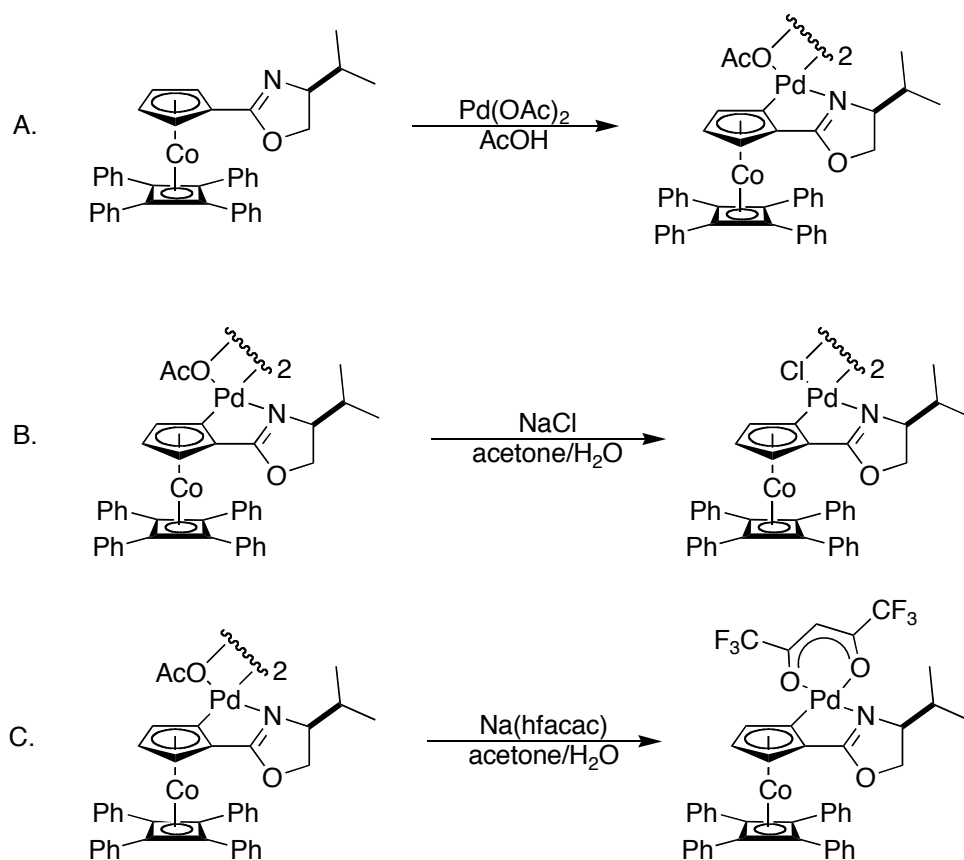


PREPARATION OF THE COP CATALYSTS: [(S)-COP-OAc]₂, [(S)-COP-Cl]₂, AND (S)-COP-hfacac



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1. Procedure

A. *Preparation of di-μ-acetatobis[(η⁵-(S)-(pR)-2-(2'-(4'-methylethyl)oxazolanyl)cyclopentadienyl, 1-C, 3'-N)(η⁴-tetraphenylcyclobutadiene)cobalt]dipalladium ([COP-OAc]₂).* A flame-dried, single-necked, 250-mL round-bottomed flask is fitted with a stirring bar and an argon inlet. The flask is evacuated, refilled with argon and then, while temporarily removing the argon inlet, charged with (η⁵-(S)-2-(4-methylethyl)oxazolanyl)cyclopentadienyl)-(η⁴-tetraphenylcyclobutadiene)-cobalt (9.6 g, 16.2 mmol)² and 96 mL of glacial acetic acid. Palladium(II) acetate (Note 1) (3.6 g, 16.2 mmol) is then added. The red solution is then

heated at 95 °C (oil bath temperature) and the formation of an orange precipitate is observed. After 30 min, the solution is cooled to room temperature and filtered to provide an orange solid. This solid is washed with 50 mL of glacial acetic acid and dried under vacuum to provide 8.9 g (5.9 mmol, 73% yield) of di- μ -acetatobis[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-C, 3'-N)(η^4 -tetraphenylcyclobutadiene)cobalt]dipalladium as a mustard-colored solid (Note 2).

