Asymmetric Synthesis

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Catalytic Enantioselective Hydrogenolysis of [Cr(CO)$_3$(5,8-Dibromonaphthalene)]**

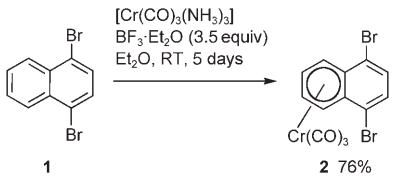
E. Peter Kündig, Piyali Datta Chaudhuri, David House, and Gérald Bernardinelli*

Highly enantiomerically enriched (η^6-arene)tricarbonylchromium(0) complexes whose chirality originates from the 1,2-disubstitution pattern of the arene and the coordination of the metal to one enantiotopic face of the arene are powerful chirons in asymmetric synthesis.[1] Robust, planar chiral arene complexes also increasingly find application as chiral ligands in asymmetric catalysis.[2]

Enantiomerically enriched arene complexes are accessible by both resolution and asymmetric synthesis. The latter method includes diastereoselective complexation, diastereoselective or enantioselective nucleophilic addition/hydride abstraction, and diastereoselective and enantioselective lithiation/electrophile addition.[1] While these approaches are potent methods that often give the target complexes in high enantiomeric purity, they rely on the use of stoichiometric quantities of chiral information and the diastereoselective methods often require additional steps for the introduction and the removal of chiral auxiliaries. A potentially very attractive catalytic route is the desymmetrization of *meso*-complexes by a chiral catalyst. In pioneering studies, Uemura, Mishimura, and Hayashi reported palladium-catalyzed asymmetric cross-coupling reactions of alkenyl metal and aryl metal compounds with [Cr(CO)$_3$(1,2-dichlorobenzene)].[3] A palladium-catalyzed Miyaura–Suzuki coupling reaction using a chiral bidentate ferrocene ligand ((*S*,*R*)-1-[1-(dimethylamino)ethyl]-2-(diphenylphosphino)ferrocene ((*S*,*R*)-PPFA) afforded the biaryl complex in 55% yield with 69% *ee*. More recently, a very similar level of induction and yield was reported for a methoxycarbonylation of the same substrate (47% yield, 63% *ee*).[4a] In this particular reaction, kinetic resolution in the second step allowed the isolation of the highly enantiomerically enriched product (95% *ee*) in 31% yield. Bidentate ferrocenyl ligands again were the best performers in this as well as in analogous reactions of [Cr(CO)$_3$(2,6-dichlorotoluene)].[4b] To complete the short list of precedents of asymmetric desymmetrizations, a report by Kamikawa et al. appeared during the preparation of this manuscript. It describes an asymmetric intramolecular Heck reaction of [Cr(CO)$_3$(2,6-bisbutenyl chlorobenzene)] with the best results reaching 78% yield and 73% *ee*.[5] We conclude that despite considerable efforts, a highly asymmetric, high-yield desymmetrization of a *meso* arene complex has not yet been realized. Herein, we present the results of our studies to carry out such a transformation and show that this goal can be realized by using a new bulky phosphoramidite ligand.

We selected [Cr(CO)$_3$($\eta^{(1-4,4a,8a)}$-5,8-dibromonaphthalene)] (**2**; see Scheme 1) as the substrate and asymmetric hydrogenolysis as the reaction. A highly enantiomerically enriched planar chiral bromonaphthalene complex could be a valuable precursor for asymmetric synthesis,[6] for planar chiral ligands,[2] and as a chiral {Cr(CO)$_3$}-transfer agent.[7] To our knowledge, desymmetrization of *meso* dihalides by asymmetric hydrogenolysis has not been reported. We were aware that by choosing a naphthalene complex we compounded the problem because of the lability of the metal–arene bond in this class of compounds.[1b]

Dibromonaphthalene complex **2** was obtained as a single regioisomer in 76% yield by treating [Cr(CO)$_3$(NH$_3$)$_3$] with $BF_3{\cdot}OEt_2$ in the presence of the arene **1** (Scheme 1). This mild and high-yielding procedure[8] avoids insertion of a zero-valent {Cr(CO)$_n$} fragment into the aryl–bromine bond, a process that results in the decomposition of the starting materials.



