1}H NMR integration. In both cases, the minor diastereomer was not detected.