Letter

Suzuki–Kumada coupling of bromoaroylmethylidenephosphoranes†

Thies Thiemann,*[a] Kuniharu Umeno,[b] Daisuke Ohira,[b] Eiko Inohae,[b] Tsuyoshi Sawada[a] and Shuntaro Mataka*[a]

[a] *Institute of Advanced Material Study*
[b] *Graduate School of Engineering, Kyushu University, 6-1, Kasuga-koh-en, Kasuga-shi, Fukuoka 816-8580, Japan. E-mail: thies@cm.kyushu-u.ac.jp; mataka@cm.kyushu-u.ac.jp*

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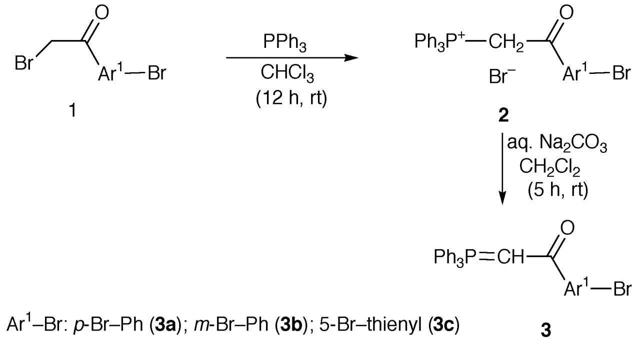
Bromoaroylmethylidenephosphoranes 3 are reacted with aryl- and hetarylboronic acids under Suzuki–Kumada conditions to yield biaryl- and arylhetaryl-carbonylmethylidenephosphoranes 4. The reaction can also be run in a one-step procedure from (bromoaroylmethyl)triphenylphosphonium bromides 2. 4 are air-stable phosphoranes that undergo Wittig olefination reactions with aldehydes under benzoic acid catalysis.

Many phosphoranes that have a carbonyl group in conjugation to their ylene P=C bond are relatively stable towards water and air. While the alkoxylcarbonylmethylidenephosphoranes, some of which are commercially available, undergo Wittig olefination with both ketones and aldehydes, the corresponding alkyl- or arylcarbonylmethylidenephosphoranes react with aldehydes[1] and with only a limited number of very reactive ketones.[2] In our quest for 7-arylalkyl-substituted estrones as diagnostica for human breast cancer[3] we were interested in the preparation of biaryl- and arylhetarylcarbonylmethylidenephosphoranes **4** for a subsequent olefination reaction[4] with a 7-formyl-substituted estrone derivative. The following describes the synthesis of these phosphoranes **4** by Suzuki–Kumada coupling of either the haloaroylmethylidenephosphoranes **3** or the phosphonium salts **2**, precursors of **3**, in a one pot elimination-coupling procedure.

4-Bromobenzoylmethylidenetriphenylphosphorane **3a**, 3-bromobenzoylmethylidenetriphenylphosphorane **3b** and 5-bromothien-2-ylcarbonylmethylidenetriphenylphosphorane **3c** (Scheme 1) can be prepared easily by reaction of the corresponding bromomethylaryl(hetaryl)ketones with triphenylphosphine in chloroform and subsequent elimination reaction in an aqueous Na_2CO_3 solution.[5] The phosphoranes undergo Suzuki–Kumada coupling[6] with a variety of phenylboronic acids (Table 1). In most cases a 2 M aqueous solution of sodium carbonate was used as the base system with DME as the organic solvent. A one-phase system with CsF as base and DME[7] as solvent or with K_3PO_4 and DMF[8,9] can also be used. The biaryl- and hetarylarylcarbonylmethylidenephosphoranes could be isolated in acceptable yields.[10,11]



