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Asymmetric Synthesis of Monodentate Phosphine Ligands Based on Chiral η^6-Cr[arene] Templates

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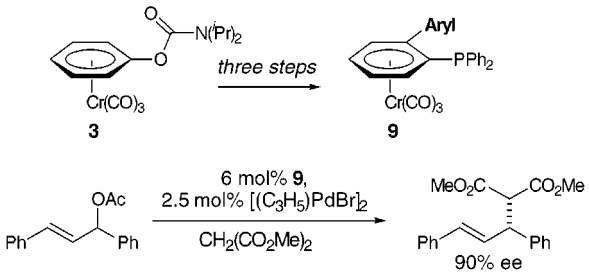
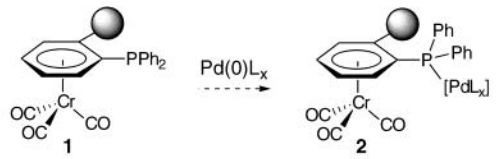
ABSTRACT



Optically active Cr-complexed arylphosphines are presented as a new class of chiral monodentate phosphine ligand for use in asymmetric catalysis. Asymmetric synthesis of the chiral phosphine ligands 9 is achieved in three steps from the achiral Cr[arene] precursor 3. A variety of ligand structures are accessed from a common synthesis intermediate. The utility of these phosphine ligands in asymmetric catalysis is highlighted in Pd(II)-catalyzed allylic alkylation reactions.

Multidentate ligand−metal binding is a common prerequisite for metal-based catalysts that mediate highly stereoselective organic transformations. However, multidentate ligands are incompatible with metal complexes in which catalytic activity is exclusive to complexes possessing monodentate ligands or to catalysts that retain only a single ligand during the critical bond-forming event. Realizing high levels of asymmetric induction under these circumstances requires chiral monodentate ligands that, despite the conformational mobility associated with univalent metal−ligand attachment, effectively relay chirality to the pertinent bond construction.[1] Chiral, nonracemic monodentate phosphine ligands satisfying these requirements are relatively rare compared to the numerous examples of bidentate phosphine ligands employed widely in asymmetric catalysis. As a contribution to the development of optically active monophosphine ligands, a modular strategy for the asymmetric synthesis of monodentate phosphine ligands **1** based on chiral η^6-Cr[arene] scaffolds is presented herein (Scheme 1). Crystal structure data for the derived Pd(0)−phosphine complex **2** and Pd(0)-catalyzed allylic alkylations employing these monodentate phosphines highlight the potential utility of these ligands in asymmetric catalysis.

Scheme 1



Catalyst optimization routinely necessitates access to a variety of ligand structures. A strategy for efficiently preparing a variety of ligand architectures from a common synthetic pathway was, therefore, considered essential in designing the phosphine ligand synthesis. These considerations led to a modular ligand synthesis based on an optically active η^6-Cr[arene] core that would provide access to a variety of ligand structures from a common synthesis

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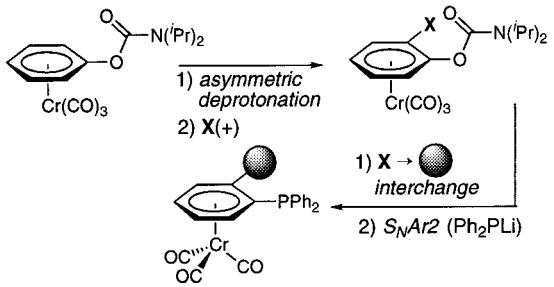
intermediate.[2,3] The carbamate-substituted arene complex **3** was targeted as an intermediate that could be elaborated to the desired optically active arylphosphine complexes via a three-step sequence (Scheme 2): (1) enantioselective arene

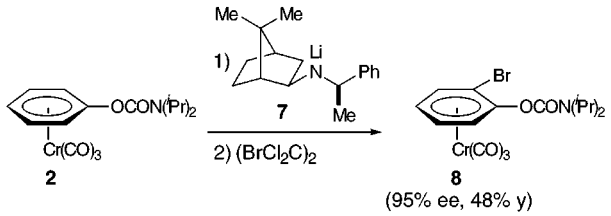
Scheme 2



lithiation and ensuing derivatization to provide the optically active Cr[arene] **4**, (2) incorporation of structural diversity by interconversion of the *ortho* substituent X, and (3) installation of the phosphine moiety via S_NAr2 displacement of the carbamate function.

