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Preparation of chiral triarylphosphines by Pd-catalysed asymmetric P–C cross-coupling†

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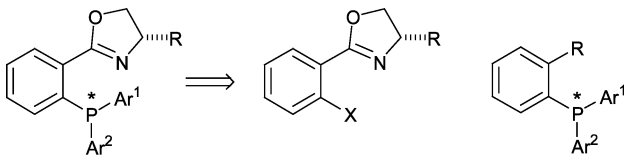
Enantioselective C–P cross-coupling of diarylphosphines and *ortho*-substituted aryl iodides has been achieved with > 90%ee, using an *in situ* catalyst prepared from Et,Et-FerroTANE, $Pd_2(dba)_3 \times CHCl_3$ and LiBr.

Several years ago, phosphinooxazoline (PHOX) ligands **A** with a chiral centre at P were introduced by this group.[1] Their synthesis was accomplished with a diastereomer ratio (d.r.) of *ca.* 3:1 by either nucleophilic or electrophilic substitutions at precursors **B**, where X = F or MgBr with phosphides or phosphorus halides, respectively. As only the major diastereomers are reasonably well accessible and compounds **A** (R = H) are not accessible *via* this route based on substrate controlled-diastereoselection, we became interested in methods that would allow external control of the configuration at phosphorus.[2] Pd-catalyzed C–P cross-coupling chemistry appeared particularly suited for this purpose, judged by exciting recent developments in this field. Accordingly, we set out to develop a method for enantioselective synthesis of compounds of type **C**.



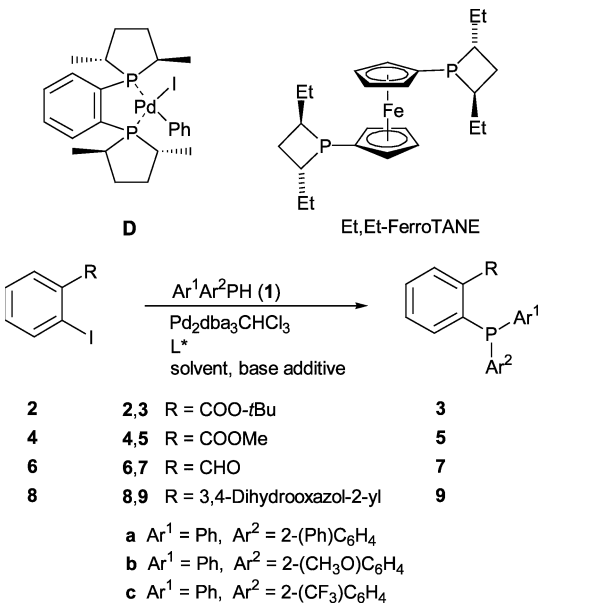
C–P cross-coupling of an aryl halide with a phosphine or a phosphine-borane is a well known reaction;[3] however, stereochemical aspects have been studied only recently. Work with enantiomerically enriched phosphine-boranes[4] indicated a possibility for asymmetric catalysis, which was indeed realized by Glueck and co-workers for the reaction of PhI with [2,4,6-(*i*-Pr)$_3$C$_6$H$_2$](CH$_3$)PH, using 2.5–7 mol% of catalyst **D** in conjunction with NaOSiMe$_3$ as base, to give PPh(CH$_3$)[2,4,6-(*i*-Pr)$_3$C$_6$H$_2$] with up to 78%ee.[5]

Complex **D** must be stored in the dark at −25 °C.[6] Therefore, it appeared desirable to develop a new, *in situ* catalyst system for the reactions described in Scheme 1. Initially, the reaction of iodide **2** with the phosphine Ph[2-(Ph)C$_6$H$_4$]PH (**1a**) was studied. Of a set of nine commercially available ligands,[7] only the ferrocene derivatives JOSIPHOS and Et,Et-FerroTANE[8] gave **3a** with a significant ee of 34 and 71%, respectively. In further work only the latter ligand was used. Results are presented in Table 1.

