Asymmetric Synthesis

Introduction of Multiple Elements of Chirality around an Aromatic Core and an Approach to Enantiomerically Pure C_3-Symmetric Ligands

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Nonracemic chiral ligands that possess planar chirality and C_2 and C_3 symmetry have delivered excellent results in the field of asymmetric catalysis.[1–4] In particular, the application of ligands that possess C_3 symmetry in asymmetric catalysis is currently attracting interest, despite the challenges associated with the synthesis of such ligands.[5–8] Having discovered a chiral-base-mediated reaction that efficiently generates a single stereogenic center,[9] we wondered whether this reaction could be used to generate multiple stereocenters in a one-pot reaction, and thus create ligands with some of the more synthetically challenging configurations that perform so well in asymmetric catalysis. The results of our study are presented herein, and their potential application in the field of ligand synthesis is illustrated by the synthesis of a C_3-symmetric

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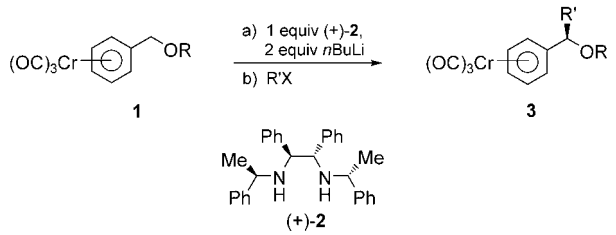
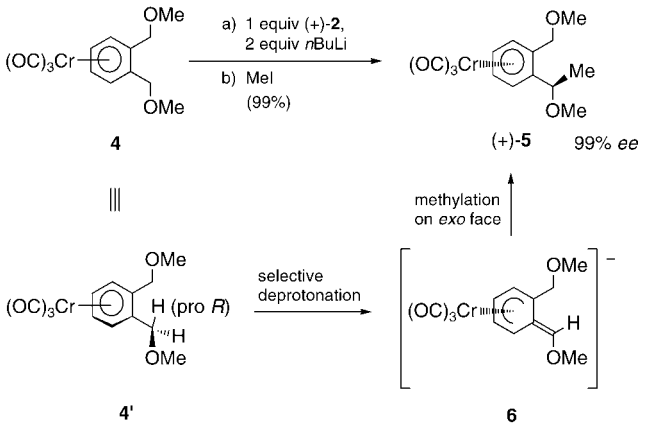
enantiomerically pure triphosphine and a C_3-symmetric enantiomerically pure tripyridine.

Tricarbonylchromium(0) complexes of alkyl benzyl ethers, such as **1**, give chiral ether complexes **3** in high yield and enantiomeric excess upon treatment with *n*-butyllithium and a chiral diamine **2** followed by an electrophile (Scheme 1).[9] The enantiomer (+)-(*R*,*S*,*S*,*R*)-**2**,[10] which is derived from (*R*)-α-methylbenzylamine, leads to an *R* configuration at the new stereocenter, presumably because the base will preferentially abstract the pro-*R* benzylic proton.



Scheme 1. Use of a chiral diamide to create a single stereocenter.

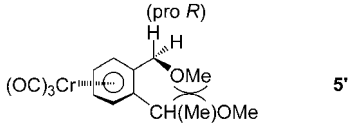
Our first experiment to determine whether this reaction could be used more than once on a single aromatic core was performed with a tricarbonylchromium(0) complex of a 1,2-disubstituted arene. As shown in Scheme 2, complex **4** was



Scheme 2. Creation of central and planar chirality by selective alkylation.