1 **2** 76%

Scheme 1. Regioselective complexation of 1,4-dibromonaphthalene.

[*] Prof. Dr. E. P. Kündig, P. D. Chaudhuri, Dr. D. House
Department of Organic Chemistry
University of Geneva
30 Quai Ernest Ansermet, 1211 Geneva 4 (Switzerland)
Fax: (+41) 223-793-215
E-mail: Peter.Kundig@chiorg.unige.ch
Dr. G. Bernardinelli
Laboratory of Crystallography
University of Geneva
24 Quai Ernest Ansermet, 1211 Geneva 4 (Switzerland)

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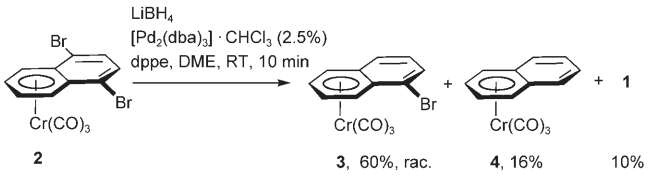
We next tested conditions for the palladium-catalyzed hydrogenolysis of one of the two C–Br bonds in complex **2**. Lewis bases readily cleave the naphthalene–chromium bond and this proved a major hurdle in this chemistry because it precluded the use of polar solvents or polar additives.[1b] We investigated sodium formiate and $NaBH_4$ as reducing agents in this reaction in combination with a number of palladium catalyst precursors ($Pd(OAc)_2/PPh_3$ or 1,2-ethanediylbis-(diphenyl)phosphine (dppe), $[Pd(PPh_3)_4]$) but found that in most of the solvents tested (DMF, acetonitrile, CH_2Cl_2, MeOH, toluene), decomplexation, induced by either the solvent or the formiate was faster than, or competitive with, arene–halide hydrogenolysis. Complex **2** is soluble and stable in toluene but hydrogenolysis with $NaBH_4$ in the presence of $[Pd(PPh_3)_4]$ was hampered by the low solubility of the reducing agent and resulted in an exceedingly slow reaction (2–3 days at 30 °C) even with 10–15 mol % catalyst. Worse, the yield of the sought after monobromonaphthalene complex **3** never exceeded 20 % of the final mixture, with 1,4-dibromonaphthalene (**1**) and starting complex **2** still present in 32 % and 47 %, respectively, after 62 h. After much experimentation, and after switching to the much more soluble $LiBH_4$ and using dimethoxyethane (DME) as solvent and $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone) as catalyst, conditions were found that afforded the monobromonaphthalene complex **3** in reasonable yield as a racemic mixture (Scheme 2). While over reduction to give **4** was a

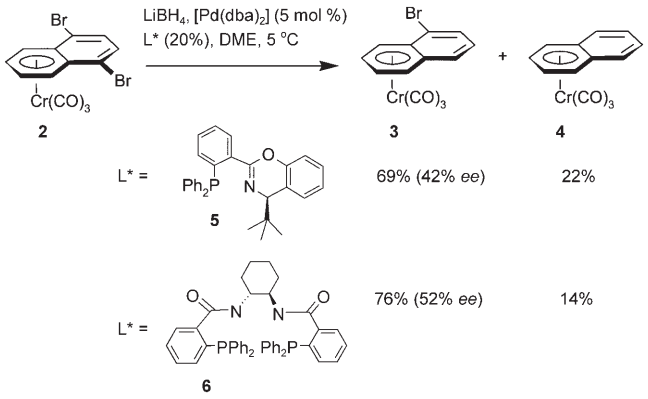


Scheme 2. Palladium-catalyzed hydrogenolysis of an aryl C–Br bond to give a racemic mixture of **3** in reasonable yield.

problem in this reaction, we hoped that with an efficient chiral catalyst the reaction would stop after one of the enantiotopic C–Br units had been converted into a C–H unit.

