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Synthesis of a C_3 -symmetric ferrocenylphosphine and its application to the Suzuki reaction of aryl chlorides

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Abstract— $({}_{p}S_{,p}S_{,p}S)$ -Tris(2-methylferrocenyl)phosphine **1** was synthesised in 62% yield from (S)-2-ferrocenyl-4-(1-methylethyl)oxazoline. In combination with Pd₂dba₃ this novel C_3 -symmetric ligand generates a catalyst for the Suzuki reaction of aryl chloride substrates, these reactions proceed readily at 60°C in dioxane. © 2001 Elsevier Science Ltd. All rights reserved.

The recent development of methods for the utilisation of aryl chlorides in C–C, C–N and C–O bond forming reactions have largely focused on palladium catalysts containing bulky, electron rich phosphine ligands. In particular, tri-*tert*-butylphosphine,¹ 1,1'-bis(di-*tert*butylphosphino)ferrocene² and biphenyls containing di*tert*-butylphosphino or dicyclohexylphosphino substituents³ have proved especially effective. Earlier work with palladacycles derived from phosphines containing 2-methylphenyl substituents, such as tris(*ortho*tolyl)phosphine, had also demonstrated that cheaper aryl chlorides could be used as alternatives to aryl bromides and iodides, in this case for the Heck reaction.⁴

The ferrocenyl group is bulkier than a phenyl group, and the electronic properties of this moiety are illustrated by its ability to stabilise an adjacent positive charge, to the extent that α -ferrocenylcarbenium ions

are easily isolated.⁵ We therefore reasoned that phosphines containing 2-methylferrocenyl substituents may be of use in palladium catalysed reactions of aryl chloride substrates, and to fully test this hypothesis, required access to a phosphine containing three such substituents. An additional feature is the planar chirality displayed by ferrocenes containing two different groups attached to one of the cyclopentadienyl rings. As a consequence, one of the two possible diastereoisomers of tris(2-methylferrocenyl)phosphine **1** displays C_3 -symmetry, this class of monodentate ligand being comparatively rare.⁶

As triarylphosphines may be synthesised by the addition of aryllithium precursors to phosphorous trichloride, a stereoselective synthesis of **1** using this method required access to enantiomerically pure 2-lithio-1methylferrocene. We,⁷ and others,⁸ have previously reported that planar chirality is conveniently generated



Scheme 1.

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by the diastereoselective lithiation of ferrocenyl oxazolines. Thus, addition of BuLi to 2 in the presence of TMEDA^{8c} followed by addition of dibromotetrachloroethane led to the formation of 3 without detection of the alternative diastereoisomer (Scheme 1). This was cleanly and rapidly ring-opened by addition of triflic anhydride at 0°C followed, after five minutes stirring, by the addition of ice-water to give 4. Subsequent ester reduction with four equivalents of DIBAL-H at room temperature gave alcohol 5 containing 17% of 6, this mixture being completely converted to $(_{D}S)$ -2bromo-1-methylferrocene by further reduction with 2 equivalents of triethylsilane in TFA, also at room temperature. Finally, bromo-lithium exchange at -78°C was followed by addition of PCl₃, warming of the reaction mixture to room temperature and isolation of **1** as a yellow crystalline solid.⁹

A synthesis of racemic 1 required racemic 2-bromo-1methylferrocene and a degree of selectivity in its transformation into 1, although the alternative ${}_{p}S^{*}, {}_{p}S^{*}, {}_{p}R^{*}$ derivative was also of interest. The first requirement was most conveniently met with the conversion of 2-ferrocenyl-4,4-dimethyloxazoline into rac-6 using the same procedure just described (overall yield 70%). However, following bromo-lithium exchange and addition of PCl₃ as before, this reaction conspicuously failed to give either of the two diastereomeric triferrocenyl phosphines. Examination of the crude reaction mixture by ³¹P NMR revealed a major peak at 34.7 ppm which we have tentatively assigned to mesochlorodi(2-methylferrocenyl)phosphine. The rapid and irreversible formation of this material, and its inability to react further with a final equivalent of 2-lithio-1methylferrocene would account for the absence of the two possible tris(2-methylferrocenyl)phosphines.

To test the suitability of 1 for use with any chloride substrates, we investigated the Suzuki cross-coupling between para-chlorotoluene and phenylboronic acid (Scheme 2). This reaction proceeded readily at 60°C, the highest conversion after a 5 h reaction time being obtained with two equivalents of Cs₂CO₃ as base $(\cong C_{sF} > K_{F} > K_{2}CO_{3})$ in dioxane $(> THF \gg CH_{3}CN)$ with Pd_2dba_3 (>Pd(OAc)₂), Table 1. Under the same conditions both tris(ortho-tolyl)phosphine and tris(ferrocenyl)phosphine¹⁰ failed to give the cross-coupled product, revealing the importance of both the ferrocenyl group and its 2-methyl substituent to the activity observed with 1.