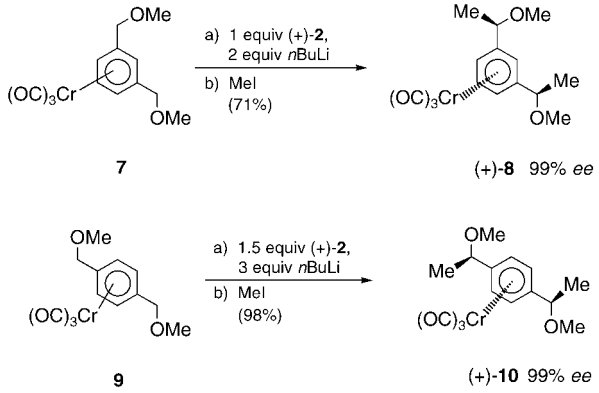
used with iodomethane as a model for the electrophile.[11] Reaction of **4** with one equivalent of diamine (+)-**2** (the *R*,*S*,*S*,*R* enantiomer) and two equivalents of *n*-butyllithium followed by quenching with iodomethane gave one monomethylated species in 99% yield and with 99% *ee*, as determined by HPLC analysis.[12,13]

The selective monomethylation of **4** can be explained as follows: first, it was assumed that the two methoxymethyl substituents adopt conformations that minimize their steric interactions. It was apparent that the pro-*R* proton in **4** (indicated in structure **4′**) is the most accessible of the four benzylic protons to the base because removal of benzylic protons is favored by an antiperiplanar relationship between the proton and the tricarbonylchromium(0) unit,[14] and the chiral base (*R*,*S*,*S*,*R* configuration) is known to selectively remove pro-*R* protons. Thus, deprotonation leads to anion **6**, which is subsequently methylated on its *exo* face (that is, antiperiplanar to the tricarbonylchromium(0) unit) to give the monomethylated product (+)-**5**. Further methylation is disfavored as the conformation that would place the remaining pro-*R* proton antiperiplanar to the tricarbonylchromium(0) unit gives rise to severe steric interactions between the two groups attached to the arene ring, as illustrated by structure **5′**. Thus, although the desired multiple selective alkylation did



not occur with this substrate, the chiral base did differentiate between the four hydrogen atoms and the monomethylation of the resulting anion generated an enantiomerically pure product with not only central chirality at one of the benzylic sites but also planar chirality that arises from the two different substituents on the chromium-complexed arene ring.

In contrast to the monomethylation described above, the treatment of complex **7**,[15] which is derived from 1,3-benzenedimethanol, with one equivalent of diamine (+)-**2** and two equivalents of *n*-butyllithium followed by quenching of the reaction with iodomethane gave a dimethylated product in 71% yield and with 99% *ee* (Scheme 3), as

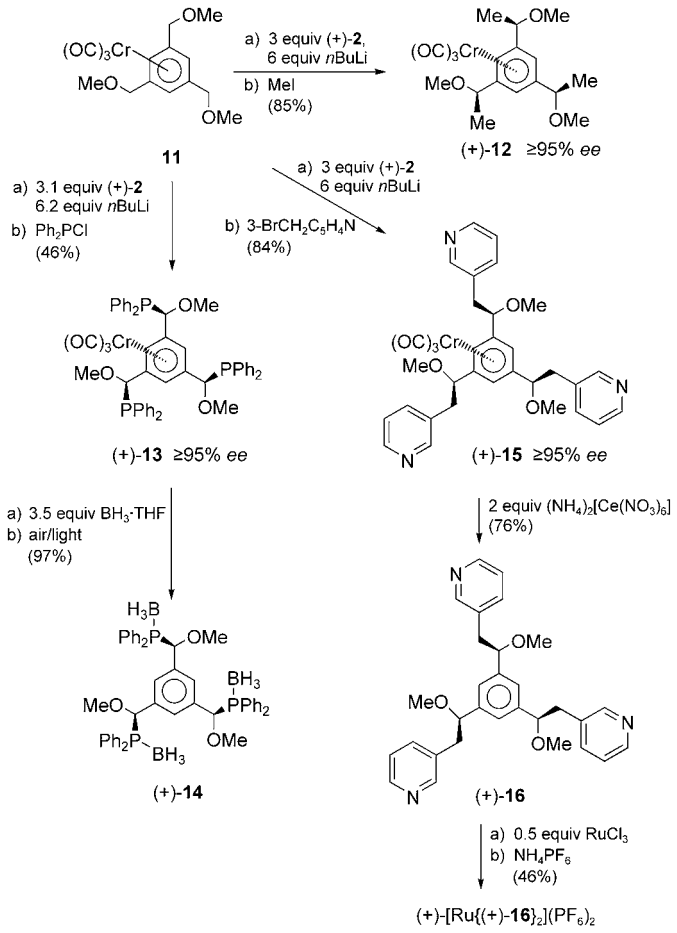


Scheme 3. Creation of two stereocenters by using a chiral diamide.