*B. Preparation of di- μ -chlorobis[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-C, 3'-N)(η^4 -tetraphenylcyclobutadiene)cobalt]dipalladium ([COP-Cl]₂).* A single-necked, 250-mL round-bottomed flask is fitted with a stirring bar. The flask is charged with di- μ -acetatobis[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-C, 3'-N)(η^4 -tetraphenylcyclobutadiene)cobalt]dipalladium (8.9 g, 5.9 mmol) and 59 mL of acetone. Aqueous sodium chloride (2 M, 30 mL) is then added, and the resulting heterogeneous mixture is stirred at room temperature (Note 3). After 4 h, the yellow solid is collected by filtration of the reaction mixture. This solid is washed with 125 mL of water followed by 20 mL of acetone and then dried under vacuum to provide 8.2 g (5.6 mmol, 95% yield) of di- μ -chlorobis[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-C, 3'-N)(η^4 -tetraphenylcyclobutadiene)cobalt]dipalladium, [COP-Cl]₂, as a mustard-colored solid (Notes 4, 5, 6).

*C. Preparation of hexafluoroacetylacetonate[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-C, 3'-N)(η^4 -tetraphenylcyclobutadiene)cobalt]palladium (COP-hfacac).* A single-necked, 25-mL round-bottomed flask is equipped with a stir bar and charged with [COP-OAc]₂ (1.0 g, 0.66 mmol), sodium hexafluoroacetylacetonate (Note 7) (1.6 g, 6.8 mmol), 6.6 mL of acetone and 3.3 mL of water. The mixture is stirred vigorously at room temperature (Note 3). After 9 h, the mixture is filtered, and the filter cake is washed with 10–20 mL of water and then dried over P₂O₅ in a vacuum desiccator for 12 h to provide 1.1 g (1.2 mmol, 91%) of hexafluoroacetylacetonate[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-C, 3'-N)(η^4 -tetraphenylcyclobutadiene)cobalt]palladium, COP-hfacac, as an orange solid (Notes 8, 9).

2. Notes

1. Palladium acetate should be an orange/red solid. It can be obtained from either Strem Chemicals or Aldrich Chemical Co. In one instance, the submitters report that a commercial sample gave poor results; good results were obtained when this sample of palladium acetate was purified by crystallization from benzene.

2. Characterization data: ^1H NMR (500 MHz, CDCl_3) δ : -0.01 (d, J = 6.6 Hz, 3 H, CH_3), 0.46 (d, J = 7.1 Hz, 3 H, CH_3), 1.72–1.81 (m, 1 H, CH), 1.96 (s, 3 H, CH_3), 2.98 (td, J = 9.0, 3.1 Hz, 1 H, CH), 3.36 (t, J = 9.0 Hz, 1 H, CH_2), 4.08 (dd, J = 8.6, 3.9 Hz, 1 H, CH_2), 4.23 (t, J = 2.4 Hz, 1 H, CH), 4.62 (d, J = 1.4 Hz, 1 H, CH), 4.68 (d, J = 2.0 Hz, 1 H, CH), 7.20–7.29 (m, 12 H, ArH), 7.64 (m, 8 H, ArH); ^{13}C NMR (125 MHz, CDCl_3) δ : 13.3, 18.8, 24.2, 29.1, 65.0, 71.2, 76.2, 79.4, 85.0, 85.4, 86.8, 98.1, 126.2, 128.1, 129.5, 136.1, 170.8, 180.9; Infrared spectrum (thin film) cm^{-1} : 3061, 2961, 1583, 1502, 1417, 1366, 1181, 1069. Anal. Calcd. for $\text{C}_{82}\text{H}_{72}\text{O}_6\text{N}_2\text{Co}_2\text{Pd}_2$: C, 65.04; H, 4.93; N, 1.85. Found: C, 64.81; H, 4.74; N, 1.98.

3. An aliquot was removed and filtered. The solid was analyzed by ^1H NMR spectroscopy to determine when the reaction was complete, which typically required 4 h.