Synthesis of the targeted arylphosphine ligands was initiated by asymmetric ortho lithiation of the Cr-complexed aryl carbamate **3** (Scheme 3). Deprotonation of aryl carbam-

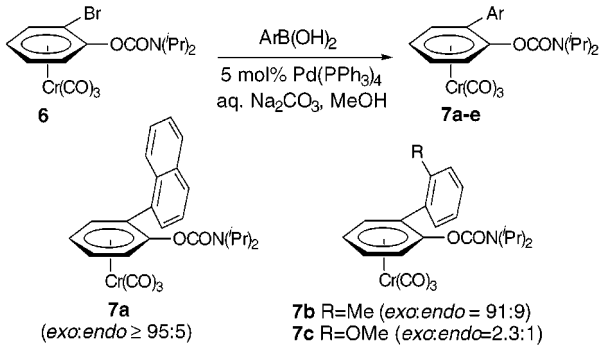
Scheme 3



ate **3** using the lithioamide **5** developed by Kündig and reaction of the resulting optically active aryllithium intermediate with 1,2-dibromo-1,1,2,2-tetrachloroethane afforded the optically active *o*-bromo carbamate **6** in 84% yield (62% ee) and 95−97% ee after a single recrystallization (48% overall yield).[4,5] This reaction sequence defines the optically active Cr[arene] ligand scaffold with concomitant introduction of an easily interchanged ortho substituent.

The enantiomerically enriched *o*-bromo carbamate complex **6** provides a platform for accessing an array of ligand structures by exploiting bond constructions based on the activation and coupling of aryl halides. To maximize the dissymmetry within the targeted phosphine ligands, aryl residues were selected for coupling to the Cr[arene] fragment as a means of introducing substituents with well-defined spatial displacements. Thus, Suzuki coupling of bromide **6** with a series of aryl boronic acids was accomplished under the reaction conditions developed by Uemura (Scheme 4).[6]

Scheme 4



Chiral biaryl complexes incorporating aryl substituents possessing electron-donating (entry b) and electron-withdrawing groups (entry d) as well as ortho substitution (entries a−c) were obtained in 63−75% yield with complete retention of optical purity (Table 1). Chromium-arenes **7a**−**c** can adopt

Table 1. Suzuki Coupling and Phosphine S_NAr2 Reactions

entry	boronic acid	% yield **7** (%ee)[a,b]	% yield **9** [b]
a	$(1\text{-}C_{10}H_7)B(OH)_2$	75 (97)	87
b	$(o\text{-}CH_3C_6H_4)B(OH)_2$	63 (97)	75
c	$(o\text{-}CH_3OC_6H_4)B(OH)_2$	66 (95)	63
d	$(p\text{-}F\text{-}C_6H_4)B(OH)_2$	73 (95)	76
e	$C_6H_5B(OH)_2$	64 (95)	57

[a]Enantiomer ratios determined by HPLC (chiral Chiralcel OD-H column). [b]Reported yields are for chromatographically purified materials.

conformations placing the ortho substituent of the auxiliary aryl ring in an endo or exo orientation relative to the $Cr(CO)_3$ fragment. Placing the ortho substituents in the naphthyl (**7a**) and *o*-tolyl (**7b**) complexes adjacent to the metal fragment

(1) For examples of optically active monodentate phosphine ligands and their use in asymmetric catalysis, see: (a) Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Phillips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301−1303. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10−11. (c) Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 954−964. (d) Hayashi, T. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, Germany, 1995; p 105. (e) Hamada, Y.; Seto, N.; Ohmori, H.; Hatano, K. *Tetrahedron Lett.* **1996**, *37*, 7565−7568. (f) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Chem. Soc., Chem. Commun.* **1997**, 561−562. (g) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang X. *J. Am. Chem. Soc.* **1997**, *119*, 3836−3837. (h) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521−4523. (i) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681−1687. (j) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195−202 and references therein. (k) Dai, X. D.; Virgil, S. *Tetrahedron Lett.* **1999**, *40*, 1245−1248. (l) Graf, C. D.; Malan, C.; Harms, K.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 5581−5588.

