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CATALYTIC ASYMMETRIC HYDROGENATION OF β-DISUBSTITUTED α-PHENYLACRYLIC ACIDS ASYMMETRIC SYNTHESIS OF CARBOXYLIC ACIDS CONTAINING TWO VICINAL CHIRAL CARBON CENTERS

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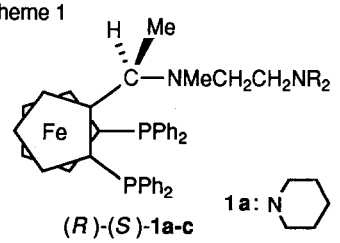
Summary: Hydrogenation of trisubstituted acrylic acids ((E)- and (Z)-MeC(R)=CPhCOOH: R = CD_3, Et, Ph) in the presence of a chiral (aminoalkyl)ferrocenylphosphine-rhodium catalyst installed asymmetric configurations at two vicinal carbons at once giving optically active carboxylic acids of high enantiomeric purities (>80% ee).

We have previously reported[1] that rhodium complexes coordinated with chiral (aminoalkyl)-ferrocenylphosphine ligands, (R)-N-methyl-N-[2-(dialkylamino)ethyl]-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamines (**1**) are catalytically active and stereoselective for asymmetric hydrogenation of 2-aryl-3-methyl-2-butenoic acids giving optically active 2-aryl-3-methylbutanoic acids of over 97% ee. The high ability of the catalyst is ascribed mainly to the attractive interactions between amino group at the terminal position on the ferrocenylphosphine ligand and carboxyl group on the olefin. Here we wish to describe an extension of the asymmetric hydrogenation to the synthesis of optically active carboxylic acids containing two vicinal chiral carbon centers.[2]

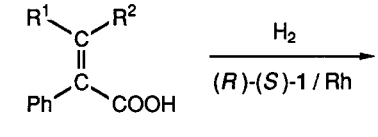
Asymmetric hydrogenation of 2-phenylpropenoic acids (**2a-2c**) containing two different substituents at 3 position was carried out in the presence of 1 mol% of rhodium catalyst containing chiral ferrocenylphosphine (R)-(S)-**1** (Scheme 1). The results are summarized in Table 1.[3] Hydrogenation of (E)-2,3-diphenyl-2-butenoic acid ((E)-**2a**) and its (Z) isomer ((Z)-**2a**) proceeded stereospecifically to give diastereomerically pure 2,3-diphenylbutanoic acids, u-**3a**[4] and l-**3a**,[4] respectively, as expected from the cis stereochemistry of the catalytic hydrogenation. Enantiomeric purities of **3a** determined by HPLC analysis of the anilides with a chiral stationary phase column were 92% ee for u-**3a** and 80% ee for l-**3a**, respectively (entries 1 and 2). The absolute configurations of (+)-u-**3a** and (+)-l-**3a** are assumed to be (2S,3R) and (2S,3S), respectively, provided that both (E)- and (Z)-**2a** undergo the attack of hydrogen on their re-face as has been observed in the hydrogenation of 2-aryl-3-methyl-2-butenoic acids[1] with the (R)-(S)-**1**/Rh catalyst. Stereospecific addition of hydrogen was also observed in the

Scheme 1



(R)-(S)-**1a-c**

1a: N
1b: NEt_2
1c: $N(n\text{-}Bu)_2$



(*E*)-**2a**: R^1 = Ph, R^2 = CH_3
(*Z*)-**2a**: R^1 = CH_3, R^2 = Ph
2b: R^1 = CD_3, R^2 = CH_3
(*E*)-**2c**: R^1 = C_2H_5, R^2 = CH_3
(*Z*)-**2c**: R^1 = CH_3, R^2 = C_2H_5

u-**3a**: (2*S*, 3*R*)
l-**3a**: (2*S*, 3*S*)
l-**3b**: (2*S*, 3*S*)
l-**3c**: (2*S*, 3*S*)
u-**3c**: (2*S*, 3*R*)

reaction of (E)-2-phenyl-3-trideuteromethyl-2-butenoic acid (**2b**), which gave diastereomerically pure hydrogenation product **3b**[5] of 98.4% ee, probably with (2S,3S) configuration, without any detectable scrambling of deuteriums on the substrate (entry 3).