4. The checkers found that the sample could be purified by filtration through a short plug of silica gel using methylene chloride as the eluent to afford the product as an orange solid (99% yield before purification, 97% yield after purification). The product, di- μ -chlorobis[$(\eta^5$ -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazoliny)l)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4 -tetraphenylcyclobutadiene)cobalt]dipalladium, exists as a 1.0:0.7 mixture of dimers in CDCl_3 . ^1H NMR (500 MHz, CDCl_3) δ : 0.70–0.74 (m, 6 H, CH_3), 0.76 (d, J = 6.8 Hz, 3 H, CH_3), 0.80 (d, J = 7.0 Hz, 3 H, CH_3), 2.20–2.33 (m, 2 H, CH), 3.03–3.15 (m, 2 H, CH), 3.34 (t, J = 9.0 Hz, 1 H, CH_2), 3.43 (t, J = 8.9 Hz, 1 H, CH_2), 4.16–4.22 (m, 2 H, CH_2), 4.28 (t, J = 2.5 Hz, 1 H, CH), 4.40 (t, J = 2.5 Hz, 1 H, CH), 4.70 (d, J = 2.0 Hz, 1 H, CH), 4.73 (d, J = 2.0 Hz, 1 H, CH), 4.98 (d, J = 1.5 Hz, 1 H, CH), 4.99 (d, J = 1.5 Hz, 1 H, CH), 7.16–7.22 (m, 12 H, ArH), 7.23–7.30 (m, 12 H, ArH), 7.58–7.62 (m, 8 H, ArH), 7.66–7.71 (m, 8 H, ArH); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.3, 14.5, 19.0 (2C), 29.0, 29.2, 65.6, 66.0, 71.4, 71.5, 76.5, 76.8, 81.0, 84.2, 84.5, 84.8, 84.9, 85.7, 87.1, 98.6, 98.7, 126.4, 126.5, 128.2, 128.3, 129.4, 129.5, 135.5, 135.6, 171.1, 171.2; Infrared spectrum (thin film) cm^{-1} : 3061, 2961, 1602, 1502, 1370, 1185.

5. The enantiomeric purity of [(*S*)-COP-Cl]₂ is best determined after conversion to the acetylacetonate derivative. A mixture of [COP-Cl]₂ (15 mg, 0.010 mmol), sodium acetylacetonate (70 mg, 0.573 mmol), acetone (0.4 mL) and water (0.2 mL) is stirred vigorously at room temperature for 20 h. Methylene chloride (0.5 mL) and water (0.5 mL) are added, and the layers were separated. The aqueous layer is extracted with methylene chloride (0.5 mL x 3). The combined organic layers is dried (MgSO₄), filtered and concentrated to provide an orange residue. This residue is filtered through a short plug of silica gel (diameter = 0.25 cm, height = 4 cm) using 4% *i*-PrOH/hexanes as eluent. The enantiopurity of this sample was determined to be >99% by HPLC analysis (AD column, 95:5 hexane:*i*-PrOH, 230 nm); retention times were: 5.8 min for (*S*)-COP-acac and 3.8 min for (*R*)-COP-acac. The checkers found that a sample of (*S*)-COP-acac gave one signal at 5.1 min that was determined to be 97% pure by HPLC analysis (Diacel Chiralpak AD-H column (0.46 cm x 25 cm), 1 mg/mL sample concentration, flow rate of 1.0 mL/min, 95:5 hexanes: *i*-PrOH).

6. The enantiomer of [COP-OAc]₂ and [COP-Cl]₂ can be prepared in an analogous fashion from (η^5 -(*R*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4 -tetraphenylcyclobutadiene)cobalt prepared from (*R*)-valinol.²

7. Sodium hexafluoroacetylacetonate was purchased from Aldrich Chemical Company, Inc., and was used as received.

8. The checkers found that in one case it was necessary to stir the reaction for 11 h in order to achieve full conversion to the product. COP-hfacac prepared by this method was of sufficient purity to catalyze allylic imidate rearrangements in polar solvents such as tetrahydrofuran or methylene chloride. COP-hfacac can be purified further by filtration through a short plug of silica gel using methylene chloride as eluent. The checkers found that purification of a sample of (*S*)-COP-hfacac yielded an orange solid (89% yield after purification).