Initially asymmetric reactions were carried out by stirring $[Pd(dba)_2]$ (5 mol %), chiral ligand (2 equiv), and a small quantity of phenanthrene (HPLC calibration) in DME at 5 °C under N_2 for 10 min and subsequent sequential addition of complex **2** and $LiBH_4$ as solids. The reaction was monitored by chiral HPLC (Chiralcel ODH column). The ferrocenyl ligands that had worked best with $[Cr(CO)_3$(1,2-dichlorobenzene)$]$[3,4] afforded **3** with less than 20 % *ee*. Subsequently, a large number of chiral bidentate ligands were screened. These included ligands from the Solvias-kit,[9] Binap, DuPhos, Phox and analogues, and many others.[10] While it was satisfying to note that yields of **3** with some ligands reached 80 %, chiral induction remained low. Of all the ligands tested, only two, **5**[11] and **6**[12] afforded **3** with an enantioselectivity exceeding 40 % (Scheme 3).

Checking if incomplete dba dissociation in $[Pd(dba)_2]$ was part of the problem, we turned to [CpPd(allyl)][OTf] (Cp = C_5H_5, OTf = $CF_3SO_3^-$) as catalyst precursor.[13] Unfortunately this brought no improvement. Leaving the reaction to proceed further and to yield substantial amounts of the naphthalene complex **4** gave no improvement of the *ee* value of **3**, thereby indicating that the second hydogenolysis takes place without kinetic resolution.



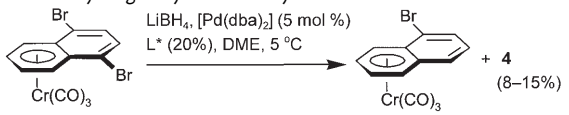
Scheme 3. The two best results in palladium-catalyzed asymmetric hydrogenolysis of an aryl-Br bond using chiral bidentate ligands (L*) are obtained with **5** and **6**.

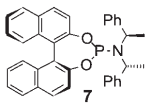
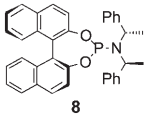
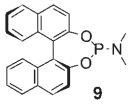
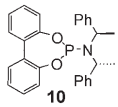
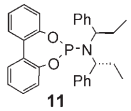
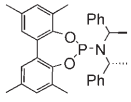
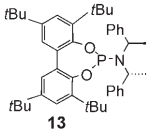
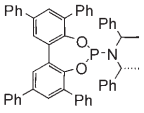
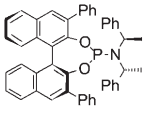
Although good yields were obtained, at this stage our work just reinforced the message of earlier work, that this transformation yields products with low to modest asymmetric induction.[3–5] We therefore decided to turn our attention to chiral monodentate phosphoramidite ligands.

We were pleased to find that phosphoramidite ligand **7**[14] (Table 1, entry 1) afforded complex **3** in good yield and a better enantiomeric purity than achieved with the bidentate ligands. Increasing the ligand equivalents brought no improvement whereas reducing the amount of ligand led to a decrease in *ee* value. The diastereomeric ligand **8** made the reaction sluggish and also afforded **3** in racemic form (Table 1, entry 2). Ligands **9** (entry 3) and **10** (entry 4) showed that the absence of one of the two chiral elements of the ligands leads to a serious erosion of chiral induction. Ligand **11** was tested because it outperforms **10** in the copper-catalyzed conjugate addition of diethyl zinc to enones.[15] However, as the result in entry 5 shows, this is not the case in the reaction at hand. Substitution in the 3,3′ position of the biaryl portion of ligand **11** by alkyl groups brought an increase from 38 % *ee* (entry 4) to a respectable 64 % *ee* and 66 % *ee* (entries 6 and 7). The breakthrough came with the 3,3′-phenyl substituted ligand **14**[15] (entry 8) with which the reaction approached 90 % *ee* for the first time. Returning to the chiral binaphthyl motive with the new phosphoramidite ligand **15**,[16] chiral induction was raised to 92 % *ee*. Optimization, by lowering the temperature and by adding $LiBH_4$ dropwise as a solution, finally yielded the result given in entry 9.[17]

Racemic **3** was subjected to the same conditions and the reaction was followed by chiral HPLC analysis. As with the bidentate ligands, no kinetic resolution was observed, that is, the residual **3** remained racemic. The chiral induction in the reaction depicted in Table 1 thus arises entirely from the recognition of one of the enantiotopic C–Br units in complex **2**.