Hydrogenation of (E)-2-phenyl-3-methyl-2-pentenoic acid (**2c**) in the presence of the (R)-(S)-**1a**/Rh catalyst was not stereospecific giving a small amount (3%) of u-**3c** in addition to the main product l-**3c** (entry 4). Both isomers were determined to be 97.3% enantiomerically pure by the HPLC analysis. The cis hydrogenation product l-**3c** has (2S,3S) configuration since the hydrogenation is expected to take place on its re face. The minor isomer u-**3c**, which arises formally from trans addition of hydrogen, was determined to have the same configuration at 2 position as l-**3c** and opposite one at 3 position, that is (2S,3R) configuration, by the following epimerization experiment. Thus, heating the hydrogenation mixture (l-**3c**/u-**3c** = 97/3) at 180 °C for 8 h resulted in thermal epimerization at 2 position giving a mixture consisting of l-**3c** and u-**3c** in a ratio of 6 to 4. The u isomer formed from l-(2S,3S)-**3c** was found to be an enantiomer of the u isomer formed in the asymmetric hydrogenation.

Hydrogenation of (E)-**2c** with deuterium (50 atm) in CH_3OD[6] was carried out to study the mechanism of formation of the trans addition product.[7] Similarly to the hydrogenation with H_2, the reaction gave a mixture of l-**3c'** and its epimer u-**3c'** in a ratio of 97/3. Deuterium distribution in the products **3c'** demonstrated by ^1H NMR studies is shown in Scheme 2. Both l-**3c'** and u-**3c'** contain 100% deuterium at 2 position but only 90% deuterium at 3 position. One

Scheme 2

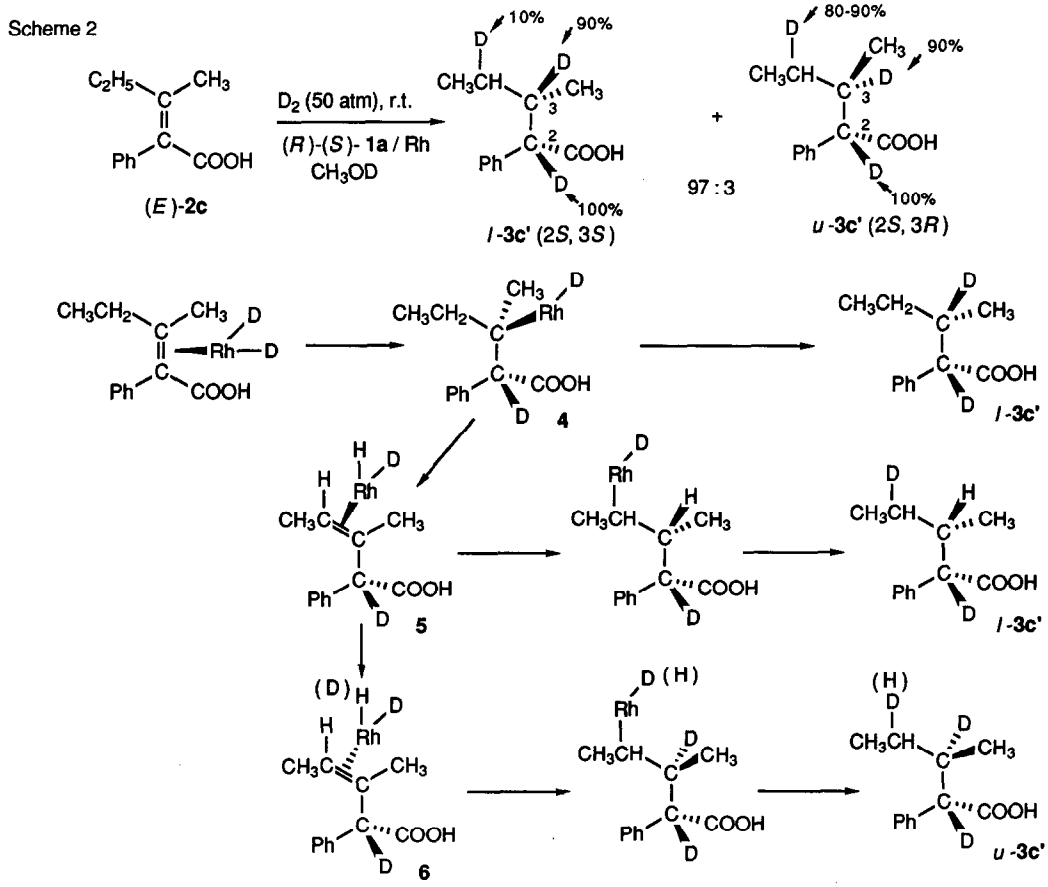
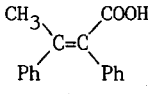
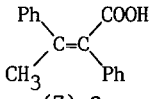
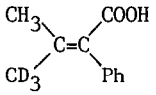
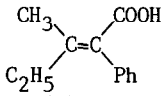
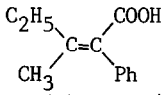


