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Palladium-catalysed asymmetric allylic alkylation in the presence of a chiral 'light fluorous' phosphine ligand

Marco Cavazzini,[a] Gianluca Pozzi,*[a] Silvio Quici,[a] David Maillard[b] and Denis Sinou*[b]

[a] *Centro CNR Sintesi e Stereochimica di Speciali Sistemi Organici, via Golgi 19, 20133 Milano, Italy. E-mail: gianluca.pozzi@unimi.it; Fax: +39 02 2663354; Tel: +39 02 2663354*

[b] *Laboratoire de Synthèse Asymétrique, UMR UCBL/CNRS 5622, Université Claude Bernard Lyon 1, 43, boulevard du 11 novembre 1918, 69622 Villeurbanne, France. E-mail: sinou@univ-lyon1.fr; Fax: +33 04 72448160; Tel: +33 04 72446263*

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The easily accessible, enantiopure (*R*)-(+)-2-diarylphosphino-2′-alkoxy-1,1′-binaphthyl 1 bearing three fluorous ponytails is an efficient ligand in the palladium-catalysed asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate affording chiral products of up to 87% ee.

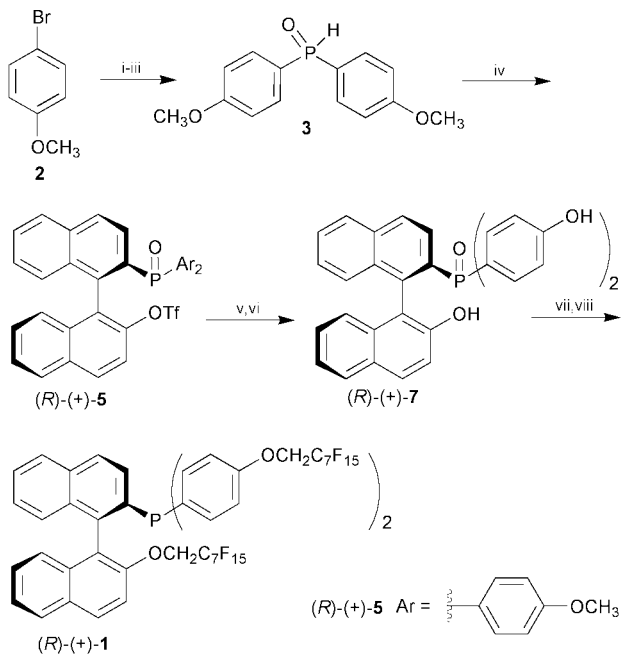
The advantages brought about by the use of CO_2 (supercritical or compressed) or fluorinated solvents in catalytic reactions are well-documented.[1,2] These novel reaction media offer the possibility of cleaner technology for the chemical industry, and might also promote reactions that are not attainable in common organic solvents, along with selectivity improvements related to the unique solvation environment.[3] In both cases, good solubility of the catalyst in the peculiar reaction medium is a major requirement. To reach this goal, several ligands featuring long-chain perfluoroalkyl substituents ('fluorous ligands') have been synthesized,[4] including a few examples of chiral compounds.[5] Indeed, the presence of long-chain perfluoroalkyl substituents increases the affinity of an organometallic compound both for CO_2 and perfluorocarbons. In the latter case, an increasing body of literature data indicates that only a fluorine content of at least 60% can ensure the very high partition coefficients required for the application of the original fluorous biphase strategy.[6] In order to circumvent this limitation, new fluorous techniques have been recently proposed, based on the recovery of fluorinated molecules by liquid–liquid or solid–phase extraction.[7] This makes 'minimally' or 'light' fluorous reagents and catalysts (*i.e.* compounds with a fluorine content below 60%) potentially useful for small-scale and discovery-oriented research.[8]

As phosphorous-based ligands are extensively used in catalytic reactions, many efforts have been devoted to the synthesis of their fluorous analogues.[1,9] However, such enantiopure compounds are not easily available yet.[10] Here we describe the simple synthesis of a fluorous chiral phosphine, namely (*R*)-(+)-2-{bis[4-(1*H*,1*H*-perfluorooctyloxy)phenyl]phosphino}-2′-(1*H*,1*H*-perfluorooctyloxy)-1,1′-binaphthyl (*R*)-(+)-**1**, a new member of this restricted family of compounds.†