Scheme 1 Synthesis of bromoaroylmethylidenephosphoranes

Under these conditions three arylboronic acids (2,6-difluorophenylboronic acid, pentafluorophenylboronic acid and, unexpectedly, furan-2-ylboronic acid) gave no coupling products. It is known that the rate of hydrolysis of the phenylboronic acid is increased by the introduction of a fluoro substituent at position 2 (relative rate of hydrolysis is 77 *vs.* phenylboronic acid).[6,12] Nevertheless, in non-aqueous media (K_3PO_4, DMF[8] and CsF, DME[7]) these boronic acids also failed to undergo the coupling reactions. In the case of the difluoro- and pentafluorophenylboronic acids this may be due to the charge distribution due to the two *ortho*-fluoro substituents surrounding the reaction site. It is generally known that in cross-coupling reactions of organo boron compounds low yields result in *ortho*-disubstituted arylboronic acids even when steric hinderance of the substituents is not a major factor.[6] Normally, in these cases stronger bases, such as aqueous NaOH or $Ba(OH)_2$ are used, which in the case of the *ortho*-difluorosubstituted compounds lead to rapid hydrolysis.

The coupling reaction of 4-formylphenylboronic acid also does not result in *p*-formylphenylbenzoylmethylidenetriphenylphosphorane (**4i**). Rather, under the reaction conditions used, the Wittig olefination already takes place in this case and a noticable amount of triphenylphosphine oxide (87%, calcd. on phosphorane used) can be isolated together with oligomeric material. Nevertheless, it is possible to react the acetal-protected 4-formylphenylboronic acid trimethylene glycol ester to phosphorane **4s**.[13] The phosphoranes **4** can also be synthesized directly from the phosphonium salts **2** (Table 2), where the basic medium works well in the elimination of HBr. For the most part, the yields are only slightly lower than for the direct coupling of the phosphoranes themselves.

While virtually no decomposition of phosphoranes and no formation of triphenylphosphine oxide was observed under basic conditions, the Wittig olefination proceeds under slightly acidic conditions[14] (Table 3). Benzoic acid serves as a catalyst. *E*-Olefins are formed selectively. Only in the case of the methoxy-substituted phosphorane **4b** was a significant amount (20%) of *Z*-isomer formed. The Wittig olefination proceeds with both arenecarbaldehydes and alkanecarbaldehydes **5**.

It is thought that the biaryl/hetarylarylcarbonylmethylidenephosphoranes can be used as a scaffold for further transformations (*e.g.*, cycloaddition reactions of **4j** and **4r**), before they are used in subsequent Wittig reactions. Studies in this direction are underway.

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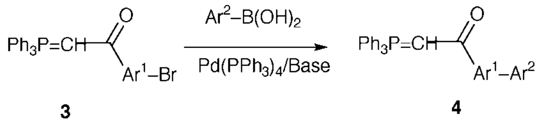
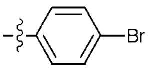
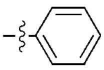
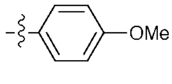
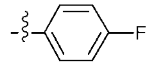
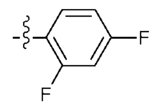
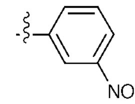
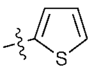
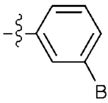
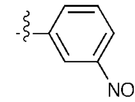
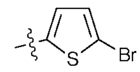
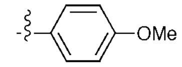
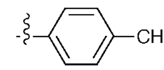
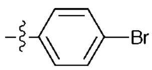
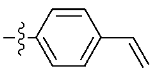
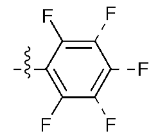
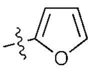
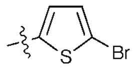
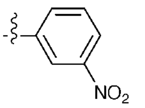
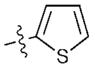
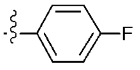
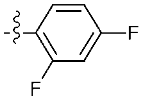
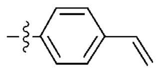
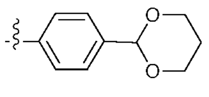
† *Supplementary material available*: structures of the products of the reactions in Tables 1–3. For direct electronic access see http://www.rsc.org/suppdata/nj/1999/1067/, otherwise available from BLDSC (No. SUP 57655, 5 pp.) or the RSC Library. See Instructions for Authors, 1999, Issue 1 (http://www.rsc.org/njc).