(2) For syntheses of phosphine ligands incorporating η^6-Cr[arene] units, see: (a) Uemura, M.; Miyake, R.; Nishimura, H.; Matsumoto, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 213-216. (b) Hayashi, Y.; Sakai, H.; Kaneta, N.; Uemura, M. *J. Organomet. Chem.* **1995**, *503*, 143−148. (c) Ariffin, A.; Blake, A. J.; Li, W.-S.; Simpkins, N. S. *Synlett* **1997**, 1453−1455.

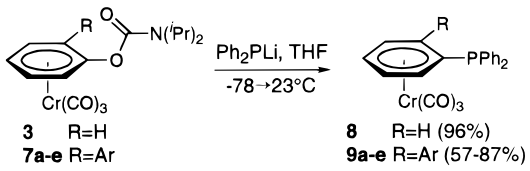
(3) For a review of syntheses of optically active Cr[arene] complexes, see: Bolm, C.; Muñiz, K. *Chem. Soc. Rev.* **1999**, *28*, 51−59.

(4) Kündig, E. P.; Quattropani, A. *Tetrahedron Lett.* **1994**, *35*, 3497−3500.

affords sufficient steric destabilization that the exo conformers predominate: exo:endo = ≥95:5 (**7a**), 91:9 (**7b**).[7] The *o*-anisyl complex **7c** is obtained as a 2.3:1 mixture of exo/endo conformers, suggesting that the methoxy substituent does not suffer especially severe steric interactions in the endo orientation.[8]

The completion of the phosphine synthesis was predicated on developing the means for transforming the arene carbamate functionality to the desired arylphosphine moiety. On the basis of the observation that chromium tricarbonyl complexation strongly activates coordinated arenes toward nucleophilic addition, we anticipated that this effect would allow successful S_NAr2 addition of phosphine nucleophiles with concomitant carbamate displacement.[9,10] To test this hypothesis, the achiral carbamate complex **3** was reacted with lithiodiphenylphosphine; standard reaction workup afforded the desired phosphine complex **8** as an air-stable crystalline solid in 96% yield (Scheme 5). In accord with this preliminary observation, efficient C−P bond construction was achieved by reacting the biaryl complexes **7a**−**e** with lithiodiphenylphosphine, providing the optically active monophosphine ligands **9a**−**e** in 63−87% yield (Table 1).[11] No erosion of the Cr[arene] optical purity is observed in the displacement reactions; phosphine complexes **9a**−**e** are obtained with enantiomer ratios directly reflecting the optical purity of the carbamate starting materials.

Scheme 5



3 R=H
7a-e R=Ar

8 R=H (96%)
9a-e R=Ar (57-87%)

Chromium tricarbonyl complexation to arene rings can impart dramatic electronic perturbations to both the coordinated aryl ring and the appended substituents.[9,12] To evaluate the effect these electronic properties have on metal coordination by the phosphinyl−Cr[arene] complexes, the X-ray crystal structure of the Pd(0) complex **10**, derived from phosphine **9a**, was determined. Thus, $[(\eta^3\text{-}C_3H_5)PdBr]_2$ was reacted with phosphine **9a** in CH_2Cl_2, with the resulting yellow crystalline product **10** affording the X-ray crystal structure depicted in Figure 1. The palladium−phosphorus bond length (2.33 Å) in **10** is nearly identical with that in the closely related $[\eta^3\text{-}(2\text{-}CH_3)C_3H_4]Pd(PPh_3)Cl$ complex (2.31 Å), suggesting that the $Cr(CO)_3$ fragment has relatively little impact on metal−phosphine bonding, with phosphine **9a** behaving much like a chiral variant of triphenylphosphine.[13] The crystal structure also provides insight into the