Palladium-catalysed coupling of bis(aryl) phosphonic acids with commercially available (*R*)- or (*S*)-1,1′-bi-2-naphthol bis(trifluoromethanesulfonate) provides an easy access to optically pure 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyls.[11] Leitner and Franciò took advantage of this versatile reaction in the synthesis of a chiral phosphine/phosphite ligand bearing two $-(CH_2)_2C_6F_{13}$ ponytails, structurally similar to (*R*,*S*)-BINAPHOS.[10] The introduction of the perfluoroalkyl substituents required the use of a properly functionalised bis(aryl) phosphonic acid at an early stage of the synthesis. In order to increase the flexibility of this approach, we decided to postpone the introduction of perfluorinated residues. This allows the insertion of the required perfluoroalkyl chains onto a preformed ligand structure, thus increasing the number of possible locations. The synthesis of enantiopure (*R*)-(+)-**1** is outlined in Scheme 1.

Bis(4-methoxyphenyl)phosphonic acid **3**, obtained from the corresponding *para*-substituted aryl bromide **2** according to a literature procedure,[12] allowed the easy monophosphinylation of the commercially available (*R*)-(−)-1,1′-bi(2-naphthol) bis(trifluoromethanesulfonate) (*R*)-(−)-**4**. This reaction was carried out in the presence of equimolar amounts of $Pd(OAc)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) in DMSO at 100 °C. Cleavage of the methoxy group of the phosphinyl derivative (*R*)-(+)-**5** with BBr_3 in CH_2Cl_2 afforded the dihydroxy derivative (*R*)-(+)-**6** in 99% yield, after recrystallisation from diethyl ether. Subsequent hydrolysis of the remaining triflate group with aqueous sodium hydroxide in a methanol–dioxane mixture led to (*R*)-(+)-2-[bis(4-hydroxyphenyl)phosphinyl]-2′-hydroxy-1,1′-binaphthyl (*R*)-(+)-**7** in 91% yield. Three fluorous ponytails were then introduced by reaction of the free hydroxy groups of (*R*)-(+)-**7** with 1*H*,1*H*-perfluorooctan-1-ol perfluorobutanesulfonate **8** in DMF, in the presence of caesium carbonate.[13] Phosphine oxide (*R*)-(+)-**9** was obtained in 70% yield after simple flash chromatography (eluent Et_2O). Finally, reduction with Cl_3SiH in boiling toluene afforded pure (*R*)-(+)-**1** in 90% yield.

The partition coefficients for (*R*)-(+)-**1** between *n*-perfluorooctane and three organic solvents (CH_2Cl_2, toluene and



Scheme 1 *Reagents and conditions*: i, Mg, THF, reflux; ii, $ClP(NEt_2)_2$, −20 °C; iii, aqueous 36% HCl, −10 °C; iv, (*R*)-(−)-**4**, $Pd(OAc)_2$, dppb, diisopropylethylamine, DMSO, 100 °C; v, BBr_3, CH_2Cl_2, 0 °C; vi, NaOH, MeOH, dioxane, rt; vii, $C_7F_{15}CH_2OSO_2C_4F_9$ **8**, Cs_2CO_3, 100 °C; viii, Cl_3SiH, toluene, 110 °C.

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Scheme 2 *Reagents and conditions*: Nucleophile (see Table 1), 2 eq.; BSA, 2 eq.; KOAc, 0.1 eq.; $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2 mol%; (*R*)-(+)-**1**, 8 mol%.

CH_3OH) were found to be 0.20, 0.23 and 7.42, respectively. As expected, the new ligand shows a certain affinity for organic solvents, due to the relatively low fluorine content of (*R*)-(+)-**1** (52.4%) and to its aromatic backbone. This mixed behaviour makes (*R*)-(+)-**1** an ideal candidate for the application of 'light fluorous' techniques. Palladium complexes of enantiopure 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyls (MOPs) catalyse several asymmetric transformations.[11] A number of applications of related fluorous compounds could be thus envisaged. It was previously shown that palladium(0)-catalysed allylic substitution reactions can be conveniently performed under fluorous biphase conditions, in the presence of a 'light fluorous' triarylphosphine with a fluorine content of 57%.[14] On the other hand, chiral MOPs have been recently used for the asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate **10** in standard solvents (Scheme 2).[15] We decided therefore to investigate the potentiality of this new fluorous MOP (*R*)-(+)-**1** as a ligand in the same reaction. The results obtained are summarized in Table 1.‡

Table 1 Asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate in benzotrifluoride

Entry	Nucleophile	*T*/°C	*t*/h	Yield[a] (%)	Ee[a] (%)	Conf.[b]
1	$CH_2(CO_2Me)_2$	25	36	99	81	*R*
2[c]	$CH_2(CO_2Me)_2$	25	25	88	87	*R*
3[cd]	$CH_2(CO_2Me)_2$	0	48	95	99	*R*
4	$CH_2(COCH_3)_2$	25	1	100	85	*R*
5	$MeCH(CO_2Me)_2$	25	48	7	76	*S*
6	$MeCH(CO_2Me)_2$	50	48	69	44	*S*
7	$AcNHCH(CO_2Et)_2$	50	25	67	85	*S*

[a] Determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm). [b] Determined by comparison with an authentic sample. [c] Reaction run in toluene. [d] See ref. 15.

