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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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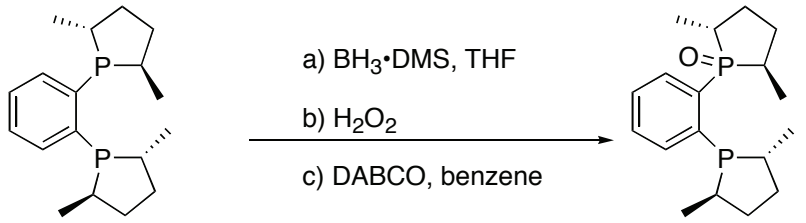
PREPARATION OF ENANTIOMERICALLY PURE (*R,R*)-BozPHOS [(*2R,5R*)-1-{2-[(*2R,5R*)-2,5-dimethylphospholan-1-yl]phenyl}-2,5-dimethylphospholane 1-oxide]



(*R,R*)-Me-DuPHOS (*R,R*)-BozPHOS

Submitted by Alexandre Côté, Jean-Nicolas Desrosiers, Alessandro A. Boezio and André B. Charette.[1]
Checked by Scott E. Denmark and Justin I. Montgomery.

1. Procedure

(2R,5R)-1-{2-[(2R,5R)-2,5-dimethylphospholan-1-yl]phenyl}-2,5-dimethylphospholane 1-oxide **(*R,R*)-BozPHOS**. A flame-dried, 100-mL, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar and a rubber septum is charged with **(*R,R*)-Me-DuPHOS** (1 g, 3.26 mmol) (Note 1) in a glove-box under argon. Anhydrous THF (32 mL) (Note 2) is added to the flask via a syringe under argon and the resulting colorless solution is cooled in a 0 °C ice bath for 15 min before BH_3•DMS 10 M (360 μL, 3.6 mmol) (Note 3) is added dropwise (Note 4) via a syringe. The colorless mixture is stirred for 45 min under argon at 0 °C and H_2O_2 35% wt. (3 x 1.15 mL, 39.2 mmol) (Note 5) is added dropwise via syringe (Note 6) at 0 °C under argon in three portions with an interval of 30 min between each addition. The mixture is stirred for an additional 45 min at room temperature, and the reaction is quenched by the dropwise addition via cannula of a saturated aqueous solution of Na_2SO_3 (40 mL) at 0 °C over 30 min (Note 7). The mixture is transferred to a 250-mL separatory funnel and the aqueous layer is extracted with ethyl acetate (3 x 100 mL), and the combined extracts are dried over Na_2SO_4 (50 g), filtered and concentrated by rotary evaporation (30 °C, 50 mmHg) to afford a white foam (1.115 g) (Note 8). The crude product and DABCO (550 mg, 4.9 mmol) (Note 9) are placed in a 100-mL, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar and a rubber septum. The flask is purged under

argon, then anhydrous benzene (32 mL) (Note 10) is added. The colorless reaction mixture is stirred for 5 h in a 50 °C oil bath and then the solvent is removed by rotary evaporation (25 °C, 40 mmHg) to afford a white residue. The crude product is purified on silica gel (Notes 11, 12) to afford 977 mg (93% yield, >99% ee) of the title compound as a white solid (Notes 13 and 14).

2. Notes

1. (*R,R*)-Me-DuPHOS was purchased from Strem Chemicals, Inc. Although, it could be briefly manipulated under moisture and oxygen, it was stored under argon atmosphere in a glove-box to prevent any undesired oxidation. It was used without any prior purification.

2. Anhydrous THF was obtained by filtration through a drying column on a GlassContour system (Irvine, CA).

3. Borane•dimethyl sulfide (BH_3•DMS) was purchased from Aldrich Chemical Company, Inc. and was used without prior purification.

4. The addition lasted 1 minute.

5. H_2O_2 35% wt. was purchased from Aldrich Chemical Company, Inc. and was used without prior purification.

6. One minute was needed for each addition.

7. The reaction is exothermic and a gas is evolved.

8. The crude product can be stored overnight under argon in a −20 °C freezer with no degradation.

9. DABCO was purchased from Aldrich Chemical Company, Inc. and was recrystallized from a 1:1 mixture of MeOH and hexanes.

10. Anhydrous benzene was obtained by filtration through a drying column on a GlassContour system (Irvine, CA).

11. The product was dissolved in dichloromethane (2 mL) and charged on a column (3 x 15 cm) of 60 g of UltraPure silica gel (40–63 μm) purchased from Silicycle. The product was eluted with 600 mL of 5% MeOH in EtOAc and collected with 8 mL fractions. The desired product was obtained in fractions 16–30, which were combined and concentrated by rotary evaporation (30 °C, 30–50 mmHg). The desired product can be visualized on TLC with a UV lamp or by developing with a $KMnO_4$ solution.

