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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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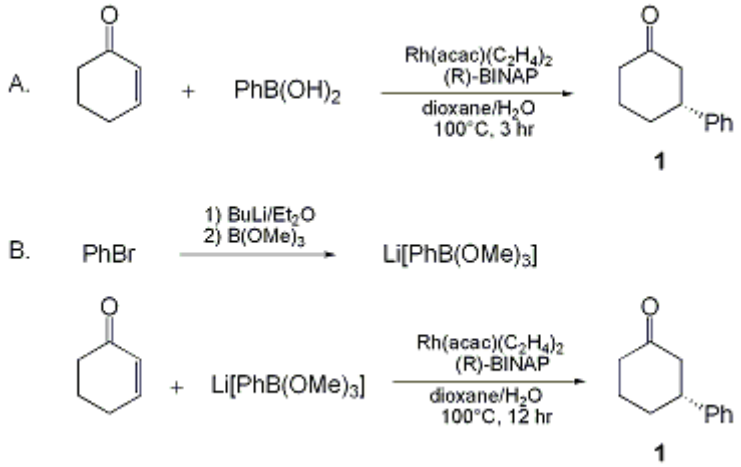
(R)-3-PHENYLCYCLOHEXANONE

[Cyclohexanone, 3-phenyl-, (R)-]



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Checked by Timothy B. Durham and Marvin J. Miller.

1. Procedure

Caution! All reactions should be conducted in a well-ventilated hood.

(R)-(+)-3-Phenylcyclohexanone (**1**).

Method A. A 500-mL, two-necked, round-bottomed flask, fitted with a magnetic stirring bar, rubber septum, and a reflux condenser attached to a gas-flow adapter with a stopcock, is charged with 12.2 g (100 mmol) of phenylboronic acid (Notes 1, 2), 300 mg (0.482 mmol) of (R)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl [(R)-BINAP] (Notes 3, 4), and 103 mg (0.399 mmol) of acetylacetonatobis(ethylene)rhodium(I) (Note 5), and the flask is flushed with nitrogen. To the flask are added 3.86 g (3.90 mL, 40.2 mmol) of 2-cyclohexenone (Note 6), 200 mL of 1,4-dioxane (Note 7), and 20 mL of water via syringe, and the entire orange mixture is immersed in a oil bath preheated to 120°C and heated at 105°C for 3 hr. After the solvent is cooled to room temperature, it is removed under reduced pressure on a rotary evaporator. After concentration of the initial reaction mixture on a rotary evaporator, the residue is dissolved in diethyl ether (100 mL). The resulting solution is transferred to a 500-mL separatory funnel and washed with 1.2 M hydrochloric acid (HCl, 100 mL) followed by 5% sodium hydroxide (NaOH) solution (100 mL). The aqueous washes are separately extracted with diethyl ether (30 mL each). The ether layers are combined and washed with saturated sodium chloride solution (100 mL), dried over anhydrous magnesium sulfate , filtered, and the filtrate concentrated on a rotary evaporator to give a brown oil. The oil is filtered through silica (200 mL) with hexanes (500 mL) followed by diethyl ether (400 mL) on a 4-cm φ column. Fractions of eluent (20 mL) are collected and those containing the product as determined by TLC are combined and concentrated on a rotary evaporator to give a brown oil that is distilled under reduced pressure (0.5 mm) to give 5.77 g (83% yield) of (R)-3-phenylcyclohexanone (**1**) (Note 8) as a colorless oil. The enantiomeric purity is 98.6% ee, which is determined by HPLC analysis using a chiral stationary phase column (Note 9).

Method B. A dry, 200-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, rubber septum, and a reflux condenser attached to a gas-flow adapter with a stopcock, is flushed with nitrogen. The flask is charged with 3.95 g (25.2 mmol) of bromobenzene (Note 10) and 12.5 mL of dry diethyl ether (Note 11) via syringe, and cooled to 0°C in an ice-water bath. At this temperature, 16.7 mL