The reaction of **10** with dimethyl malonate using MOP (*R*)-(+)-**1** (8 mol%) and $[Pd(C_3H_5)Cl]_2$ (2 mol%) in the presence of bis(trimethylsilyl)acetamide (BSA, 2 eq.) and potassium acetate (10.1 eq.) in benzotrifluoride (a standard solvent for 'light fluorous' compounds) proceeded quantitatively at rt to give, after 36 h, the corresponding alkylated product in 99% yield with 81% ee (Table 1, entry 1). This value is quite close to the value obtained using toluene as the solvent (Table 1, entry 2). It is to be noticed that non-perfluorinated MOP gave the alkylated product in 95% yield and 99% ee using toluene as the solvent (Table 1, entry 3).

Next we investigated the asymmetric reaction with other carbon nucleophiles. Reaction of **10** with acetylacetone gave the product nearly quantitatively after 1 h with 85% ee (Table 1, entry 4). Substituted dimethyl malonate gave lower chemical yields. Dimethyl methylmalonate gave the alkylated product with 69% yield and 44% ee at 50 °C (Table 1, entry 6), although 76% ee was obtained at rt, but in 7% yield (Table 1, entry 5). Diethyl acetamidomalonate gave also the expected alkylated compound in 67% yield with 85% ee (Table 1, entry 7).

When toluene was used as a solvent, the simple extraction of the reaction mixture with *n*-perfluorooctane (2 × 5 ml) allowed the complete removal of the fluorous ligand and of the corresponding palladium complexes, as shown by the absence of phosphine resonances in the ^{1}H-NMR of the crude product. As pointed out by Curran, this ease of separation together with the possible use of standard reaction conditions could be helpful in discovery-oriented synthesis and parallel synthesis.[8] However, a drawback of this 'light fluorous' approach is the absence of catalytic activity of the recovered fluorous palladium complex. We are currently investigating this problem, which seems to be due to the separation procedure followed. Indeed, recyclability of a 'light fluorous' phosphine used in the same reaction under classical fluorous biphase conditions was feasible.[14]

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Notes and references

† ^{1}H-NMR (300 MHz, $CDCl_3$): 4.16 (dt, *J* = 24.6 Hz, 12.6 Hz, 2H), 4.48 (dt, *J* = 13.1 Hz, 13.1 Hz, 4H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.86–6.92 (m, 3H), 7.03 (dd, *J* = 7.1 Hz, 8.5 Hz, 2H), 7.06–7.12 (m, 1H), 7.17–7.35 (m, 6H), 7.41 (dd, *J* = 3.0 Hz, 8.5 Hz, 1H), 7.44–7.50 (m, 1H), 7.86–7.91 (m, 3H), 8.01 (d, *J* = 9.1 Hz, 1H); ^{13}C-NMR (75.4 MHz, $CDCl_3$): 65.5 (t, *J* = 27 Hz), 66.7 (t, *J* = 27 Hz), 105–120 (m, C_7F_{15}), 124.9–131.4, 133.4–136.4, 140.7, 141.1, 153.0, 158.0, 158.2; ^{31}P-NMR (122 MHz, $CDCl_3$): −15.5; mp = 49 °C, $[\alpha]^{20}_D$ = +23.1 (*c* 0.3, $CHCl_3$). Anal. Calcd. for $C_{56}H_{26}F_{45}O_3P$: C, 41.17; H, 1.61; P, 1.90. Found: C, 40.56; H, 1.53; P, 2.19%.

‡ Reactions were run under nitrogen in Schlenk glassware. $[Pd(C_3H_5)Cl]_2$ and the ligand (*R*)-(+)-**1** was dissolved in 2 ml of solvent. After stirring for 40 min at rt, a solution of **10** in 2 ml of solvent was added. After 20 min, the resulting solution was transferred into a reactor previously charged with BSA, KOAc and the nucleophile dissolved in 4 ml of solvent. The reaction mixture was stirred at the desired temperature for the time indicated in Table 1.

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