According to Glueck and co-workers, deprotonation of a reversibly formed intermediate [PdL*(Ar)(PHR^{1}R^2)]$^+$Hal$^-$ is an essential step in the catalytic cycle.[5a] In the reaction with diarylphosphines, studied here, tertiary amines such as NEt$_3$ suffice to promote the reaction (Table 1, entries 1–3).‡

Lithium halides were found to influence the reaction of **2a** with phosphine **1a** (entries 4–7) considerably;[10] the optimal rate as well as the enantioselectivity was obtained with LiBr as additive. Exchanging Li$^+$ by NBu$_4^+$ led to erosion of enantioselectivity (entry 8). The effects of base and LiBr are not additive (*cf.* entries 1 and 3 with entries 6 and 9). Generally, THF was the solvent giving rise to the highest yields as well as enantioselectivities.

The scope of the new catalyst system was investigated using the examples described in Scheme 1. For the reaction of ester **2** with phosphines **1b** and **1c** containing an electron donor and an acceptor substituent, respectively, low and high enantioselectivities were obtained (entry 10 *vs.* entry 11). The substituent R of the iodide was also varied. For the dihydrooxazole **8** up to 90%ee was achieved. Remarkably, the additive LiBr gave rise to a marked decrease of enantioselectivity (*cf.* entries 14 and 15).



Scheme 1

Table 1 Pd-catalysed C–P cross-coupling according to Scheme 1 [L*: (*R*,*R*)-Et,Et-FerroTANE; solvent: THF; r.t.]

Entry	Aryl iodide	Phosphine **1**	Base	Additive	t^a/d	Yield (%)^b	Ee (%)^c (Config.)
1	**2**	**1a**	NEt$_3$	—	3	63	71 (*S*)
2	**2**	**1a**	NBnMe$_2$	—	2	45	77 (*S*)
3	**2**	**1a**	N-Me-piperidine	—	3	76	84 (*S*)
4	**2**	**1a**	NEt$_3$	LiF	2	76	66 (*S*)
5	**2**	**1a**	NEt$_3$	LiCl	3	66	86 (*S*)
6	**2**	**1a**	NEt$_3$	LiBr	1	76	90 (*S*)
7	**2**	**1a**	NEt$_3$	LiI	2	58	87 (*S*)
8	**2**	**1a**	NEt$_3$	Bu$_4$NBr	2	76	25 (*S*)
9	**2**	**1a**	N-Me-piperidine	LiBr	1	43	86 (*S*)
10	**2**	**1b**	NEt$_3$	LiBr	2	79	40 (+)
11	**2**	**1c**	NEt$_3$	LiBr	2	39	93 (*R*)^d
12	**4**	**1a**	NEt$_3$	LiBr	2	69	85 (*S*)
13	**6**	**1a**	NEt$_3$	LiBr	2	71	63 (*S*)
14	**8**	**1a**	NEt$_3$	—	1	45	90 (−)
15	**8**	**1a**	NEt$_3$	LiBr	1	58	68 (−)

^{a} Reaction time. ^{b} Yield of isolated product. ^{c} Determined by HPLC (see ref. 9); ± refer to the sign of the optical rotation. ^{d} Note that the Cahn–Ingold–Prelog priorities of groups Ar^2 and C$_6$H$_4$R of **3a** and **3c** are reversed.

† Electronic supplementary information (ESI) available: crystallographic data for (*R*)-**10a**, (*S*)-**10a** and (*R*)-**10c**. See http://www.rsc.org/suppdata/cc/b3/b315009g/

DOI: 10.1039/b315009g

The absolute configuration of phosphine **3a** was determined by crystal structure analysis of the corresponding phosphine sulfide (Scheme 2). Thus, reaction of (*S*)-**3** (83%ee) with sulfur (THF, r.t.) gave the phosphine sulfide (*R*)-**10** in 98% yield. Slow evaporation of a solution of this compound in methanol gave first racemic **10a** as a crystalline powder. The mother liquor was concentrated *in vacuo* and the residue crystallised from 2-propanol to give the enantiomerically pure[11] compound in the form of large needles (yield: 67%), which were suitable for X-ray structure analysis.§ Reaction of the enantiomerically pure (+)(*R*)-**10a** with Raney nickel gave (*S*)-**3a** with >99%ee in 86% yield.[12] In the case of enantiomerically enriched **3c** the absolute configuration was determined by X-ray structure analysis of **3c** as well as of the phosphine sulfide **10c**.