12. No over-oxidation occurred during the chromatography, but the pure compound is typically stored under argon.

13. The physical properties are as follows: R_f 0.33 (5% MeOH in EtOAc) mp 125−127 °C; HRMS (ESI$^+$) *m/z* calc. for $C_{18}H_{29}P_2O$ [M^+ + 1]: 323.1694, found: 323.1688; Elemental Analysis calc. for $C_{18}H_{28}P_2O$: C, 67.07; H, 8.75, found: C, 67.13; H, 9.00; IR (neat) cm^{-1} 730, 738, 758, 1116, 1130, 1159, 1253, 1374, 1455, 2860, 2925; ^{1}H NMR (400 MHz, C_6D_6) δ: 0.85 (dd, *J* = 17.3, 7.4 Hz, 3 H), 0.91−1.03 (m, 1 H), 1.06 (dd, *J* = 9.1, 7.1 Hz, 3 H), 1.26−1.37 (m, 2 H), 1.28 (dd, *J* = 17.6, 8.3 Hz, 3 H), 1.30 (dd, *J* = 13.7, 6.9 Hz, 3 H), 1.64−1.76 (m, 2 H), 1.84−2.06 (m, 4 H), 2.41−2.52 (m, 1 H), 2.58−2.71 (m, 1 H), 2.71−2.83 (m, 1 H), 7.05 (tddd, *J* = 7.5, 2.6, 1.3, 0.5 Hz, 1 H), 7.13 (tt, *J* = 7.4, 1.5 Hz, 1 H), 7.27−7.34 (m, 1 H), 7.45−7.50 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ: 13.1 (dd, $J_{C\text{-}P}$ = 2.9, <1 Hz), 17.5 (d, $J_{C\text{-}P}$ = 8.8 Hz), 18.6 (d, $J_{C\text{-}P}$ = 3.9 Hz), 20.6 (d, $J_{C\text{-}P}$ = 36.1 Hz), 31.7 (dd, $J_{C\text{-}P}$ = 67.9, <1 Hz), 31.8 (d, $J_{C\text{-}P}$ = 9.8 Hz), 32.2 (dd, $J_{C\text{-}P}$ = 8.8, 1.9 Hz), 34.4 (d, $J_{C\text{-}P}$ = 11.7 Hz), 35.0 (d, $J_{C\text{-}P}$ = 13.6 Hz), 36.5 (d, $J_{C\text{-}P}$ = 6.8 Hz), 36.8 (dd, $J_{C\text{-}P}$ = 66.9, 4.9 Hz), 36.9 (d, $J_{C\text{-}P}$ = 2.0 Hz), 128.5 (d, $J_{C\text{-}P}$ = 10.8 Hz), 130.9 (dd, $J_{C\text{-}P}$ = 2.9, <1 Hz), 131.5 (dd, $J_{C\text{-}P}$ = 11.2, 9.3 Hz), 134.2 (dd, $J_{C\text{-}P}$ = 10.7, 2.9 Hz), 140.3 (dd, $J_{C\text{-}P}$ = 82.0, 33.2 Hz), 144.0 (dd, $J_{C\text{-}P}$ = 37.1, 9.3 Hz); ^{31}P NMR (202 MHz, C_6D_6) δ: 8.99 (d, *J* = 4.6 Hz), 62.05 (d, *J* = 4.6 Hz); $[\alpha]_D^{20}$ −221.6 (c = 0.836, EtOH). The enantiomeric excess of the product is determined by HPLC analysis at 254 nm [Chiralpak AD, 95:5 hexanes: *i*-PrOH, 1mL/min: (R,R) t_r (major) = 7.3 min, (S,S) t_r (minor) = 10.1 min)] or determined by SFC analysis [Chiralpak AD, 20% i-PrOH, 150 bar CO_2, 1 mL/min, 65° Cl.

14. The checkers found that the appearance of the NMR spectra was highly concentration dependent. The spectra reported were taken as follows: ^{1}H NMR, 4 mg/1.0 mL; ^{13}C NMR, 309 mg/1.5 mL.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The hemilabile ligand **BozPHOS** is useful for the copper-catalyzed asymmetric addition of diorganozinc reagents to *N*-diphenyl-phosphinoylimines.[2–5] This bis-phosphine monoxide ligand can be prepared

from both enantiomers of the commercially available **Me-DuPHOS** by mono-oxidation. Various methods have been reported to oxidize bidentate phosphines.[6] Among them, Grushin's method involving palladium acetate[7] was unsuitable because it afforded a mixture of the unreacted bis-phosphine, its mono-oxide (40%), its bis-oxide and an unidentified phosphonium salt. The procedure described above employs a selective mono-protection of the bis-phosphine with BH_3•DMS followed by a mono-oxidation with H_2O_2. During this process, no bis-oxidation is obtained even if an excess of H_2O_2 is used. Traces of unreacted **Me-DuPHOS** can be separated easily by silica gel flash chromatography since **BozPHOS** is air stable. The procedure described above can be accomplished on a 0.5 to 10 g-scale to obtain **BozPHOS** in an 87 to 93% yield.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*R,R*)-Me-DuPHOS: Phospholane 1,1'-(1,2-phenylene)bis[2,5-dimethyl-, [2*R*-[1(2'*R**,5'*R**),2a,5b]]-; (147253-67-6)
DABCO: 1,4-Diazabicyclo[2.2.2]octane; (280-57-9)
(*R,R*)-BozPHOS: Phospholane, 1-[2-[(2*R*,5*R*)-2,5-dimethyl-1-oxido-1-phospholanyl]phenyl]-2,5-dimethyl-, (2*R*,5*R*)-; (38132-66-8

JIM-XV-13F1_4mg_1mL_PhD6

exp1 std1h

SAMPLE		DEC. & VT	
date	Jul 6 2005	dn	H1
solvent	Benzene	dof	0
file	/export/home/~	dm	nnn
data/u400/montgome~		dmm	c
ry/JIM-XV-13F1_4mg~		dmf	200
_1mL_PhD6.fid		dpwr	20
ACQUISITION		PROCESSING	
sfrq	399.951	lb	0.30
tn	H1	wtfile	
at	4.096	proc	ft
np	65536	fn	not used
sw	8000.0	math	f
fb	4400		
bs	16	werr	
tpwr	63	wexp	
pw	7.3	wbs	
d1	0	wnt	
tof	-425.7	DISPLAY	
nt	16	sp	-200.2
ct	16	wp	4399.4
alock	n	vs	151
gain	not used	sc	0
FLAGS		wc	250
il	n	hzmm	17.60
in	n	is	2161.84
dp	y	rfl	4846.2
hs	nn	rfp	2859.6
	th		13
	ins		1.000
	nm	ph