(25.1 mmol) of a 1.50 M solution of n-butyllithium in hexane (Note 12) is added. The ice-water bath is removed and the mixture is stirred at room temperature for 1 hr. The flask is cooled to −78°C in a dry ice-acetone bath, and 2.59 g (24.9 mmol) of trimethoxyborane (Note 13) is added dropwise over a period of 10 min via syringe. The mixture is stirred at −78°C for 30 min and slowly warmed to room temperature by removal of the dry ice-acetone bath. In a second flask, a 100-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, rubber septum, and a gas-flow adapter with a stopcock, are placed 74.7 mg (0.120 mmol) of (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(R)-BINAP] (Notes 3, 4), and 25.8 mg (0.100 mmol) of acetylacetonatobis(ethylene)rhodium(I) (Note 5). After the flask is flushed with nitrogen, 50 mL of 1,4-dioxane is added via syringe, and the mixture is stirred at room temperature for 10 min. To the first flask containing the phenylborate reagent, Lithium phenyltrimethoxyborate , are added successively, via syringe 0.975 g (10.1 mmol) of 2-cyclohexenone (Note 6), 0.54 mL of water, and the catalyst solution from the second flask. The entire mixture is heated in an oil bath at 100°C for 12 hr. After the solvent is cooled to room temperature, it is removed under reduced pressure on a rotary evaporator. The dark brown residue is diluted with diethyl ether (100 mL) and transferred to a 500-mL separatory funnel. The ether solution is washed with 10% hydrochloric acid (100 mL) and 5% aqueous sodium hydroxide (100 mL). The aqueous layers are extracted with diethyl ether (30 mL each). The organic layers are combined, washed with aqueous saturated sodium chloride (100 mL), and dried over anhydrous magnesium sulfate . The solvent is removed under reduced pressure on a rotary evaporator to give a brown oil, which is dissolved in 5 mL of diethyl ether and chromatographed on silica gel [4 cm Φ, 200 mL of silica gel (Note 14)]. Elution with 500 mL of hexane (Note 15) followed by elution with 400 mL of diethyl ether gives crude 3-phenylcyclohexanone (**1**), collected as 20-mL fractions and combined. Distillation under reduced pressure (bp 125-130°C at 0.5 mm) gives 1.55 g (88.1% yield) of (R)-3-phenylcyclohexanone (**1**) (Note 8) as a colorless oil. The enantiomeric purity is 98.3% ee, which is determined by HPLC analysis using a chiral stationary phase column (Note 9).

