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An Improved Procedure for the Resolution of (*rac*)-Ethylenebis(tetrahydroindenyl)-Titanium Derivatives

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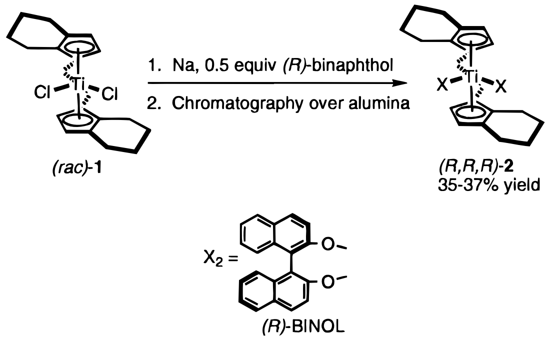
Brintzinger's *ansa*-titanocene complex **2** is an effective precatalyst in the asymmetric hydrogenation of imines,[1−4] enamines,[5] and unfunctionalized trisubstituted olefins.[6] It also serves as the precatalyst in the kinetic resolution of disubstituted 1-pyrrolines[7] and in the asymmetric hydrosilylation of ketones.[8]

The existing method for preparing **2** involves the kinetic resolution of (*rac*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride [(*rac*)-**1**] using optically pure 2,2′-binaphth-1-ol in the presence of excess sodium, yielding 35−37% of optically pure **2**.[9] (See Scheme 1.) This method suffers from several drawbacks: (1) purification requires chromatography over activated alumina; (2) the separation of the finely divided sodium upon completion of the reaction, requires filtration, which constitutes a fire hazard; and (3) only one enantiomer of **1** can be recovered; the other is destroyed.

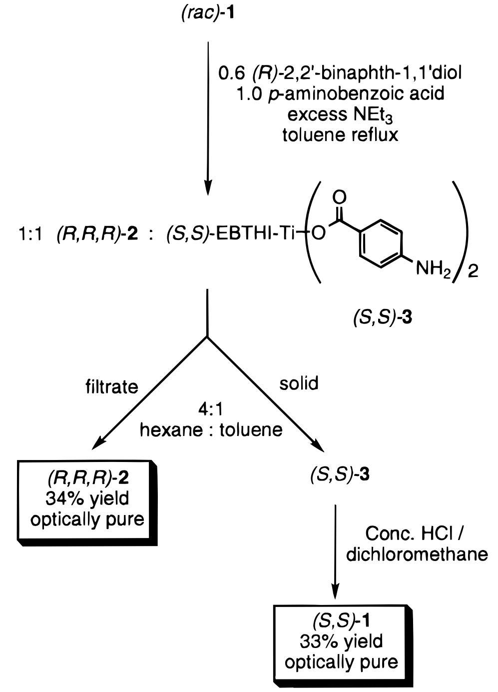
We have developed a new procedure, described here, which allows the preparation of ca. optically pure **1** and **2**, without the need for chromatographic separation or the use of sodium metal. In addition, the yield is effectively doubled as both enantiomers can be isolated. The enantiomer which does not react with 2,2′-binaphth-1-ol to form binaphtholate is isolated as **1**, which can also serve as a precatalyst for asymmetric hydrogenation.

In a typical experiment, (*rac*)-**1**, 0.6 equiv of (*R*)-2,2′-binaphth-1-ol, 1.0 equiv of *p*-aminobenzoic acid, and 2.5 equiv of NEt_3 are refluxed in toluene for 4 h. After the reaction mixture is allowed to cool to room temperature, hexane is added to precipitate the bis(benzoate) complex, (*S,S*)-**3**. This solid is separated by filtration, redissolved in toluene, and reprecipitated with hexane to remove any trace binaphtholate complex, the absence of which is confirmed by ^1H NMR. Acidification of (*S,S*)-**3** and recrystallization from hot heptane/CH_2Cl_2 yields (*S,S*)-**1**.[10,11] Removal of solvent *in vacuo* from the combined filtrates and recrystallization from pentane/CH_2Cl_2 yield pure (*R,R,R*)-**2**[12] (see Scheme 2).