determined by HPLC analysis. In this case, the two pro-*R* hydrogen atoms can readily adopt an antiperiplanar relationship to the tricarbonylchromium(0) unit, so that both are cleanly removed by the chiral base. Quenching of the resulting dianion leads to the dimethylated product (+)-**8**. It was anticipated that the use of electrophiles that contain groups such as phosphines and subsequent removal of the tricarbonylchromium(0) unit (see below) would provide rapid access to enantiomerically pure C_2-symmetric pincer ligands.[16] The 1,4-disubstituted complex **9** behaved in a similar manner to the 1,3-disubstituted complex **7** (Scheme 3). In this case, the yield and the enantiomeric excess of the C_2-

symmetric product (+)-**10** were optimized by using 1.5 equivalents of diamine **2** and 3 equivalents of *n*-butyllithium.[17]

To determine whether three stereoselective alkylations could be carried out in a one-pot reaction, we turned our attention to the 1,3,5-trisubstituted complex **11**.[18] After optimization of the reaction conditions with the iodomethane quench, it was found that three chiral centers could be installed to give the complex (+)-**12** in good yield and with high enantioselectivity (Scheme 4).



Scheme 4. Creation of three stereocenters by using a chiral diamide.

To demonstrate the potential of the reactions described above for the preparation of structurally distinct ligands for application in asymmetric catalysis, we introduced phosphine and pyridine moieties into the electrophile and applied the resulting compounds to the most challenging reaction in which the model electrophile had been used: the trifunctionalization of **11**. Pleasingly, when chlorodiphenylphosphane was used as the electrophile in the reaction of **11**, the C_3-symmetrical triphosphine (+)-**13** was formed in reasonable yield and with high enantiomeric excess (Scheme 4 and Figure 1). Similarly, when the reaction was quenched with 3-bromomethylpyridine, the C_3-symmetric tripyridine (+)-**15** was prepared in very good yield and with high enantiomeric excess.[19] The subsequent oxidative removal of the tricarbonylchromium(0) unit proceeded smoothly to give enantiomerically pure products (+)-**14** and (+)-**16**. Heating (+)-**16** with $RuCl_3$ followed by anion exchange gave (+)-[Ru{(+)-**16**}$_2$](PF$_6$)$_2$, which is the first example of a structurally characterized chiral bis(tripyridyl)ruthenium complex (Figure 2).

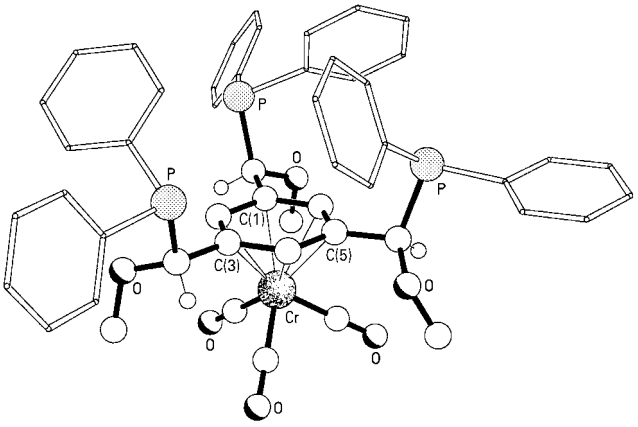


Figure 1. The molecular structure of (+)-**13**.[20]

