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Synthesis of fluoroalkyl-derivatised BINAP ligands

David J. Birdsall,[a] Eric G. Hope,[a] Alison M. Stuart,[a,*] Weiping Chen,[b] Yulai Hu[b] and Jianliang Xiao[b]

[a]*Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK*
[b]*Leverhulme Centre for Innovative Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK*

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Abstract—Fluoroalkyl-derivatised *R*-BINAP ligands have been prepared, characterised and applied in the ruthenium-catalysed asymmetric hydrogenation of dimethyl itaconate.

The attachment of long perfluoroalkyl chains to conventional ligand scaffolds has been widely utilised for the synthesis of ligand systems and metal-based catalysts compatible with supercritical CO_2 ($scCO_2$) and fluorous solvents.[1–6] However, there have been relatively few reports on the application of perfluoroalkylated chiral ligand systems. Notable examples include the epoxidation of alkenes with fluorous chiral salen manganese complexes,[7] the asymmetric alkylation of aromatic aldehydes using fluorous BINOL titanium alkoxides,[8] the asymmetric protonation with a BINOL-related perfluoroalkylated chiral diol[9] in the fluorous phase, and asymmetric hydroformylation in $scCO_2$ using a perfluoroalkylated-BINAPHOS derivative.[10] Although asymmetric hydrogenation with metal–BINAP complexes is one of the most extensively used reactions in synthesis, fluoroalkylated BINAP ligands have not appeared in the literature. In the examples above, the direct influence of the perfluoroalkyl substituents on the reactivity and enantioselectivity has not been unequivocally established, since spacer units are often incorporated into the ligands in an attempt to ameliorate the powerful electron withdrawing influence of the perfluoroalkyl substituents. However, we have established from a comparison of derivatised and underivatised ligands in the rhodium-catalysed hydrogenation of styrene[11] and Gladysz et al. from the variations in ν(CO) with perfluoroalkyl-derivatised phosphine ligands in *trans*-[IrCl(CO)L_2] (L = phosphine)[12] and from basicity studies of perfluoroalkyl-derivatised amines,[13] that it is virtually impossible to completely eliminate the electronic effect arising from incorporation of these fluorinated chains. Consequently, we thought that it would be interesting to prepare fluoroalkylated BINAP ligands that may find applications in asymmetric transformations in $scCO_2$ and fluorous solvents and allow the electronic effect of the fluoroalkyl tails to be determined. We report herein the synthesis of two fluoroalkylated BINAP ligands and a preliminary evaluation of these ligands in asymmetric hydrogenation in conventional organic solvents.

Our groups have recently developed two simple, efficient routes to perfluoroalkylated aryl phosphines.[14,15] The direct attachment of a C_6F_{13} group to the aryl ring is available via a copper-mediated cross coupling reaction between a perfluoroalkyl iodide and an aryl iodide or bromide,[14,15a] whilst the incorporation of an additional C_2H_4 spacer group (i.e. attachment of a $C_2H_4C_6F_{13}$ group) is possible via a Heck coupling of aryl halides with $CH_2{=}CHC_6F_{13}$, followed by reduction of the resultant double bond.[15b] We have applied both of these methodologies to the derivation of the protected (*R*)-6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl for the preparation of the fluoroalkylated BINAP ligands **3** and **4** (Scheme 1). The copper-mediated perfluoroalkylation of (*R*)-6,6′-dibromo-2,2′-diacetoxy-1,1′-binaphthyl, derived from 6,6′-dibromo-1,1′-bi-2-naphthol and acetic anhydride, with perfluorohexyl iodide was performed in C_6H_5F–DMSO (1:1) at 80°C for 72 h to give (*R*)-6,6′-bis(perfluorohexyl)-2,2′-diacetoxy-1,1′-binaphthyl in 99% yield.[16] Following hydrolysis the perfluoroalkylated (*R*)-binaphthol **1** was obtained in 89% overall yield. The Heck reaction of (*R*)-6,6′-dibromo-2,2′-dibenzyloxy-1,1′-binaphthyl with 1*H*,1*H*,2*H*-perfluoro-1-octene was completed in 24 h at 125°C.[15c] Following hydrogenation catalysed by Pd/C

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* Corresponding author. Tel.: 0116 252 2136; fax: 0116 252 3789; e-mail: amc17@le.ac.uk