Table 1: Chiral phosphoramidite ligands in the palladium-catalyzed asymmetric hydrogenolysis of an aryl-Br bond.[a]



Entry	Ligand	*pR*-**3** yield [%]	*ee* [%]
1	 **7**	78	62
2	 **8**	62	rac.
3	 **9**	60	22
4	 **10**	74	38
5	 **11**	78	18
6	 **12**	78	64
7	 **13**	80	66
8	 **14**	79	89
9	 **15**	80 78[b] (65)[c]	92 97[b]

[a] All yields determined by HPLC (calibration: phenanthrene). [b] Conditions: −10 °C, 35 min, $LiBH_4$ added as solution, see Experimental Section for full details. [c] Yield of *pR*-**3** isolated after chromatography.

All the reactions shown in Table 1 afforded the dextrorotatoy enantiomer as the major product (see Experimental Section). The absolute configuration (*pR*) was assigned by an X-ray structure determination (Figure 1).[18]

The final catalytic step in this reaction is likely to involve a reductive elimination of a *cis*-{Pd(aryl)(H)} moiety. Models show that it is unlikely that two of the very bulky chiral phosphoramidite units are coordinated to the metal in a *cis*-fashion at this stage. Further studies will be required to probe the mechanism and the scope of this reaction.

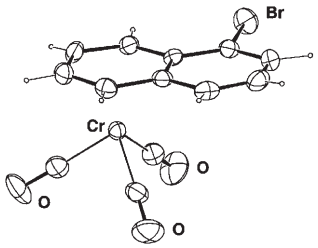


Figure 1. ORTEP view of the crystal structure of compound *pR*-**3**. Thermal ellipsoids are set at 40% probability.

Herein we show the dominant role that ligands play in governing both rates and selectivities of asymmetric reactions. The unusual application in asymmetric hydrogenolysis opens the door to a range of new applications of planar chiral arene complexes. Complex *pR*-**3** promises to be an attractive starting material for further transformations.

Experimental Section

2: $[Cr(CO)_3(NH_3)_3]$ (2.89 g, 15.5 mmol) and **1** (4.00 g, 15.5 mmol) were combined in a Schlenk tube. Dry diethyl ether (60 mL) was added followed by boron trifluoride etherate (6.9 mL, 6.11 g, 55 mmol) and the reagents were thoroughly degassed with four freeze-pump-thaw cycles. After approximately 1 h the yellow suspension began to turn red. Stirring was continued for five days at room temperature and the reaction mixture was then filtered through a pad of celite washing with small portions of toluene until all of the red material (filtrate) had been collected. The solid-liquid interface was stirred frequently with a glass rod to facilitate the filtration process. The solvent was removed under reduced pressure. The dark red solid was dried thoroughly under vacuum and transferred to a small flask. Residual **1** was removed by sublimation (heating to 60–70 °C at 0.2 mmHg). Compound **2** was obtained as a deep red solid (4.50 g, 76%), m.p. 128–132 °C (decomp); IR: $\tilde{\nu}=(CH_2Cl_2)$ 1969, 1898 cm^{-1}. ^1H NMR (400 MHz; C_6D_6): $\delta = 6.68$ (2H, s), 5.91–5.88 (2H, m, $H_{AA'}H_{BB'}$), 4.58–4.55 ppm (2H, m, $H_{AA'}H_{BB'}$); ^{13}C NMR (101 MHz; $CDCl_3$): $\delta = 230.2$ (CO), 130.7, 122.3 (C quaternary), 104.6 (C quat.), 91.7, 88.4 ppm; UV (λ_{max} nm; CH_2Cl_2) 358, 295, 234; MS *m*/*z* (EI) 424 (2%, $[M^+]$, $2\times{}^{81}Br$), 422 (3, $[M^+]$, $^{79}Br+{}^{81}Br$), 420 (2, $[M^+]$, $2\times{}^{79}Br$), 288 [3, $[M-Cr(CO)_3]$, $2\times{}^{81}Br$], 286 [6, $[M-Cr(CO)_3]$, $^{79}Br+{}^{81}Br$], 284 [3, $[M-Cr(CO)_3]$, $2\times{}^{79}Br$), 126 (62, $[C_{10}H_6^+]$), 52 (100, [Cr]); HRMS(EI) (Found: $[M^+]$, 423.8049. $C_{13}H_6CrO_3{}^{81}Br_2$ calcd: *M*, 423.8048).