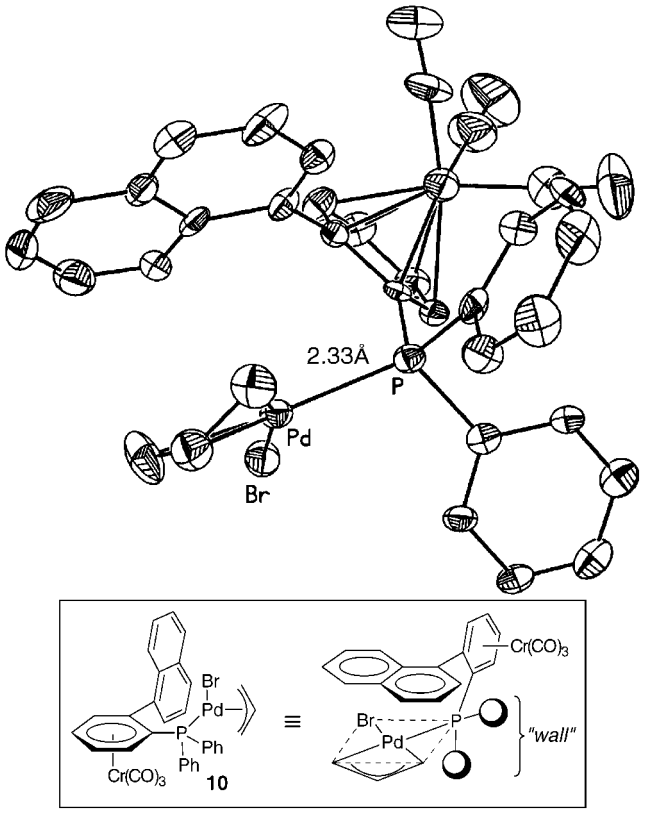


Figure 1. X-ray crystal structure of Pd^{II}[allyl] complex **10**.

(5) Arene **3** was reacted with the lithio amide **5** (1.02 equiv) in THF (0.3 M) at −78 °C. After the mixture was stirred for 2 h, a 0.13 M solution of 1,2-dibromotetrachloroethane (1.1 equiv) in Et_2O was added and the reaction mixture was warmed to ambient temperature. After 12 h, the reaction mixture was filtered through a silica gel pad and purified by column chromatography (hexanes/ethyl acetate). Recrystallization of the purified bromide (Et_2O/pentane) afforded **6** in ≥95% ee.

(6) (a) Uemura, M.; Nishimura, H.; Hayashi, T. *J. Organomet. Chem.* **1994**, *473*, 129−137. (b) Uemura, M.; Kamikawa, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2697−2698. (c) Watanabe, T.; Kamikawa, K.; Uemura, M. *Tetrahedron Lett.* **1995**, *36*, 6695−6698.

(7) The assignment of **7a**−**c** as adopting the thermodynamically favored exo conformation is consistent with the structure of related Cr[arene] complexes prepared under thermodynamic control; see: Uemura, M.; Nishimura, H.; Kamikawa, K.; Shiro, M. *Inorg. Chim. Acta* **1994**, *222*, 63−70. The conformation of the 1-naphthyl derivative **7a** was further established by X-ray crystal structure determination of the related phosphine complex **10**. See the Supporting Information for full details.

(8) The observed exo:endo ratio in **7c** appears to represent the ground-state conformer population, as the isomers can be interconverted at elevated temperatures while cooling reestablishes the original 2.3:1 ***exo***:endo ratio.

(9) Semmelhack, M. F. Nucleophilic Addition to Arene-Metal Complexes. In *Comprehensive Organic Synthesis*; Trost; B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 517−549.

(10) For an example of S_NAr2 reactions of chiral Cr[arene] complexes, see: Kamikawa, K.; Uemura, M. *Tetrahedron Lett.* **1996**, *37*, 6359−6362.