9. The product, hexafluoroacetylacetonate[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4 -tetraphenylcyclobutadiene)cobalt]palladium, displayed the following characterization data: ¹H NMR (500 MHz, CDCl₃) δ : 0.79 (d, *J* = 6.9 Hz, 3 H, CH₃) 0.83 (d, *J* = 7.0 Hz, 3 H, CH₃), 2.05–2.08 (m, 1 H, CH), 3.45 (td, *J* = 9.4, 5.1 Hz, 1 H, CH), 3.72 (t, *J* = 9.4 Hz, 1 H, CH₂), 4.33 (dd, *J* = 8.6, 5.3 Hz, 1 H, CH₂), 4.53 (t, *J* = 2.3 Hz, 1 H, CH), 4.90 (d, *J* = 2.3 Hz, 1 H, CH), 4.68 (d, *J* = 2.3 Hz, 1 H, CH), 5.95 (s, 1 H, CH), 7.19–7.29 (m, 12 H, ArH), 7.54–7.56 (m, 8

H, ArH); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.9, 18.4, 29.3, 65.3, 72.3, 76.7, 78.9, 84.1, 84.8, 87.7, 90.1, 97.6, 116.5, 118.8, 126.5, 127.9, 128.9, 135.5, 173.3, 173.6, 174.1; Infrared spectrum (thin film) cm^{-1} : 3061, 2964, 1629, 1598, 1509, 1475, 1258, 1208, 1150.

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

This synthesis of (*S*)-COP-OAc dimer, is a modification of the procedure originally reported by Richards and Stevens.³ The procedure has been streamlined and modified to enable large-scale preparation of this and related COP catalysts. Using the procedure detailed here and in the accompanying procedure,² 8.9 g [(*S*)-COP-OAc]₂ or 8.2 g of [(*S*)-COP-Cl]₂ can be made in 40% overall yield from sodium cyclopentadienide with only one chromatographic purification being required.

Palladation of (η^5 -(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4 -tetraphenylcyclobutadiene)cobalt occurs in a diastereoselective fashion because of the large steric floor provided by the tetraphenylcyclobutadiene moiety. This floor forces the oxazoline into a single diastereomeric conformation, allowing *ortho*-palladation to proceed on only one of the diastereotopic positions of the cyclopentadienyl ring.³

[COP-OAc]₂ is a planar, chiral palladium(II) complex, which catalyzes the reaction of carboxylic acids with prochiral primary (*Z*)-allylic trichloroacetimidates to provide enantioenriched 3-acyloxy-1-alkenes.⁴ These reactions proceed with predictable high stereoselection and are accomplished at room temperature using low catalyst loadings. This acetate-bridged dimer serves also as a convenient precursor of enantiopure [COP-Cl]₂ and the enantiopure monomeric hexafluoroacetylacetonate complex, COP-hfacac.

[COP-Cl]₂ is a planar chiral palladium(II) complex, which catalyzes the [3,3]-sigmatropic rearrangement of (*E*)-allylic trichloroacetimidates to the corresponding trichloroacetamides in high yields and enantioselectivities for a wide range of substituted trihaloacetimidates.⁵ The use of [COP-Cl]₂ for the

catalytic asymmetric rearrangement of allylic trihaloacetimidates is described in an *Organic Syntheses* procedure.⁶ The corresponding hexafluoroacetylacetonate complex, COP-hfacac, also catalyzes asymmetric allylic trichloroacetimidate rearrangements.⁷ It is more soluble than [COP-Cl]₂ and can be used in a wider variety of solvents. This enhanced solubility allows catalytic asymmetric allylic trichloroacetimidate rearrangements to be conducted at high substrate concentrations using as little as 1 mol % of COP-hfacac.

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2. Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards, C. J.; and Watson, M. P. *Org. Synth.* **2007**, *84*, 139-147.
3. Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346–1348.
4. Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866–2867.
5. Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413.
6. Anderson, C. E.; Overman, L. E.; Watson, M. P. *Org. Synth.* **2005**, *82*, 134–139.
7. Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101–8104.