A variety of other substrate combinations were examined under these optimised conditions, and as expected the presence of an electron withdrawing substituent in the aryl chloride promoted high conversion (Scheme 3, Table 2, entry 1). Although the use of ortho-substituents reduced the effectiveness of the reaction (entries 2 and 3), they did not prevent moderate conversions from being achieved with sterically and electronically demanding substrate combinations (entries 4 and 5).

A feature of these reactions is the relatively high conversions observed after a short reaction time. For



Scheme 2.

Table 1. Results of the Suzuki cross-coupling of 7 with 8

Entry	Ligand	Base	Pd source	Solvent	Yield of 9 ^a (%)
1	1	Cs ₂ CO ₃	Pd ₂ dba ₃	Dioxane	80 (86) ^b
2	1	CsF	Pd ₂ dba ₃	Dioxane	76 (91)
3	1	KF	Pd ₂ dba ₃	Dioxane	63 (64)
4	1	K ₂ CO ₃	Pd ₂ dba ₃	Dioxane	50 (57)
5	1	Cs_2CO_3	Pd ₂ dba ₃	THF	11 (11)
6	1	Cs_2CO_3	$Pd(OAc)_2$	Dioxane	41 (41)
7	(o-tolyl) ₃ P	Cs_2CO_3	Pd ₂ dba ₃	Dioxane	<1
8	Fc ₃ P	Cs ₂ CO ₃	Pd ₂ dba ₃	Dioxane	<1

^a As determined by GC.

^b Yield after 24 h in parentheses.



0.036 eq.1 0.015 eq. Pd₂dba₃ dioxane (1.6 ml) 2 eq. Cs₂CO₃ 60 °C, 5 h.

dioxane (1.6 ml)

2 eq. base

60 °C, 5 h.



Table 2. Results of Suzuki cross-couplings with 1

Entry	R	\mathbb{R}^1	Yield ^a (%)
1	$p-NO_2$	Н	90
2	H	o-Me	57
3	o-Me	Н	49
4	o-Me	o-Me	46
5	o-OMe	o-Me	36

^a As determined by GC.

example under the optimised conditions (Table 1, entry 1), 17% of **9** was present after only 10 minutes, and 51% after 1 h. Longer reaction times resulted in the formation of palladium black in the reaction vessel, but this did not effect the integrity of the ligand which could be recovered in essentially quantitative yield. Interestingly, despite the similarity of **1** to tris(*ortho*-tolyl)phosphine, no palladacycles have yet been observed.

In conclusion, we have demonstrated that a tris(2methylferrocenyl)phosphine is readily synthesised provided attention is paid to the absolute stereochemistry of the 2-methylferrocenyl substituents. These result in an efficient ligand promoting the Suzuki cross-coupling of aryl chlorides under mild conditions, and both the ferrocenyl group and the 2-methyl substituent are required for activity. Given the recent interest in asymmetric variants of this reaction,¹¹ further work is on going to explore the full utility of **1** and its derivatives.

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- 9. Data for 1: mp 238–240°C (found: C, 62.19; H, 5.26. $C_{33}H_{33}Fe_{3}P\cdot1/2H_{2}O$ requires C, 62.21; H, 5.38); $[\alpha]_{D}^{20}$ -72 (*c* 0.22, CH₂Cl₂); δ_{H} (400 MHz, CDCl₃) 2.35 (3H, s, Me), 3.73 (5H, s, C₅H₅), 4.24 (2H, t, *J* 2.3 Hz, 2×Fc), 4.33 (1H, d, *J* 1.54 Hz, Fc); δ_{C} (100 MHz, CDCl₃) 15.24 (d, *J* 14.4 Hz, Me), 68.41 (Fc), 69.27 ($C_{5}H_{5}$), 70.60 (d, *J* 5.2 Hz, Fc), 71.07 (d, *J* 5.8 Hz, Fc), 81.19 (d, *J* 6.3 Hz, Fc-*ipso*), 89.38 (d, *J* 36.3 Hz, Fc-*ipso*); δ_{P} (122 MHz, CDCl₃) -72.6; *m*/*z* (APCI), 628 (M⁺, 100), 429 (M–2–MeFc, 82%).
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