Direct synthesis of 1,1-diarylalkenes from alkenyl phosphates *via* nickel(0)-catalysed Suzuki–Miyaura coupling†

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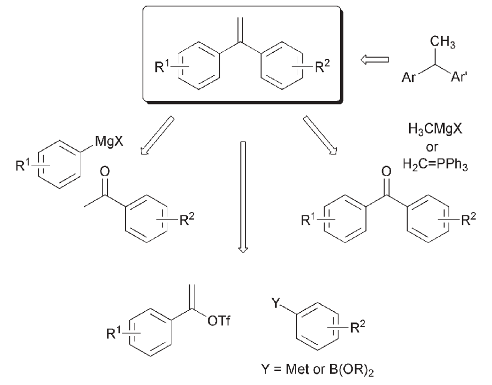
A combination of $Ni(COD)_2$ and PCy_3 promotes effectively the Suzuki–Miyaura cross coupling of 1-arylalkenyl phosphates with aryl boronic acids with yields attaining 99%.

1,1-Diarylalkenes represent important constituents of a variety of biologically active compounds, as well as being the main precursors to the corresponding 1,1-diarylethane.[1] The most general protocol to accessing such compounds relies on the addition of Grignard reagents to either aceto- or benzophenones followed by dehydration, or Wittig reactions with functionalised benzophenones (Scheme 1).[2] Structural variations to the 1,1′-diarylalkenes are however limited to the conditions applied, as well as the availability of the reagents. Many alternative methods have also been developed but are typically less flexible than the Grignard approach. Pd(0)-catalysed cross coupling reactions between aryl boronic acids/esters or other aryl metallic species and 1-arylvinyl triflates represents a mild route to diarylalkenes. Although there are only few examples in the literature,[1a,3] the low stability of the vinyl triflates in combination with the use of expensive triflating agents for their generation nevertheless limits the usefulness of this methodology. Alternative coupling reagents would therefore be desirable.

In a recent publication, we reported an effective procedure for promoting the Heck coupling of nonactivated vinyl phosphates and tosylates with electron deficient alkenes.[4,5] In particular the



Scheme 1 Previous approaches to the synthesis of 1,1′-diarylalkenes.

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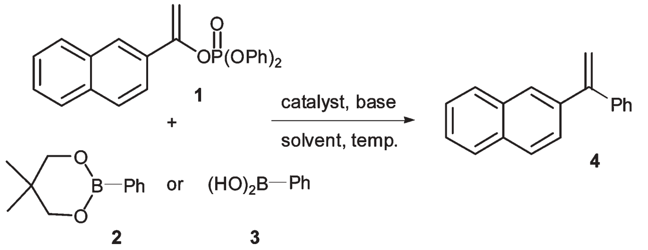
Table 1 Optimisation of Suzuki–Miyaura coupling with vinyl phosphates



Entry	Boronic acid/ester	Reaction conditions	Yield[a] (%)
1	**2**	$Pd_2(dba)_3$ (2.5%), $HBF_4P(t\text{-}Bu)_3$ (10%), KF (3 equiv.), THF, 70 °C, 21 h	0
2	**2**	$PdCl_2(COD)$ (5%), $HBF_4P(t\text{-}Bu)_3$ (10%), LiCl (1 equiv.), K_3PO_4 (3 equiv.), DMF, 70 °C, 16 h	0
3	**2**	$Ni(COD)_2$ (4%), PPh_3 (8%), K_3PO_4 (3 equiv.), THF, 70 °C, 24 h	42
4	**2**	$Ni(COD)_2$ (4%), Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), THF, 70 °C, 17 h	89[b]
5	**2**	$Ni(COD)_2$ (4%), Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), dioxane, 65 °C, 16 h	68
6	**2**	$Ni(COD)_2$ (4%), Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), toluene, 65 °C, 16 h	16
7	**3**	$Ni(COD)_2$ (4%), Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), THF, 65 °C, 16 h	92[b]
8	**3**	$Ni(COD)_2$ (2%), Cy_3PHBF_4 (4%), K_3PO_4 (3 equiv.), THF, 65 °C, 17 h	84
9	**3**	$Ni(COD)_2$ (4%), Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), THF, 65 °C, 17 h	72[c]
10	**3**	$Ni(COD)_2$ (4%), $HBF_4P(t\text{-}Bu)_3$ (8%), K_3PO_4 (3 equiv.), THF, 65 °C, 18 h	10
11	**3**	Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), THF, 65 °C, 17 h	0
12	**3**	$Pd_2(dba)_3$ (2%), PPh_3 (8%), K_3PO_4 (3 equiv.), THF, 65 °C, 18 h	0
13	**3**	$Pd_2(dba)_3$ (2%), Cy_3PHBF_4 (8%), K_3PO_4 (3 equiv.), THF, 65 °C, 18 h	9

[a] Conversion yield according to ^1H NMR. [b] Isolated yields after column chromatography. [c] The corresponding diethyl phosphate was used.