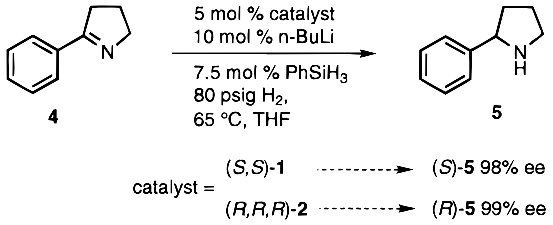
Scheme 1



Scheme 2



Scheme 3



Both purified (*S,S*)-**1**[13] and (*R,R,R*)-**2** were tested in the asymmetric hydrogenation of ketimine **4**; product **5** was isolated with an ee of 98−99%,[3] (see Scheme 3), demonstrating that (*S,S*)-**1** is an equally effective precatalyst.

In summary, we have developed an improved method for the resolution of (*rac*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium derivatives. This new method is safer and avoids the necessity of a chromato-

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(1) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.

(2) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627.

(3) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.

(4) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703.

(5) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985.

(6) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569.

(7) Viso, A.; Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 9373.

(8) Carter, M. B.; Schiøtt, B.; Gutiérrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667.

(9) (a) Wild, F. R. W. P.; Zsolnai, J.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233. (b) Collins, S.; Kuntz, B. A.; Hong, Y. *J. Org. Chem.* **1989**, *54*, 4154.

(10) Derivatization of (*S,S*)-**1** complex using (*R*)-O-acetylmandelic acid formed only one diastereomer as characterized by its ^1H NMR spectrum.

(11) Schafer, A.; Karl, E.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1987**, *328*, 87.

(12) Treatment of (*R,R,R*)-**2** with concentrated HCl/CH_2Cl_2 gave (*R,R*)-**1** (97% yield, $[\alpha]_{436} = +3440° \pm 40°$, $c = 7.2$ mg/10 mL in CH_2Cl_2) and (*R*)-2,2′-binaphthol (91% yield, 96% ee by HPLC in MeOH on Chiralpak OT(+) chiral stationary phase). Hydrogenation of **4** with (*R,R*)-**1** as precatalyst yielded (*R*)-**5** in >99% ee.

(13) The activation of (*S,S*)-**1** using *n*-BuLi was carried out at 0 °C.

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graphic purification which limited the scale up of the previous method. Importantly, this procedure provides equal quantities, as well as both enantiomers, of ca. optically pure precatalyst in a single protocol.

Experimental Section

General Considerations. All reactions were conducted under an atmosphere of purified argon, nitrogen, or hydrogen using standard Schlenk and glove box techniques. Hydrogenation reactions were conducted in a Fisher-Porter Bottle (purchased from Aerosol Lab Equipment, Walton, NY.) Toluene (anhydrous in SureSeal bottles from Aldrich Chemical Co., Milwaukee, WI), (*rac*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride[3] (Boulder Scientific Co., Mead, CO), (*R*)-2,2′-binaphth-1-ol (Aldrich Chemical Co. and Strem Chemicals, Newburyport, MA), and all other reagents are commercially available and were used as received. Yields refer to isolated yields of products of greater than 95% purity as determined by ^{1}H NMR spectrometry and gas chromatographic or elemental analysis (E + R Microanalytical Laboratory, Inc., Corona, NY).

Resolution of (*rac*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dichloride. A solution of (*rac*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride (10.0 g, 26.0 mmol), 4-aminobenzoic acid (3.58 g, 26.0 mmol), (*R*)-2,2′-binaphth-1-ol (4.48 g, 15.6 mmol) in dry toluene (350 mL) was heated to 80 °C under Ar to dissolve all solids. Triethylamine (9.1 mL, 65.2 mmol) was added by syringe, and then the reaction mixture was allowed to reflux for 4 h and then was cooled to rt. To the vigorously stirred solution, hexane (1.4 L) was added to precipitate the titanium bis(benzoate) complex as a yellow solid. This solid was isolated by filtration, redissolved in 350 mL of toluene, and reprecipitated with hexane (1.4 L), and the yellow solid was isolated by filtration. ^{1}H NMR ($CDCl_3$) showed the absence of **2** in the yellow solid.