Appendix

Chemical Abstracts Nomenclature; (Registry Number)

(η^5 -(*S*)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4 -tetraphenylcyclobutadiene)cobalt: Cobalt, [1,1',1'',1'''-(η^4 -1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]][(1,2,3,4,5- η)-1-[[[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]-2,4-cyclopentadien-1-yl]-; (222400-02-4)

Palladium(II) acetate; (3375-31-3)

(*S*)-COP-OAc: Di- μ -Acetatobis[(η^5 -(*S*)-(p*R*)-2-(2'-4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4 -tetraphenylcyclobutadiene)cobalt]dipalladium; (849592-74-1)

(*S*)-COP-Cl: Cobalt, bis[1,1',1'',1'''-(η^4 -1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]](di- μ -chlorodipalladium)bis[μ -[(1- η :1,2,3,4,5- η)-2-[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl- κ N3]-2,4-cyclopentadien-1-yl]]di-; (581093-92-7)

Sodium hexafluoroacetylacetonate: 2,4-Pentanedione, 1,1,1,5,5,5-hexafluoro-, ion(1-), sodium; (22466-49-5)

(*S*)-COP-hfacac: Hexafluoroacetylacetonate[(η^5 -(*S*)-(p*R*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4 -tetraphenylcyclobutadiene)cobalt]palladium; (805315-08-6)



Larry Overman was born in Chicago, Illinois, in 1943 and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971 where he is now Distinguished Professor of Chemistry. Professor Overman was Chair of the UC Irvine Department of Chemistry from 1990–1993.



Carolyn Anderson received her B.Sc. degree in Chemistry from the University of Michigan in 1998 and her Ph.D. in Chemistry from the University of California at Irvine (with Larry Overman) in 2003. She was a Dreyfus Postdoctoral Fellow at Pomona College (Claremont, California) under the mentorship of Daniel O'Leary (2004–2006). In 2006, she joined the faculty of Calvin College (Grand Rapids, Michigan) as an Assistant Professor of Chemistry. Her current research interests include using organometallic methods to synthesize libraries of strained carbocycles.



Chris Richards was born in Woking, England, and obtained a B.Sc degree in Chemistry from the University of Bath in 1989. This was followed by a Ph.D. in 1990 working with Professor Sue Gibson at the University of Warwick. After spending 1 year as an Alexander von Humboldt Research Fellow with Professor Helmchen at the University of Heidelberg, he took up a Lectureship at Cardiff University in Wales. In 2001 he moved to his current position of Reader at Queen Mary, University of London. His research interests encompass organometallic chemistry, organic synthesis, stereochemistry and catalysis.



Mary P. Watson received her B.A. from Harvard University in 2000, where she studied organic chemistry under the direction of Prof. David Evans. She then moved to University of California, Irvine, to work with Prof. Larry Overman. Her graduate research focused on the palladium(II)-catalyzed asymmetric allylic imidate rearrangement, including mechanistic studies performed in collaboration with Prof. Robert Bergman at the University of California, Berkeley. During her graduate work, she received the Allergan graduate student fellowship. She received her Ph.D. in 2006 and is currently a postdoctoral researcher at Harvard University with Prof. Eric Jacobsen.



Nicole S. White received her B.S. from the University of California, San Diego, in 2002. She then accepted a position in the medicinal chemistry department of Neurocrine Biosciences, where she worked on development of an MC4 antagonist aimed towards the treatment of cachexia. In 2004 she moved to the University of California, Irvine, to work with Prof. Larry Overman. Currently, her graduate research focuses on the use of palladium(II) catalysts to construct carbon-heteroatom bonds asymmetrically.



Brian S. Bodnar, born in 1981 in Trenton, NJ, obtained his B. S. degree from The College of New Jersey in Ewing, NJ, where he studied lithiation of benzamides under Dr. Lynn M. Bradley and analyzed microsatellite DNA of diatoms under Dr. James V. Bricker. After internships at Colgate-Palmolive Co. and Wyeth, he went to the University of Notre Dame in Notre Dame, IN to pursue a Ph. D. in organic chemistry under Dr. Marvin J. Miller. His research focuses on applications toward the synthesis of novel heterocyclic scaffolds and biologically useful molecules using acylnitroso hetero Diels-Alder chemistry.