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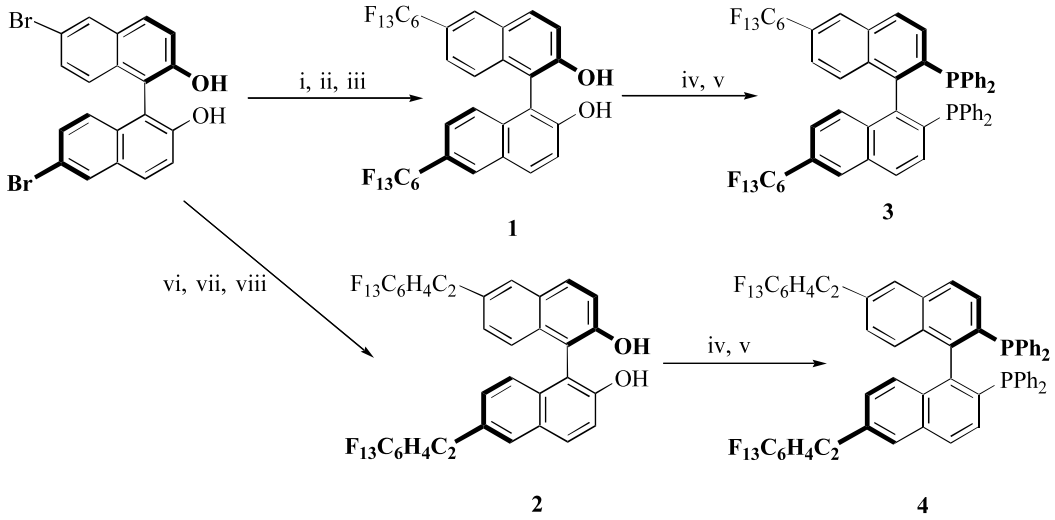

Scheme 1. (i) Ac_2O, Et_3N, DMAP, DCM; (ii) $C_6F_{13}I$, Cu, bipy, DMSO, C_6H_5F, 80°C, 72 h; (iii) NaH, MeOH; (iv) $(CF_3SO_2)_2O$, py, DCM, 0°C, 4 h; (v) $NiCl_2$(dppe), Ph_2PH, DABCO, DMF, 110°C, 74 h; (vi) BnCl, K_2CO_3, acetone; (vii) $CH_2{=}CHC_6F_{13}$, NaOAc, palladacycle, DMF, 125°C, 24 h; (viii) 10% Pd/C, EtOAc, H_2 (30 bar), rt, 16 h.

to reduce the double bonds and deprotect at the same time, the fluoroalkylated (*R*)-binaphthol **2** was obtained in 86% overall yield. The phosphination of **1** and **2** was conducted according to a literature method developed for non-fluoroalkylated binaphthols. The perfluoroalkylated binaphthol **1** was treated with triflic anhydride in the presence of a base[17] to form the chiral ditriflate, which was then reacted with diphenylphosphine, [$NiCl_2$(dppe)] and DABCO[18] to give the perfluoroalkylated (*R*)-BINAP ligand **3** in 48% yield.[19] The same reaction involving **2** led to the isolation of **4** in 85% yield. The higher yield with **2** is probably an indication of the influence of the additional C_2H_4 units on the P–C coupling step of the synthesis. The resultant off-white solids were characterised by a combination of elemental analysis and multinuclear NMR. The ^{19}F NMR spectra revealed the anticipated six mutually-coupled multiplets and the $^{31}P\{^1H\}$ NMR spectra revealed singlets at −13.5 and −15.4 ppm, respectively.

To test if the fluorous BINAP ligands **3** and **4** are capable of asymmetric induction and if the CH_2CH_2 spacers are necessary for high activity and enantioselectivity, we first carried out the asymmetric hydrogenation of dimethyl itaconate in CH_3OH. The catalysts Ru-**3** and Ru-**4** were prepared from the reaction of [$RuCl_2$(benzene)]$_2$ with **3** and **4** in DMF, respectively, according to a method designed by Noyori.[20] The hydrogenation reaction was carried out at ambient temperature under 20 bar H_2 in CH_3OH for 15 min (substrate/catalyst = 2000, 1.0 μmol of catalyst,[20] 2 mL solvent). For comparison, the same hydrogenation was also performed with Ru-(*R*)-BINAP. The conversions with Ru-**3**, Ru-**4** and Ru-(*R*)-BINAP were 42, 83 and 88%, respectively, while the ee values with the three catalysts were 95.3, 95.7, and 95.4%, with the *S* enantiomer dominating the product in each case.[21] Clearly, fluorous ponytails impose no detectable effects on the enantioselectivity of prochiral olefins such as dimethyl itaconate, but affect the rates of the hydrogenation, as can be judged by the excellent ees obtained with the three ligands and the lower conversion observed with Ru-**3**. These results indicate that the electronic effects arising from 6,6′-fluoroalkylation of BINAP only impact on the hydrogenation activity of the Ru-BINAP catalysts. Electronic effects have been shown to play an important role in a number of asymmetric catalytic reactions including hydrogenation.[22]

In conclusion, the synthesis of perfluoroalkylated-derivatives of BINAP, potential ligands for asymmetric catalysis in $scCO_2$ and fluorous solvents, has been achieved using established methodologies. The application of these ligands in the ruthenium-catalysed hydrogenation of dimethyl itaconate in methanol establishes that fluorous ponytails can impose significant effects on the hydrogenation activity (the more electron withdrawing the ponytails the less active the catalysts), but not on the enantioselectivity. We will report the scope and application of these ligands for asymmetric induction in $scCO_2$ in due course.