Table 1 Cross-coupling of phosphoranes with arylboronic acids



Ar^1—Br	–Ar^2	Variant[a]	Yield (%)
 **3a**		A	**4a** (65)
3a		A B C	**4b** (64) **4b** (89) **4b** (62)
3a		A	**4c** (68)
3a		A	**4d** (66)
3a		A	**4e** (94)
3a		A	**4f** (58)
 **3b**		A	**4g** (89)
 **3c**		A	**4h** (72)
3a		A	**4i** (-)
 **3a**		A	**4j** (70)
3a		[b] A	**4k** (–)
3a		A	**4m** (3)
 **3c**		A	**4n** (32)
3c		A	**4o** (13)
3c		A	**4p** (57)
3c		A	**4q** (78)
3c		A	**4r** (95)
3a		B	**4s** (34)[c] (56)[d]

[a] **A**: DME, 2 M Na_2CO_3; **B**: CsF, DME; 3 h, 75 °C; **C**: K_3PO_4, dry DMF, 4 h, 100 °C. Note: for methods **B** and **C** the corresponding boronic trimethylene esters were used.

[b] Denotes results for both 2,6-difluorophenylboronic acid and pentafluorophenylboronic acid.

[c] 3 h, 4 equiv. CsF.

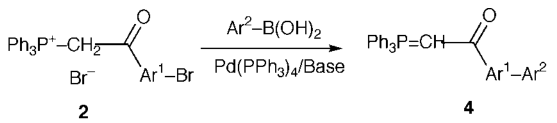
[d] 9 h, 2 equiv. CsF, calcd. on boronic ester.

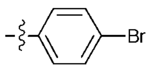
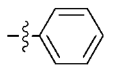
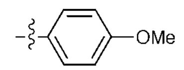
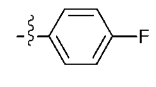
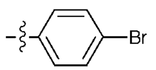
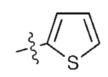
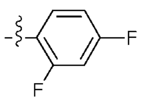
Experimental

Typical coupling reaction of the phosphoranes. *m*-Nitrophenylbenzoylmethylidenetriphenylphosphorane (4e)

A mixture of **3a** (153 mg, 0.33 mmol), *m*-nitrophenylboronic acid (110 mg, 0.66 mmol) and Pd(PPh$_3$)$_4$ (19 mg, 1.6 × 10^{-2} mmol) in DME (3 mL) and 2 M aq. Na_2CO_3 (1.3 mL) were held at 75 °C for 5 h. Water (20 mL) was added and the mixture was extracted with chloroform (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel [eluant ether to ethyl acetate–ether (1 : 10)] and gave **4e** (155 mg, 94%) as yellow rhombic plates, mp 219–221 °C (ether); IR (KBr) ν 3064, 2924, 1584, 1515, 1505, 1403, 1347, 1105, 890, 692 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 4.47 (1H, d, ill-resolved), 7.45–7.80 (m, 18H), 7.94 (d, 1H, ^3J 7.5 Hz), 8.09 (d, 2H, ^3J 7.9 Hz), 8.19 (d, 1H, ^3J 8.2 Hz), 8.48 (s, 1H). ^{13}C NMR (67.9 MHz): δ 51.46 (J_{C2P} 112.1 Hz), 121.90, 122.01, 126.57, 126.92 ($J_{C\text{–}P}$ 91.3 Hz), 127.81, 128.95 ($J_{C\text{–}P}$ 13.3 Hz), 129.66, 132.18 ($J_{C\text{–}P}$ 2.4 Hz), 133.04, 133.19 ($J_{C\text{–}P}$ 9.0 Hz), 139.32, 141.32 (J 14.0 Hz), 142.73, 148.78, 183.85 ($J_{C\text{–}P}$ 3.7 Hz, C=O). MS (FAB, 3-nitrobenzyl alcohol): *m*/*z* (%) 502 (MH$^+$, 100); MS (EI, 70 eV): *m*/*z* (%) 501 (M$^+$, 100), 303 (49). HRMS Found: 501.1494; Calcd. for $C_{32}H_{24}NO_3P$: 501.1494. Anal. Calcd. for $C_{32}H_{24}NO_3P$ (501.52) C, 76.64; H, 4.82; N, 2.79. Found C, 76.58; H, 4.87; N, 2.75.