Table 1. Asymmetric Hydrogenation of Trisubstituted Acrylic Acids (**2**) Catalyzed by Chiral Ferrocenylphosphine-Rhodium Complexes.[a]

entry	olefin 2	ligand **1**	reaction conditions H_2 (atm)	solvent	time (h)	product	% ee[b] (config)[c]	$[\alpha]_D^{25}$
1	 (E)-**2a**	(R)-(S)-**1a**	100	MeOH/THF (2/8)	100	u-**3a**	92 (2S,3R)	+49.1° (c 1.0, MeCOMe)
2	 (Z)-**2a**	(R)-(S)-**1b**	100	MeOH/THF (2/8)	120	l-**3a**	80 (2S,3S)	+123° (c 1.3, MeCOMe)
3	 (E)-**2b**	(R)-(S)-**1a**[d]	50	MeOH/THF (2/8)	50	l-**3b**	98.4 (2S,3S)	+58.6° (c 1.5, $CHCl_3$)
4	 (E)-**2c**	(R)-(S)-**1a**	100	i-PrOH	120	**3c** (l/u = 97/3)	97.3 (2S,3S) (l-**3c**) 97.3 (2S,3R) (u-**3c**)	
5	 (Z)-**2c** (E/Z = 47/53)	(R)-(S)-**1a**	100	i-PrOH	150	**3c** (l/u = 50/50)	96.7 (2S,3S) (l-**3c**) 93.8 (2S,3R) (u-**3c**)	

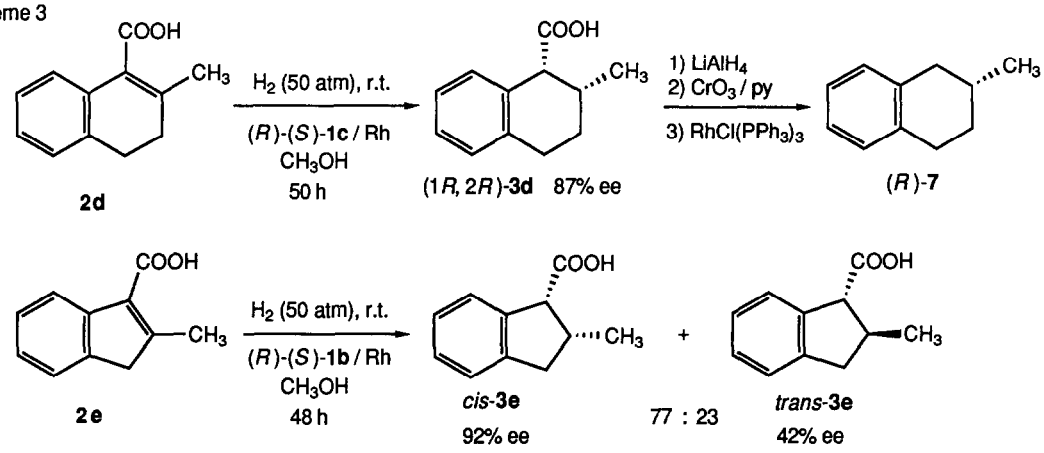
[a] The hydrogenation was carried out at room temperature in the presence of 1 mol% of the rhodium catalyst prepared in situ by mixing RhCl(NBD), $AgBF_4$, and ligand **1** in a ratio of 1:1:1.3 and 5 mol% of triethylamine. The chemical yields are quantitative. [b] Determined by HPLC analysis of anilides of the products with a chiral stationary phase column (Sumipax OA series and hexane/dichloroethane/ethanol = 250/20/1 or 500/20/1 as eluent: OA-2000 for **3a**, OA-1000 for **3b**, OA-4100 for **3c**, and OA-1100 for **3d** and **3e**). [c] The configuration 2S of **3a**, **3b**, and **3c** was assumed on the basis of the data obtained for the hydrogenation of 2-aryl-3-methyl-2-butenoic acids (ref 1). [d] Reaction with 0.5 mol% of the catalyst.