(*R*,*R*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium (*R*)-1,1′-binaphth-2-olate, (*R*,*R*,*R*)-2. The combined filtrates were concentrated *in vacuo* to give a red solid, which was dissolved in a minimum amount of CH_2Cl_2. To the vigorously stirred solution was added methanol until precipitation ceased. The solid was filtered and recrystallized from CH_2Cl_2/pentane to give (*R*,*R*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium (*R*)-1,1′-binaphth-2-olate (5.32 g, 34% yield). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.78 (d, 2H), 7.75 (d, 2H), 7.16 (t, 2H), 7.10 (d, 2H), 7.01 (t, 2H), 6.88 (d, 2H), 5.56 (m, 4H), 3.33 (m, 2H), 3.09 (m, 2H), 2.56 (m, 4H), 1.71 (m, 6H), 1.49 (m, 4H), 1.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 137.13, 134,72, 132.88, 128.61, 128.30, 127.61, 126.94, 125.43, 125.09, 121.79, 121.42, 117.75, 116.20, 106.42, 27.44, 23.91, 23.17, 22.09, 21.81. Anal. Calcd for $C_{40}H_{36}O_2Ti$: C, 80.51; H, 6.09. Found: C, 80.59; H 6.19. $[\alpha]_{578} = -3620° \pm 20°$ ($c = 5.0$ mg/10 mL in $CHCl_3$, $l = 1.000$ cm).[14] Lit.[3] $[\alpha]_{578} = -3690°$ ($c = 0.45$ mg/mL in $CHCl_3$). Literature rotations for the (*S*,*S*,*S*) diastereomer were reported as $[\alpha]_{578} = +3100°$ ($c = 40$ mg/100 mL in $CHCl_3$)[9a] and $[\alpha]_{578} = +4085°$ ($c = 4.5$ mg/100 mL in $CHCl_3$).[9b]

(*S*,*S*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dichloride, (*S*,*S*)-1. The titanium benzoate complex was dissolved in CH_2Cl_2 (100 mL). Concentrated HCl (25 mL) was added, and the solution was stirred for 2 h open to the air. The organic layer was washed with water, 1 M KOH (3 × 50 mL), water, and 1 M HCl (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a red-brown solid. This solid was dissolved in hot toluene (50 mL) and hexane (20 mL) was added. After the mixture was cooled to rt, a small amount of red (*rac*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride crystals formed, which were isolated by filtration. The filtrate was concentrated *in vacuo*, and the resulting solid was recrystallized from hot heptane/CH_2Cl_2 to give (*S*,*S*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride (3.3 g, 33% yield). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 6.6 (d, 2H), 5.56 (d, 2H), 3.3−3.0 (m, 6H), 2.7−2.5 (m, 4H), 2.5−2.3 (m, 2H), 2.05−1.8 (m, 4H), 1.6−1.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.79, 134.69, 128.94, 126.32, 111.55, 27.87, 24.50, 24.17, 21.77, 21.75. Anal. Calcd for $C_{20}H_{24}Cl_2Ti$: C, 62.69; H, 6.31. Found: C, 62.95; H 6.56. $[\alpha]_{436} = -3190° \pm 40°$ ($c = 7.0$ mg/10 mL in CH_2Cl_2, $l = 1.000$ cm).[14] Lit.[11] $[\alpha]_{435} = -2986°$ ($c = 1.2$ g/100 mL in CH_2Cl_2, $l = 0.1$ cm). Lit.[9a] $[\alpha]_{435} = -3300°$ ($c = 50$ mg/100 mL in $CHCl_3$). Lit.[9b] extrapolated from the value in this reference $[\alpha]_{435} = -3317°$ ($c = 2.5$ mg / 100 mL in $CHCl_3$).

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(14) A large range of values exist for the specific rotations of **1** and **2**. The reason for these discrepencies is not understood. It should be noted that in general, the temperature at which the measurements were carried out is not reported.