Table 2 Cross-coupling of phosphonium salts with arylboronic acids



Ar^1——Br	–Ar^2	Variant	Yield (%)
 **2a**		A^a	**4a** (64)
2a		A	**4b** (49)
2a		A	**4c** (62)
 **2a**		A	**4f** (42)
2a		A	**4d** (74)

^{a} DME, 2 M Na_2CO_3, 5 h, 75 °C

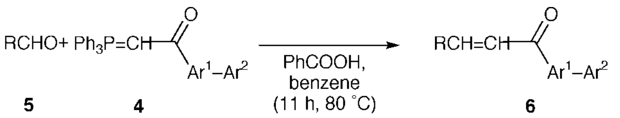
Typical coupling procedure for phosphonium salts. 4-(2,4-Difluorophenyl)benzoylmethylidenetriphenylphosphorane (4d)

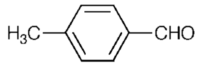
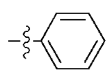
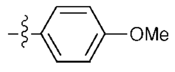
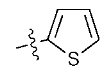
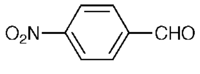
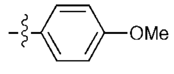
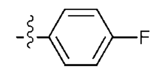
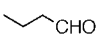
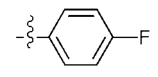
A mixture of **2a** (268 mg, 0.50 mmol), 2,4-difluorophenylboronic acid (158 mg, 1.00 mmol) and $Pd(PPh_3)_4$ (19 mg, 1.6 × 10^{-2} mmol) in DME (2.5 mL) and 2 M aq. Na_2CO_3 (1.85 mL) were heated for 5 h at 75 °C. After the reaction mixture was cooled, water (15 mL) was added and the mixture was extracted with ether (10 mL) and chloroform (2 × 15 mL). The combined organic phase was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel gave **4d** (182 mg, 74%) as colorless rhombic crystals, mp 190–192 °C (ether); IR (KBr) ν 3052, 2924, 1598, 1573, 1514, 1492, 1481, 1436, 1401, 1385, 1103, 885, 846, 714 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.48 (d, ill-resolved, 1H), 6.92 (m, 2H), 7.37–7.77 (m, 18H), 8.04 (d, 2H, ^3J 7.9 Hz). ^{13}C NMR (67.8 MHz): δ 51.23 ($^1J_{C2P}$ 112.3 Hz), 104.33 ($^2J_{C–F}$ 25.6 Hz, $^2J_{C–F}$ 25.6 Hz), 111.48 ($^2J_{C–F}$ 20.7 Hz, $^4J_{C–F}$ 3.7 Hz), 127.02 ($J_{C–P}$ 90.2 Hz), 127.13, 128.35 ($J_{C–P}$ 2.4 Hz), 128.91 ($J_{C–P}$ 12.1 Hz), 131.52 (J 4.9 Hz), 131.39 (J 4.9 Hz), 132.09, 133.28 ($J_{C–P}$ 9.0 Hz), 135.88, 140.61 (J 14.6 Hz), 159.21 ($^1J_{C–F}$ 169.7 Hz, $^3J_{C–F}$ 12.2 Hz), 162.89 ($^1J_{C–F}$ 166.3 Hz, $^3J_{C–F}$ 11.0 Hz), 184.25 ($^2J_{C–P}$ 2.4 Hz, C=O). MS (70 eV): *m*/*z* (%) 492 (M$^+$, 100), 463 (19), 303 (Ph_3PCHCO^+, 72). HRMS Found: 492.1458; Calcd. for $C_{32}H_{23}OF_2P$: 492.1455. Anal. Calcd. for $C_{32}H_{23}OF_2P$ (492.50) C, 78.04; H, 4.71. Found C, 77.97; H, 4.75.