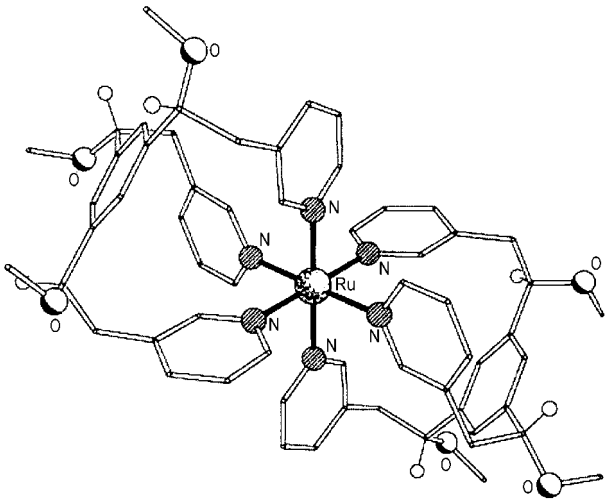


Figure 2. The molecular structure of (+)-[Ru{(+)-**16**}$_2$](PF$_6$)$_2$.[21]

In summary, we have demonstrated that chiral bases can be used to readily generate a range of stereochemical arrays around an aromatic core. Initial experiments reveal that replacement of the model electrophile that was used as a quench with other electrophiles that can introduce important donor groups, such as phosphanes and pyridines, leads to structurally distinct enantiomerically pure chiral ligands. Finally, the reactions described may also be applied to the synthesis of chiral cores of organometallic and organic dendrimers.

Experimental Section

(+)-**13**: *n*-Butyllithium (1.49 mL, 2.50 M in hexanes, 3.72 mmol, 6.2 equiv) was added dropwise to a stirred solution of diamine **2** (208 mg, 1.86 mmol, 3.1 equiv) in dry THF (100 mL) at −78 °C. The

solution was then allowed to warm to room temperature over a period of 30 min to allow the formation of a diamide. The resulting deep-red solution was cooled to −78 °C, and a solution of lithium chloride (80 mg, 1.86 mmol, 3.1 equiv; dried with a heat gun) in THF (10 mL) was added through a cannula. The reaction mixture was stirred for a further 5 min before a precooled solution (−78 °C) of **11** (208 mg, 0.6 mmol, 1.0 equiv) in THF (10 mL) was introduced dropwise through a short cannula. Stirring was continued for a period of 60 min before chlorodiphenylphosphane (0.99 mL, 5.4 mmol, 9.0 equiv) was added in one portion through a syringe. The reaction was then stirred for 1 h at −78 °C followed by a further 2 h at −40 °C before methanol (2 mL) was added and the solvent removed in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/diethyl ether, 99:1–90:10) afforded (+)-**13** (253 mg, 0.28 mmol, 47 % yield) as a yellow solid. The enantiomeric excess was determined by HPLC analysis (chiralcel OD-H; *n*-hexane/2-propanol, 99.6:0.4, 1.0 $cm^3 min^{-1}$, 330 nm); *S* enantiomer: t_R = 12.5 min (minor); *R* enantiomer: t_R = 20.6 min (major): ≥ 95 % *ee*; $[\alpha]_D^{20} = +226.9$ ($c = 0.67$, CH_2Cl_2); m.p. 155–157 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.43$ (s, 9H; OCH_3), 4.75 (d, $J = 4.7$ Hz, 3H; $CHPPh_2$), 5.54 (s, 3H; $C_{Cr}H$), 7.28–7.40 (m, 24H; PPh_2), 7.46–7.51 ppm (m, 6H; PPh_2); ^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 13.38$ ppm (PPh_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 61.0$ (OCH_3), 83.6 (d, J = 24 Hz; $CHPPh_2$), 89.8 (d, $J = 10$ Hz; $C_{Cr}H$), 107.2 (d, $J = 19$ Hz; $C_{Cr}CHPPh_2$), 128.3–128.5 (m; C_{Ar}), 128.9, 129.5 (C_{Ar}), 132.2 (d, J = 15 Hz; C_{Ar}), 133.2 (d, $J = 19$ Hz; C_{Ar}), 135.2 (d, $J = 20$ Hz; C_{Ar}), 135.9 (d, $J = 15$ Hz; C_{Ar}), 233.6 ppm (CO); IR ($\tilde{\nu}_{max}$, CH_2Cl_2): 1967 (CO), 1882 (CO) cm^{-1}; MS(FAB): *m*/*z* (%): 898 (72) [M^+], 814 (100) [M^+−3 CO], 629 (38) [M^+−3 CO−PPh_2]; elemental analysis (%) calcd for $C_{51}H_{45}O_6P_3Cr$ (898.833): C 68.15, H 5.05; found: C 68.15, H 4.96.