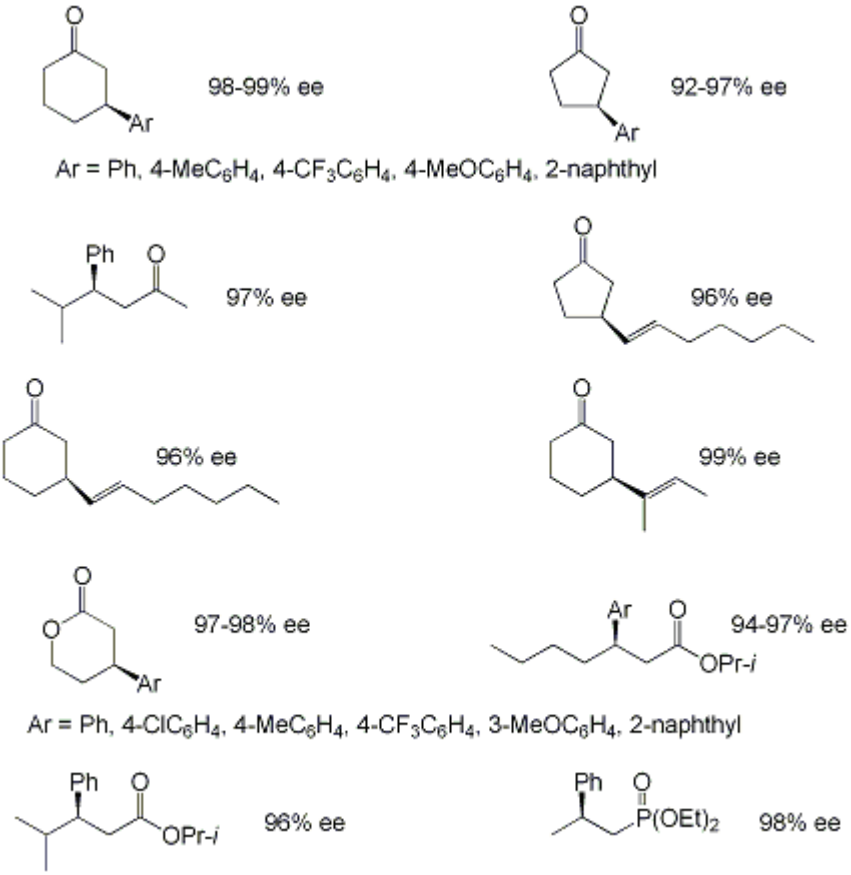
2. Notes

1. Phenylboronic acid was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as received.
2. The use of 2.5 equiv (to 2-cyclohexenone) of phenylboronic acid is important for a high yield. With 1.0 equiv of phenylboronic acid , the yield is less than 70%.
3. (R)-BINAP is commercially available from Aldrich Chemical Company, Inc. , although the submitters have prepared it according to the reported procedures.[2]
4. This molar ratio (1.2 : 1) of BINAP to the rhodium(I) is required for high enantioselectivity. With a 1 : 1 ratio, the enantioselectivity is usually 1 or 2% lower.
5. Acetylacetonatobis(ethylene)rhodium(I) is commercially available from Strem Chemicals, Inc. , although the submitters have prepared it according to a reported procedure.[3]
6. 2-Cyclohexenone was purchased from Tokyo Kasei Kogyo Co., Ltd. and distilled before use.
7. 1,4-Dioxane was purchased from Wako Pure Chemical Industries, Ltd. and distilled from benzophenone ketyl before use.
8. Specific rotation value of **1**: $[\alpha]_D^{20}$+21° ($CHCl_3$, *c* 0.96) [literature rotation for (*R*)-**1** (98.7% ee);[4] $[\alpha]_D^{20}$+20.5° (*c* 0.58, $CHCl_3$)]. The spectra are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.77 (qdd, 1 H, J = 12.6, 4.4, 3.3), 1.85 (qd, 1 H, J = 12.3, 3.3), 2.07 (dm, 1 H, J = 13.1), 2.14 (ddq, 1 H, J = 12.7, 6.0, 3.1), 2.37 (tdd, 1 H, J = 12.6, 6.3, 1.1), 2.45 (dm, 1 H, J = 14.5), 2.52 (td, 1 H, J = 12.4, 1.1), 2.59 (ddt, 1 H, J = 14.0, 4.5, 2.0), 3.00 (tt, 1 H, J = 11.9, 3.8), 7.19-7.25 (m, 3 H), 7.32 (t, 2 H, J = 7.5) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.88, 32.10, 40.46, 44.04, 48.21, 126.01, 126.03, 128.06, 143.86, 209.80 .
9. The column contained Daicel Chiralcel OD-H (eluent, hexane/2-propanol = 98/2).
10. Bromobenzene was purchased from Kanto Chemical Company Inc. , and used as received.
11. Diethyl ether was purchased from Nacalai Tesque Company Inc. , and distilled from benzophenone ketyl before use.
12. n-Butyllithium in hexane was purchased from Kanto Chemical Company Inc. , and used as received.
13. Trimethoxyborane (trimethyl borate) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
14. Silica gel 60 100-210 μm (Kanto Chemical Company Inc.) was used.
15. Biphenyl as a by-product is removed by this elution.

3. Discussion

Conjugate addition of organometallic reagents to electron-deficient olefins constitutes one of the versatile methodologies for forming carbon-carbon bonds. Although considerable efforts have been made to develop efficient chiral catalytic systems for asymmetric conjugate addition, the successful examples are rare in terms of enantioselectivity, catalytic activity, and generality.[5] In 1997, Miyaura and co-workers[6] found that a phosphine-rhodium complex catalyzes the 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones giving β-substituted ketones. Based on this finding, the submitters developed rhodium-catalyzed, asymmetric, 1,4-addition reactions of organoboron reagents to electron-deficient olefins. High enantioselectivity has been achieved in the reaction of α,β-unsaturated ketones with aryl- and alkenylboronic acids, which was carried out in dioxane/H_2O at 100°C in the presence of a rhodium catalyst generated from acetylacetonatobis(ethylene)rhodium(I) and (S)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (BINAP).[7] Both acyclic and cyclic enones gave the corresponding optically active ketones of over 90% ee. In place of isolated organoboronic acids, 2-alkenyl-1,3,2-benzodioxaboroles, readily accessible by hydroboration of alkynes with catecholborane ,[8] and arylborates, generated by reaction of aryllithiums with trimethoxyborane ,[9] can also be used for the asymmetric 1,4-addition. α,β-Unsaturated esters[10] and 1-alkenylphosphonates[11] undergo the rhodium-catalyzed asymmetric addition of organoboron derivatives to give the corresponding 1,4-addition products of over 90% ee. The submitters also studied some basic factors, including reaction temperature, solvent, rhodium precursor, and chiral ligand, which are capable of affecting the enantioselectivity and catalytic activity.[12] Some of the optically active products obtained by the rhodium-catalyzed, asymmetric, 1,4-addition of aryl- and alkenylboronic acids or their derivatives are shown in Figure 1.

Figure 1. Products obtained by the rhodium-catalyzed asymmetric 1,4-addition [(S)-BINAP is used]



References and Notes

1. Department of Chemistry, Faculty of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
2. Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem*. **1994**, *59*, 7180.
3. Cramer, R. *Inorg. Synth*. **1974**, *15*, 14.
4. Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc*. **1991**, *113*, 4926.
5. For a pertinent review, see Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. (Eds.); Springer, **1999**; *3*, pp 1105-1120.
6. Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.
7. For leading references, see Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc*. **1998**, *120*, 5579.
8. Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479.
9. Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett*. **1999**, *40*, 6957.
10. Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.
11. Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc*. **1999**, *121*, 11591.
12. Takaya, Y.; Ogasawara, M.; Hayashi, T. Chirality **2000**, *12*, 469.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-3-Phenylcyclohexanone:
Cyclohexanone, 3-phenyl-, (R)- (9); (34993-51-6)

Phenylboronic acid:
Benzeneboronic acid (8);
Boronic acid, phenyl- (9); (98-80-6)

(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl [(R)-BINAP]:
Phosphine oxide, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (R)- (11); (94041-16-4)

Acetylacetonatobis(ethylene)rhodium (1):
Rhodium, bis(ethylene)(2,4-pentanedionato)- (8);
Rhodium, bis(η2-ethene)(2,4-pentanedionato-O,O'- (9); (12082-47-2)

Cyclohexenone: *HIGHLY TOXIC*:
2-Cyclohexen-1-one (8,9); (930-68-7)

Bromobenzene:
Benzene, bromo- (8,9); (108-86-1)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Trimethoxyborane: ALDRICH;
Trimethyl borate:
Boric acid, trimethyl ester (8,9); (121-43-7)