Typical procedure for the Wittig olefination under benzoic acid catalysis. (*E*)-1-(*p*-Phenylbenzoyl)-2-(*p*-tolyl)ethene (6a)

A mixture of *p*-tolualdehyde (**5a**, 45 mg, 0.36 mmol), **4a** (100 mg, 0.22 mmol) and benzoic acid (11 mg, 8.9 × 10^{-2} mmol) in benzene (1.5 mL) was held under reflux for 11 h. After the reaction solution was cooled, the solvent was evaporated *in vacuo*. Column chromatography of the residue on silica gel ($CHCl_3$–hexane 3 : 2) yielded **6a** (64 mg, 98%) as pale yellow crystals, mp 183–185 °C (ether); IR (KBr) ν 3036, 2914, 1852, 1658, 1610, 1332, 1203, 1039, 980, 813, 734 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$, ^{1}H-^{1}H COSY): δ 2.40 (s, 3H, CH_3), 7.24 (d, 2H, ^3J 8.2 Hz), 7.38–7.58 (m, 6H), 7.66 (d, 2H, ^3J 8.2 Hz), 7.73 (d, 2H, ^3J 8.6 Hz), 7.84 (d, 1H, ^3J 15.5 Hz), 8.11 (d, 2H, ^3J 8.6 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135): δ 21.54 (CH_3), 121.00 (CH), 127.26 (CH), 128.17 (CH), 128.50 (CH), 128.95 (CH), 129.09 (CH), 129.72 (CH), 132.18 (C_{quat}), 137.05 (C_{quat}), 139.98 (C_{quat}), 141.09 (C_{quat}), 144.87 (CH), 145.41 (C_{quat}), 190.06 (C_{quat}, C=O). MS (70 eV): *m*/*z* (%) 298 (M$^+$,

Table 3 Acid-catalysed Wittig olefination with elongated phosphoranes (Ar^1 = C_6H_4)



RCHO	–Ar^2	Yield (%)
 **5a**		**6a** (98)
5a		**6b** (98)
5a		**6c** (98)
 **5b**		**6d** (97)
5a		**6e** (90)
 **5c**		**6f** (50)

100), 283 ($M^+ - CH_3$, 73), 152 (35); HRMS Found: 298.1363; Calcd. for $C_{22}H_{18}O$: 298.1358. Anal. Calcd. (298.38) C, 88.55; H, 6.08. Found C, 88.22; H, 6.12.

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9 Here, the arylboronic acid trimethylene glycol esters were used, which can be easily prepared from the corresponding arylboronic acids and trimethylene glycol in refluxing benzene.

10 All compounds were fully analyzed by ^1H-NMR, ^{13}C-NMR, IR and MS spectroscopy and gave satisfactory analytical and/or high resolution mass data.

11 While the use of the system CsF–DME (method B) gives equivalent and in some cases slightly superior results in the coupling reactions, the authors have mainly used method A (two-phase system, aq. Na_2CO_3) for reasons of cost and environmental waste containment.

12 See: ref. 6, p. 72; H. G. Kuivila and V. V. Nahabedian, *J. Am. Chem. Soc.*, 1961, **83**, 2159; *ibid.*, 1961, **83**, 2164; *ibid.*, 1961, **83**, 2167; H. G. Kuivila, J. F. Reuwer and J. A. Mangravite, *J. Am. Chem. Soc.*, 1964, **86**, 2666.

13 4-Formylphenylboronic acid trimethylene glycol ester can be prepared by refluxing 4-formylphenylboronic acid and trimethylene glycol. For the additional protection of the formyl group, the addition of another acid as catalyst (*e.g.*, 5 wt% *p*-TsOH) is necessary.

14 For acid-catalyzed Wittig reactions, see also: C. Rüchardt, S. Eichler and P. Panse, *Angew. Chem.*, 1963, **75**, 858; *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 619; H. J. Bestmann and J. Lienert, *Chem. Ztg.*, 1970, **94**, 487.

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