(11) Carbamates **7a**−**e** were reacted with the lithiodiphenylphosphine (2 equiv) in THF (0.16 M) at −78 °C. After the mixtures were stirred for 20 min, they were warmed to ambient temperature. After 12 h, the reaction mixtures were filtered through a silica gel pad and purified by column chromatography (hexanes/ethyl acetate). The optically active triarylphosphine complexes **9a**−**e** are highly crystalline, air-stable solids.

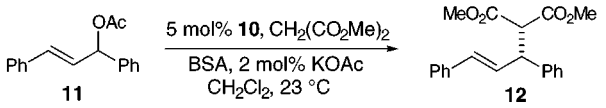
(12) (a) Davis, R.; Kane-Maguire, L. A. P. Chromium Compounds with η^2−η^8 Carbon Ligands. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1982; Vol. 3, pp 953−1077. (b) Morris, M. J. Arene and Heteroarene Complexes of Chromium, Molybdenum, and Tungsten. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 5, pp 471−549.

(13) Mason, R.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1966**, 26−28.

chiral environment created by the monodentate phosphine ligand with the planar naphthyl substituent shielding the "top" of the square-planar Pd(II) ion while the phosphine phenyl groups create a "wall" perpendicular to the metal ion's ligand plane. Furthermore, this ligand architecture is predicted to restrict conformational mobility about the Pd−P bond, as significant deviation from the solid-state conformation would induce considerable nonbonded interactions between the Pd fragment and the naphthyl or phosphine aryl residues.

Considering the structural information gained from the Pd(II)[allyl] complex **10**, reactions involving palladium−allyl intermediates emerged as logical platforms for assaying the effectiveness of these ligands in asymmetric catalysis.[14] To this end, the palladium(0)-catalyzed alkylation of allylic acetates was selected as a test reaction for evaluating the optically active triphenylphosphine surrogates.[15] The palladium(II) precatalyst was prepared by reacting $[(\eta^3\text{-allyl})\text{-PdBr}]_2$ with the naphthyl-substituted phosphine **9a** (0.6 equiv; phosphine:Pd(II) = 1.2:1) in CH_2Cl_2. The catalyzed alkylation of 1-phenylcinnamyl acetate **11** with dimethyl malonate was conducted using 5 mol % **10** under Trost's alkylation conditions (*N*,*O*-bis(trimethylsilyl)acetamide, KOAc) to afford the alkylated product **12** in 90% ee and 97% yield (Scheme 6).[16,17] Reaction times and enantioselection are nearly identical for reactions employing catalysts derived from 1:1.2 or 1:2 metal:ligand stoichiometry. This observation in conjunction with the X-ray structure of complex **10** strongly supports a Pd(0)−monophosphine complex as the catalytically active species in these reactions rather than a transient bisphosphine complex derived from disproportionation of **10**.

Scheme 6



Catalyst stoichiometry **9a** : Pd	%ee **12** (%y)
1.2:1	90 (97)
2.0:1	92 (89)

Chromium-complexed arylphosphines provide optically active equivalents of triarylphosphine ligands that are ubiquitious in late transition-metal chemistry and catalysis. The synthesis sequence described herein provides access to numerous structural analogues of the phosphine ligands from a single intermediate, the optically active bromide **6**. Investigations into the structural and reactivity properties of the metal complexes incorporating these monodentate phosphine ligands are expected to prove valuable in the design and development of new chiral monophosphine-derived catalysts.

Acknowledgment. The University of Pittsburgh and the National Science Foundation (Grant No. CHE-9875735) are gratefully acknowledged for support of this work.

Supporting Information Available: Experimental procedures, details of compound characterization, and X-ray data for **9c** and **10** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For asymmetric allylic substitution reactions catalyzed by monophosphine−palladium catalysts, see ref 1e,f,h−l.

(15) For reviews of catalyzed allylic substitution reactions, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355−364. (c) Helmchen, G, *J. Organomet. Chem.* **1999**, *576*, 203-214.

(16) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143−1145.

(17) Similar enantioselection is obtained in alkylation of **11** catalyzed by 5 mol % **10** employing the sodium salt of dimethyl malonate (86% ee).