pR-**3** (optimized, Table 1, entry9): Under N_2 (S_a*R*,*R*)-**15** (248 mg, 0.36 mmol) was added at room temperature to a solution of $[Pd(dba)_2]$ (54 mg, 0.09 mmol) in freshly distilled, dry and degassed DME (20 mL) in a Schlenk reaction vessel. The mixture was stirred for 30 min at room temperature and then cooled to −10 °C. Then **2** (750 mg, 1.8 mmol) was added at the same temperature. A freshly prepared solution of $LiBH_4$ in DME (5.5 M in DME, 0.66 mL, 3.6 mmol) was diluted with DME (6.0 mL) at room temperature and then added by cannula over 10 min to the stirred reaction mixture maintained at −10 °C. Stirring was continued at −10 °C under N_2. Formation of **3** was monitored by thin layer chromatography (TLC) (pentane/toluene 3/1, $R_f = 0.3$). The reaction was stopped after 35 min and the reaction mixture was filtered over celite under N_2, and washed with dry DME. HPLC indicated **3** to be formed in a yield of 78%. The *ee* value (97%) was determined by chiral HPLC (Chiralcel-ODH, 0.5 × 20 cm, hexane:*i*PrOH, 95:5, 1 mL min^{-1}, 17 min:(*pR*-**3**); 32 min:((1*S*)-**3**). To isolate the bulk product silica gel was added to the

filtrate and solvent was evaporated. Chromatography (silica, pentane/toluene 3/1, column: OD 5 cm, length 15 cm) afforded p*R*-**3** as a bright red solid (395 mg, 1.15 mmol, 65%); m.p. 118–122 °C (decomp); $[\alpha]_D^{20} = (+)\ 401$ ($c = 0.12$ in $CHCl_3$); IR (methylcyclohexane): $\tilde{\nu} = 1969$, 1897 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): $\delta = 6.96$ (dd, $J = 7.3$, 1.0 Hz, 1H), 6.66 (d, $J = 8.5$ Hz, 1H), 6.32 (dd, $J = 8.5$, 7.3 Hz, 1H), 5.93–5.91 (m, 1H), 5.05–5.03 (m, 1H), 4.53–4.51 ppm (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 231.1$ (CO), 131.0, 127.9, 127.7, 123.2 (C quaternary), 106.0 (C quat.), 103.9 (C quat.), 91.8, 91.7, 89.4, 88.7 ppm; MS: *m*/*z* (%) 342 (4, $[M^+]$, ^{79}Br), 258 (21), 208 (5, $[M-Cr(CO)_3]$, ^{79}Br), 127 (5, $[C_{10}H_6^+]$), 52 (100, [Cr]); HRMS(EI) calcd for $C_{13}H_7CrO_3{}^{81}Br$: *M* 341.8984; found: $[M^+]$ 341.9027. Elemental analysis (%) calcd for $C_{13}H_7O_3CrBr$: C 45.51, H 2.06; found: C 45.71, H 2.32.

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[16] Ligand **15** was readily prepared from 3,3′diphenyl binaphthol, Whitesell amine, and PCl_3.

[17] The reaction is clean and affords the product in 78% yield and 97% *ee* as indicated by chiral HPLC. The major contaminants are **1** and **4**. On small scale reactions, column chromatography is the best way to purify **3**. The lability of naphthalene complexes causes a drop in yield to 65% of isolated **3** after chromatography. Efforts to scale up and use crystallization to overcome this problem are underway.

[18] Crystallographic data: Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. ($\lambda = 0.71073$ Å). Data were corrected for Lorentz and polarization effects and for absorption. The structures were solved by direct methods (SIR97),[19] all other calculations were performed with XTAL system.[20] $C_{13}H_7BrCrO_3$, $M_r = 343.1$, Orthorhombic, $P2_12_12_1$, $a = 9.0686$ (4), $b = 10.1876(4)$, $c = 27.0683(13)$ Å, $V = 2500.8(2)$ Å^3, $Z = 8$, $\mu = 4.11$ mm^{-1}, $d_x = 1.823$ $g\,cm^{-3}$, Flack parameter $x = -0.01(2)$, $R = 0.025$, $\omega R = 0.027$. Both molecules of the asymmetric unit show the same *pR* configuration. CCDC-277480 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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