Our previously employed methods for the synthesis of ligands of type **A** allowed only one of the diastereomeric phosphines to be prepared with moderate selectivity. Thus, phosphines **12** (Scheme 3) were previously prepared by nucleophilic aromatic substitution yielding mainly **12a** (d.r. = 3.5:1).[1a] It was, therefore, of interest to investigate double asymmetric induction as described in Scheme 3. The results presented in Table 2 clearly demonstrate that catalyst control dominates over substrate control. Thus, it is possible to prepare **12b** as well as **12a** selectively using enantiomeric chiral ligands. Assuming an analogous steric course for reactions of aryl iodides **8** and **2** with phosphine **1a**, *i.e.* the (*S*)-configuration in entry 14 of Table 1, entries 1 and 2 of Table 2 represent the mismatched and matched case, respectively.

It has not escaped our attention that the P–C cross-coupling is potentially prone to autocatalysis, particularly in the case of bidentate ligands such as **9**. We are investigating this aspect.

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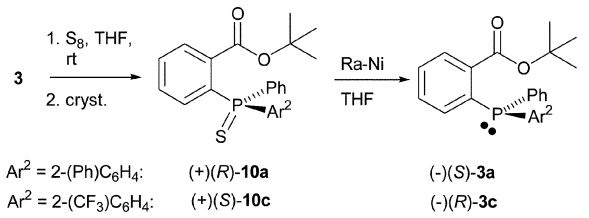
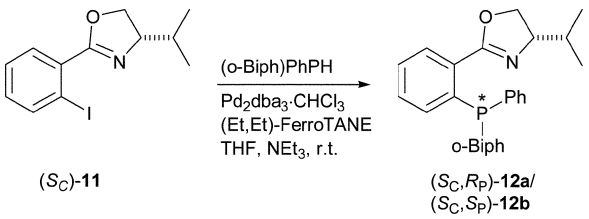


Scheme 2



Scheme 3

Table 2 Preparation of PHOX ligands according to Scheme 3

Entry	Config. Ferro-TANE	*t*/d	d.r.[a] (Config.)	Yield (%)[b]
1	(*R*,*R*)	1.5	(S_C,S_P)-**12b**/(S_C,R_P)-**12a** = 4:1	53 (S_C,S_P)-**12b** 14 (S_C,R_P)-**12a**
2	(*S*,*S*)	1.5	(S_C,R_P)-**12a**/(S_C,S_P)-**12b** = 13:1	66 (S_C,R_P)-**12a** 5 (S_C,S_P)-**12b**

[a] Determined by preparative chromatographic separation of the diastereoisomers. [b] Yield of pure compounds after chromatography. For the configurational assignment of the diastereoisomers see ref. 1*a*.

Notes and references

‡ Typical procedure: Under an atmosphere of argon, a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (4.6 mg, 4.4 μmol) and (*R*,*R*)-Et,Et-FerroTANE (4.1 mg, 9.3 μmol) in THF (2 ml) was heated at reflux for 3 min (colour change from red to orange). After cooling to r.t. LiBr (88 mg, 1.0 mmol) was added. The resultant solution was treated subsequently with **2** (271 mg, 0.89 mmol), **1a** (255 mg, 0.97 mmol) and NEt_3 (0.3 ml, 2.1 mmol). After stirring at r.t. for 1 d the reaction mixture was transferred (by syringe) to a chromatographic column packed with silica gel (30 × 2 cm) and the product was eluted with degassed *n*-pentane/Et_2O 98:2. (*S*)-**3a** was obtained as a colourless resin in 76% yield with an ee of 90%.