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[11] Complex **4** was synthesized in two steps by heating 1,2-benzenedimethanol with hexacarbonylchromium(0) (81 % yield) and then stirring the resultant complex with acidic methanol (90 % yield).
[12] A sample of (±)-**5** was prepared for HPLC analysis by the treatment of **4** with *tert*-butyllithium followed by iodomethane.[13] Treatment of **7**, **9**, and **11** with *tert*-butyllithium and an electrophile led to complex mixtures, so products (+)-**8**, (+)-**10**, (+)-**12**, (+)-**13**, and (+)-**15** were analyzed by using samples of their respective enantiomers prepared by using the chiral base derived from (−)-(*S*,*R*,*R*,*S*)-**2**.
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[15] Satisfactory spectroscopic (IR, ^{1}H NMR, ^{13}C NMR), low-resolution mass-spectrometric, and microanalytical data were obtained for the novel compounds **7**–**16**.
[16] Pincer complexes exhibit a rich and varied chemistry, but surprisingly little attention has been paid to the development of nonracemic chiral versions of these compounds; for reviews, see: a) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759–1792; b) M. Albrecht, G. van Koten, *Angew. Chem.* **2001**, *113*, 3866–3898; *Angew. Chem. Int. Ed.* **2001**, *40*, 3750–3781.
[17] HPLC analysis of products (+)-**8** and (+)-**10** from some experiments revealed small amounts (< 5 %) of the corresponding *meso* complexes.
[18] Complex **11** was synthesized in four efficient steps by esterification of the commercially available benzene-1,3,5-tricarboxylic acid with acidic methanol (99 %), reduction with $LiAlH_4$ (98 %), methylation with sodium hydride/iodomethane (99 %), and heating with hexacarbonylchromium(0) (98 %).
[19] Products (+)-**12**, (+)-**13**, (+)-**14**, (+)-**15**, and (+)-**16** were diastereoisomerically pure (determined by high-field NMR spectroscopic analysis) after isolation by column chromatography.
[20] Crystal data for (+)-**13**: $C_{51}H_{45}CrO_6P_3$, $M_r = 898.78$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 11.497(5)$, $b = 17.024(8)$, $c = 23.651(10)$ Å, $V = 4629(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.290$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 3.403$ mm^{-1}, $T = 293$ K, yellow plates; 4388 independent measured reflections, F^2 refinement, $R_1 = 0.060$, wR_2 = 0.149, 3294 independent observed absorption-corrected reflections ($|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 130°$), 479 parameters. The absolute structure of (+)-**13** was determined by a combination of *R*-factor tests ($R_1^+ = 0.0601$, $R_1^- = 0.0928$) and by use of the Flack parameter ($x^+ = 0.000(14)$). CCDC-246809 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
[21] Crystal data for (+)-[Ru{(+)-**16**}$_2$](PF$_6$)$_2$: $[C_{60}H_{66}N_6O_6Ru](PF_6)_2 \cdot 2CH_2Cl_2$, $M_r = 1528.05$, monoclinic, space group $P2_1$ (no. 4), $a = 10.5334(5)$, $b = 18.2106(8)$, $c = 17.6404(9)$ Å, β = 90.877(4)°, $V = 3383.4(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.500$ g cm^{-3}, $\mu_{MoK\alpha}$ = 0.524 mm^{-1}, $T = 173$ K, yellow shards; 21626 independent measured reflections, F^2 refinement, $R_1 = 0.108$, $wR_2 = 0.182$, 20273 independent observed absorption-corrected reflections ($|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 66°$), 838 parameters. The absolute structure of (+)-[Ru{(+)-**16**}$_2$](PF$_6$)$_2$ was determined by a combination of *R*-factor tests ($R_1^+ = 0.1075$, $R_1^- = 0.1091$) and by use of the Flack parameter ($x^+ = 0.11(4)$, $x^- = 0.89(4)$). CCDC-264307 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