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16. A typical procedure is given for (*R*)-6,6′-bis(perfluorohexyl)-2,2′-diacetyloxy-1,1′-binaphthyl: A mixture of (*R*)-6,6′-dibromo-2,2′-diacetoxy-1,1′-binaphthyl (4.0 g, 7.57 mmol), perfluorohexyl iodide (10.13 g, 22.8 mmol), copper powder (2.94 g, 45.4 mmol), 2,2′-bipyridine (0.240 g, 1.5 mmol), C_6H_5F (75 ml) and DMSO (75 ml) was stirred for 72 h at 80°C. After cooling to room temperature, the reaction mixture was diluted with water (200 ml) and DCM (300 ml), and filtered. The organic layer was separated, washed with water (5×100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting green solid was extracted using perfluoro-1,3-dimethylcyclohexane (50 ml) and the solvent removed in vacuo. Azeotropic distillation from DCM yielded the title compound as an off-white solid (7.60 g, 99%). ^{1}H NMR ($CDCl_3$): δ 1.90 (6H, s), 7.30 (2H, d, J=8.9 Hz), 7.45 (2H, d, J=8.9 Hz), 7.59 (2H, d, J=8.9 Hz), 8.15 (2H, d, J=8.9 Hz), 8.25 (2H, bs). ^{19}F{^{1}H} NMR ($CDCl_3$): δ −81.21 (6F, m), −110.67 (4F, m), −121.87 (8F, m), −123.19 (4F, m), −126.54 (4F, m).
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19. A typical procedure is given for (*R*)-6,6′-bis(perfluorohexyl) - 2,2′ - bis(diphenylphosphino) - 1,1′ - binaphthyl: A solution of $NiCl_2$(dppe) (0.133 g 0.25 mmol) and Ph_2PH (0.58 g, 3.14 mmol) in DMF (50 ml) was heated to 100°C for 30 min when DABCO (1.129 g, 10.0 mmol) and a DMF solution (40 ml) of (*R*)-6,6′-bis(perfluorohexyl)-2,2′-ditriflate-1,1′-binaphthyl (3.00 g, 2.51 mmol) were added. The resulting green solution was stirred at 110°C for 2 h before an additional portion of Ph_2PH (0.58 g, 3.14 mmol) was added and the heating was continued for a further 72 h. After cooling the reaction mixture to room temperature, DMF was removed by distillation. The resulting brown solid was stirred for 30 min in methanol (30 ml), filtered, washed with methanol and dried in vacuo before being recrystallised from DCM and methanol (1.53 g, 48%). Anal. calcd for $C_{56}H_{30}F_{26}P_2$: C, 53.42; H, 2.38; found C, 52.76; H, 2.35%. ^{1}H NMR ($CDCl_3$): δ 6.65 (2H, d, J=8.9 Hz), 6.85 (2H, d, J=8.9 Hz), 7.02 (8H, m), 7.25 (12H, m), 7.59 (2H, d, J=8.5 Hz), 8.00 (2H, d, J=8.5 Hz), 8.10 (2H, s). ^{31}P{^{1}H} NMR ($CDCl_3$): δ −13.5. ^{19}F{^{1}H} NMR ($CDCl_3$): δ −81.19 (6F, m), −110.67 (4F, m), −121.79 (8F, m), −123.17 (4F, m), −126.50 (4F, m). $[\alpha]_D$=+104 (benzene, *c* 0.1).
(*R*) - 6,6′ - Bis(1*H*,1*H*,2*H*,2*H* - perfluoro - 1 - octyl) - 2,2′ - bis-(diphenylphosphino)-1,1′-binaphthyl was prepared similarly in 85% yield. Anal. calcd for $C_{60}H_{38}F_{26}P_2$. CH_2Cl_2: C, 52.33; H, 2.89; P, 4.42; found C, 52.81; H, 2.81; P, 4.87%. ^{1}H NMR ($CDCl_3$): δ 2.37 (4H, m), 2.95 (4H, m) 6.68 (2H, d, J=8.9 Hz), 6.72 (2H, d, J=8.9 Hz), 7.10 (12H, m), 7.18 (8H, m), 7.41 (2H, d, J=8.5 Hz), 7.64 (2H, s), 7.83 (2H, d, J=8.5 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ −15.4. ^{19}F{^{1}H} NMR ($CDCl_3$): δ −81.22 (6F, m), −114.97 (4F, m), −122.27 (4F, m), −123.26 (4F, m), −123.92 (4F, m), −126.52 (4F, m). $[\alpha]_D$=+169 (benzene, *c* 0.1).
20. Ru-**3** and Ru-**4** are probably structurally similar to [$RuCl_2$(BINAP)$(DMF)_2$] or its polymeric form. For details of preparation, see: Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163.
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