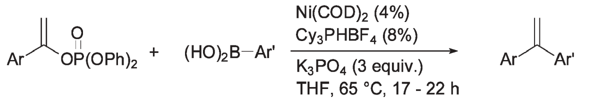
vinyl phosphates display higher stability than the corresponding triflates and show no signs of decomposition after several months in the freezer (−18 °C).‡ In our continued interest to examine the suitability of the alkenyl phosphates as viable coupling partners in cross coupling reactions, we now disclose an efficient Suzuki–Miyaura coupling[6] of these substrates with aryl boronic acids/esters using a nickel(0) catalyst for the preparation of 1,1-diarylalkenes in good to excellent yields.

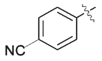
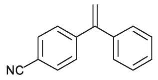
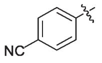
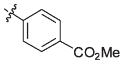
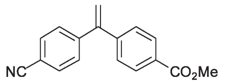
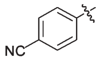
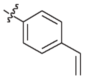
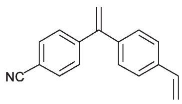
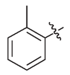
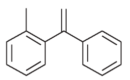
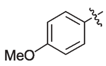
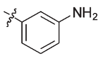
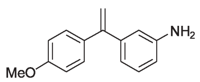
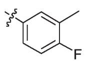
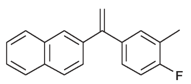
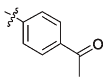
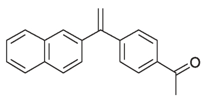
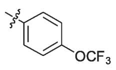
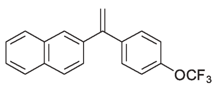
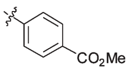
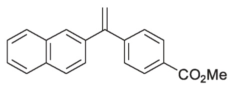
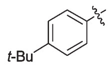
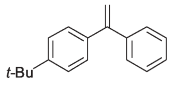
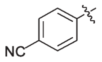
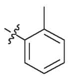
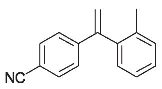
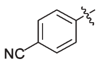
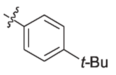
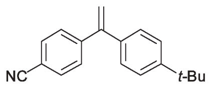
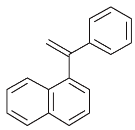
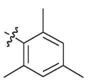
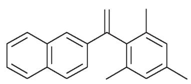
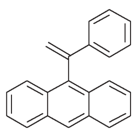
Initial optimisation efforts to promote the Suzuki–Miyaura cross coupling of vinyl phosphates§ with aryl boronic acids were carried out with the phosphate **1** and the phenyl boronic ester **2** (Table 1). Whereas successful C–C bond formation has previously been reported in Suzuki–Miyaura couplings with difficult substrates such as aryl chlorides and tosylates using palladium(0)-catalysis with bulky electron rich phosphine ligands,[8,9] extrapolation to promoting the coupling of **1** and **2** were unrewarding (entry 1). Even the conditions which successfully promoted the Heck coupling of nonactivated vinyl phosphates and acrylamides/acrylates with K_3PO_4 as base were nonproductive (entry 2).[4]

On the other hand, switching to a nickel(0) catalyst provided a more effective system for promoting these coupling reactions.[10] Use of the nickel(0) source, $Ni(COD)_2$ in combination with PPh_3 in THF showed a 42% conversion after 24 h at 70 °C (entry 3), conditions which have been successfully exploited for the Suzuki – Miyaura cross coupling of aryl chlorides with boronic acids.[10h] Exploiting the more electron rich ligand, tricyclohexylphosphine, led to full conversion affording an 89% isolated yield of the 1-phenyl-1-naphth-2-ylethene (**4**).[10e]¶ ‖ Although the coupling proceeded slowly at 20 °C, the reaction temperature was raised in order to assure complete conversion after 24 h. Potassium phosphate also proved to be a more effective base than the corresponding fluoride salt which promoted decomposition of the vinyl phosphate. Use of solvents such as dioxane and toluene were less fruitful for the conversions compared to THF (entries 5 and 6). Exchanging the boronic ester for the boronic acid **3** led to a slight improvement in the yield of **4** (92%), although reducing the catalyst loading from 4 to 2% also effected the conversion rate (entries 7 and 8). Interestingly, the diethyl phosphate proved less effective for these cross couplings than with corresponding diphenyl ester as in **1** (entry 9). Exchange of the ligand salt $HBF_4P(Cy)_3$ to $HBF_4P(t\text{-}Bu)_3$ led to a significant decrease in the coupling efficiency (entry 10). As expected the omission of the nickel(0) source led to no cross coupling revealing the absence of metal contaminants in both reagents and solvent (entry 11). Finally, the importance of nickel was also confirmed through reactions performed as indicated in entries 12 and 13, where a palladium(0) source was used.