of the methylene hydrogens of ethyl group on the 3 position is partly substituted with deuterium, 10% on l-**3c'** and 80-90% on u-**3c'**. The deuterium distribution may be illustrated as follows. The olefin (E)-**2c** coordinates to a rhodium dideuteride species on its re face and inserts regioselectively in rhodium-deuterium bond to form alkylrhodium intermediate **4** where rhodium is attached to the carbon at 3 position. Reductive coupling of alkyl and deuterium groups on 4 produces l-(2S,3S)-**3c'**. Elimination of β-hydrogen on the ethyl group forms olefin complex 5 which has hydride and deuteride on rhodium. Addition of rhodium hydride to the coordinated olefin followed by transfer of deuterium from rhodium to the alkyl gives l-(2S,3S)-**3c'** that contains deuterium on 2 and 4 positions. Dissociation of the olefin from rhodium dihydride **5** and recoordination on the other face forms diastereomeric olefin complex **6**, which will lead to u-(2S,3R)-**3c'**. Hydrogen-deuterium exchange on rhodium during the olefin

dissociation will produce u-**3c'** substituted with deuterium atoms on 2, 3, and 4 positions. The mechanism described above is consistent with the stereochemical results that l-**3c** and u-**3c** have the same configuration at 2 position and opposite one at 3 position.

Cyclic tetrasubstituted olefin **2d** underwent the asymmetric hydrogenation with the rhodium-**1c** catalyst to give **3d**[8] ($[\alpha]_D^{25}$ +146° (c 1.2, chloroform)) of 87% ee selectively without any detectable amount of the trans isomer (Scheme 3). The absolute configuration determined by conversion into known (+)-(R)-2-methyltetrahydronaphthalene **7**[9] was (1R,2R). Hydrogenation of indene derivative **2e** was not cis selective, which gave a mixture of cis and trans isomers[10] in a ratio of 77 to 23. The cis isomer **3e** was 92% enantiomerically pure.

Scheme 3



REFERENCES AND NOTES

1 T. Hayashi, N. Kawamura, and Y. Ito, J. Am. Chem. Soc., **109**, 7876 (1987).

2 Asymmetric hydrogenation of tetrasubstituted olefins has been reported: K. Achiwa, Tetrahedron Lett., 2583 (1978).

3 Some of the results obtained for the hydrogenation of (E)-**2a** and (E)-**2c** have been reported in ref 1.

4 R. A. Auerbach and C. A. Kingsbury, Tetrahedron, **27**, 2069 (1971).

5 ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 7 Hz, 3H), 2.31 (dq, 1H), 3.15 (d, J = 10 Hz, 1H), 7.15-7.40 (m, 5H), 11.63 (broad s, 1H).

6 Use of CH_3OH as a solvent for the rhodium-catalyzed deuteration of **2c** resulted in the formation of **3c** containing a considerable amount of hydrogen both at 2 and 3 positions.

7 For reviews concerning mechanism of rhodium-catalyzed hydrogenation: a) J. M. Brown and P. A. Chaloner, "Homogeneous Catalysis with Metal Phosphine Complexes," ed by L. H. Pignolet, Plenum, New York, (1983), p 137. b) B. R. James, "Comprehensive Organometallic Chemistry," ed by G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon, New York (1982), Vol. 8, p 285.

8 ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 7 Hz, 3H), 1.52-2.30 (m, 3H), 2.72-3.00 (m, 2H), 3.76 (d, J = 5 Hz, 1H), 7.04-7.30 (m, 4H), 11.47 (broad s, 1H).

9 $[\alpha]_D^{20}$ +72° (c 1, dioxane). a) J. Barry, H. B. Kagan, and G. Snatzke, Tetrahedron, **27**, 4737 (1971). b) S. Hagishita and K. Kuriyama, Bull. Chem. Soc. Jpn., **55**, 3216 ((1982).

10 ^{1}H NMR ($CDCl_3$). cis-**3e**: δ 1.19 (d, J = 6.7 Hz, 3H), 2.83 (dd, J = 7.8 and 14.2 Hz, 1H), 2.90 (septet, 1H), 3.02 (dd, J = 6.8 and 14.2 Hz, 1H), 4.01 (d, J = 7.6 Hz, 1H), 7.16-7.33 (m, 4H). trans-**3e**: δ 1.24 (d, J = 6.8 Hz, 3H), 2.56 (dd, J = 7.5 and 15.7 Hz, 1H), 2.87 (septet, 1H), 3.22 (dd, J = 7.9 and 15.7 Hz, 1H), 3.66 (d, J = 7.3 Hz, 1H), 7.16-7.38 (m, 4H).

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