§ Crystal data: for (*R*)-**10a**: $C_{29}H_{27}O_2PS$, M = 470.54, hexagonal column, space group $P6_5$, a = 10.9348(4), b = 10.9348(4), c = 35.379(3) Å, V = 3663.5(3) Å^3, T = 100 K, Z = 6, μ = 0.22 mm^{-1}, 50 418 reflections measured, 6079 unique (R_{int} = 0.029), 5949 observed [$I > 2\sigma(I)$], $R1$ = 0.026, $wR2$ = 0.065 [$I > 2\sigma(I)$], Flack −0.01(3). For (*S*)-**10a**: $C_{29}H_{27}O_2PS$, M = 470.54, hexagonal pyramid, space group $P6_1$, a = 10.9341(3), b = 10.9341(3), c = 35.377(2) Å, V = 3662.8(3) Å^3, T = 100 K, Z = 6, μ = 0.22 mm^{-1}, 50 489 reflections measured, 6067 unique (R_{int} = 0.035), 5730 observed [$I > 2\sigma(I)$], $R1$ = 0.026, $wR2$ = 0.060 [$I > 2\sigma(I)$], Flack −0.02(3). For (*R*)-**10c**: $C_{24}H_{22}F_3O_2PS$, M = 462.45, polyhedron, space group $P2_12_12_1$, a = 8.9795(9), b = 14.313(1), c = 18.102(2) Å, V = 2326.5(4) Å^3, T = 100 K, Z = 4, μ = 0.25 mm^{-1}, 18 072 reflections measured, 3972 unique (R_{int} = 0.0558), 3834 observed [$I > 2\sigma(I)$], $R1$ = 0.052, $wR2$ = 0.104 [$I > 2\sigma(I)$], Flack 0.08(11). CCDC 227101–227103. See http://www.rsc.org/suppdata/cc/b3/b315009g/ for crystallographic data in .cif or other electronic format.

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6 *Cf.* ref. 5*a*, supporting information p. 2.

7 BINAP, BPE, CHIRAPHOS, DIOP, DUPHOS, NORPHOS, PPFA, JOSIPHOS and FerroTANE.

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9 For **3a**–**c**, **5a**: column = Daicel AD-H (25 × 0.46 cm), *n*-hexane/*i*-PrOH 95:5, flow rate = 0.3 ml min^{-1}, 10 °C, t_R[(*S*)-**3a**] = 12.3, t_R[(*R*)-**3a**] = 13.6 min; t_R[(+)-**3b**] = 17.6, t_R[(−)-**3b**] = 21.9 min; t_R[(*R*)-**3c**] = 12.2, t_R[(*S*)-**3c**] = 13.1 min; t_R[(*S*)-**5a**] = 15.4, t_R[(*R*)-**5a**] = 16.6 min. For **7a**: column = Daicel OD-H (25 × 0.46 cm), *n*-hexane/*i*-PrOH 90:10, flow rate = 0.5 ml min^{-1}, 20 °C, t_R[(*R*)-**7a**] = 13.0, t_R[(*S*)-**7a**] = 17.4 min. For **9a**: column = Daicel AD-H (25 × 0.46 cm), *n*-hexane/*i*-PrOH 98:2, flow rate = 0.5 ml min^{-1}, 20 °C, t_R[(−)-**9a**] = 22.1, t_R[(+)-**9a**] = 25.5 min.

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11 The enantiomeric purity of **10a** was determined by HPLC: column = Daicel AD-H (25 × 0.46 cm), *n*-hexane/*i*-PrOH 99:1, flow rate = 0.5 ml min^{-1}, 20 °C, t_R[(*S*)-**10a**] = 51.3, t_R[(*R*)-**10a**] = 58.2 min.

12 The reaction of a phosphine with sulfur as well as the desulfuration with Raney Ni are known to proceed with retention of configuration: *cf.* ref. 2*b*.