With these successful cross coupling conditions in hand, we next proceeded to examine the generality of these reactions as illustrated in Tables 2 and 3. A variety of substituted isocyclic and heterocyclic diarylalkenes were successfully prepared. In Table 2, examples of 1-aryl vinyl phosphates and boronic acids with both electron rich and poor substituents could be couple to the corresponding diarylalkene in good to excellent yields (entries 1–13). Increasing the steric bulk as exemplified in entries 14 and 15 reduced the coupling yield and, as with entry 14, led to the formation of the monosubstituted alkene (2-vinylnaphthalene) as the major product. Heterocyclic systems were equally productive

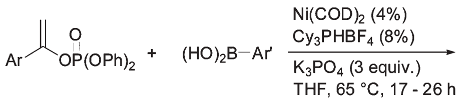
Table 2 Cross couplings with vinyl phosphates and boronic esters

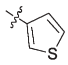
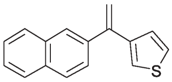
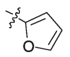
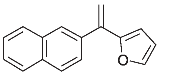
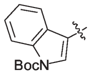
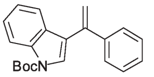
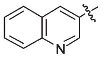
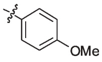
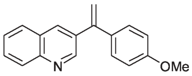
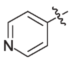
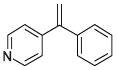
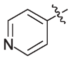
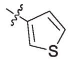
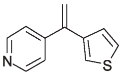


Entry	Ar	Ar′	Product	Yield[a] (%)
1		Ph		99
2				80[b]
3				96
4		Ph		69[c]
5				60
6	2-Naphthyl			73
7	2-Naphthyl			66
8	2-Naphthyl			58
9	2-Naphthyl			60[b]
10		Ph		93
11				74[b]
12				91
13	1-Naphthyl	Ph		96
14	2-Naphthyl			16[d]
15	9-Anthracyl	Ph		34[c]

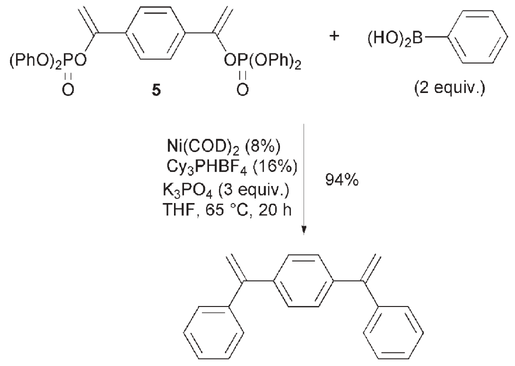
[a] Isolated yields after column chromatography. [b] The boronic ester of neopentylglycol was used. [c] The reaction was run for 44 h. [d] 2-Vinylnapthalene was isolated as the major product in a 50% yield.

Table 3 Suzuki–Miyaura couplings with heterocyclic systems



Entry	Ar	Ar′	Product	Yield[a] (%)
1	2-Naphthyl			93
2	2-Naphthyl			75
3		Ph		92
4				99
5		Ph		52
5				86

[a] Isolated yields after column chromatography.



6

Scheme 2 An example of a double Suzuki coupling with a divinyl diphosphate.

as depicted with the six examples in Table 3 with cross coupling yields ranging from 52 to 99%.

Finally, a double cross coupling was attempted with the divinyl phosphate **5** and two equivalents of the phenyl boronic acid **3** (Scheme 2). This provided the 1,4-divinyl-substituted benzene 6 in a gratifyingly high yield (94%).

In conclusion, we have provided an easy and effective access to a variety of 1,1-diarylalkenes in acceptable to high yields with a Ni(0)-catalyst, starting from easy accessible and stable starting materials. Further work is in progress to exploit these reactions for the synthesis of nonsymmetrical 1,1-diarylalkenes of medicinal interest.

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Notes and references

‡ Unlike the triflates, the vinyl phosphates showed no signs of decomposition when heated at 100 °C in DMF for 24 h.

§ The vinyl phosphates were prepared according to ref. 4 and 7 by base promoted proton abstraction of an aryl ketone with lithium hexamethyldisilazide (LiHMDS) followed by treatment with diphenyl chlorophosphate.

¶ A single example has been previously been reported Suzuki–Miyaura coupling of cyclohexenyl phosphate with aryl boronic acids using a Ni(0) catalyst prepared from the reduction of NiCl$_2$(dppf) with *n*-BuLi (ref. 5*c*).

‖ Netherton and Fu have demonstrated that trialkylphosphonium salts are air-stable and practical replacements for air-sensitive trialkylphosphines (ref. 11).

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