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Palladium-Catalyzed Phosphonylation: Synthesis of C3-, C4-, and C5-Phosphonylated Pyrazoles

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A palladium-catalyzed cross-coupling between 3-, 4-, and 5-halo-pyrazoles and H-phosphonates, H-phosphinates, and secondary phosphine oxides has been developed. This coupling reaction constitutes the first general method allowing the introduction of a great diversity of phosphorus substituents on the different carbons of the pyrazole ring in a one-step process.

Pyrazoles and their derivatives belong to an important class of heterocyclic compounds, as they possess a wide range of biological properties in medicine and agrochemistry.¹ Furthermore, it is known that the presence of phosphorus substituents is able to modulate the biological activities of pesticides as well as antiviral and antimicrobial compounds.²

Phosphonylated pyrazoles are accessible by three different routes that include the ring closure of acyclic phosphorus-containing compounds,³ [3 + 2]-dipolar cycloaddition,⁴ or phosphonylation of the preformed pyrazole ring.³ Numerous methods to synthesize phosphonylated pyrazoles have already been reported based on cyclization and cycloaddition.^{3,5} By contrast, phosphonylation of the pyrazole ring is much less documented, and the majority of available methods only deal with introduction of phosphorus at the C4-position using environmentally problematic phosphorus trichloride and related P–Cl derivatives.³

Recently, palladium-catalyzed cross-couplings have emerged as powerful and reliable tools for $C(sp^2)-P$ bond formation, and different examples of heterocycle phosphonylation using these methods have been reported in the literature.⁶ However, to the best of our knowledge, only two examples of pyrazole phosphonylation by palladiumcatalyzed cross-coupling have been reported.⁷ Thus, the

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development of general conditions for the palladiumcatalyzed cross-coupling between a phosphorus derivative and a pyrazole halogenated at the C3-, C4-, or C5-position would be of interest. In this paper, we describe our effort toward the development of such a coupling.

At first, N-SEM protected 5-iodo-pyrazole 1a and diethylphosphite 2a were chosen to commence our investigations. Compounds 1a and 2a were engaged in the crosscoupling using the conditions described by Stawinski et al. for the cross-coupling between arvl halides and H-phosphonates.⁸ Under these conditions, product 3a was formed in 37% yield (Table 1, entry 1). Montchamp et al. recently reported that the use of additives, such as ethylene glycol, can considerably increase the yield of the cross-coupling by preventing palladium-black precipitation and by stabilizing the P(III) tautomeric form of phosphonylidene compounds.⁹ However, these conditions did not appear to be beneficial in our case, as product 3a was formed in only 30% yield (Table 1, entry 2). A screening of ligands was achieved, and among dppf, S-Phos, and XantPhos, this latter was revealed to be the best ligand. A 97% isolated yield in 3a was obtained when 1a (1.0 equiv), $H-P(O)(OEt)_2$ (1.1 equiv), $Pd(OAc)_2$ (10 mol %), XantPhos (20 mol %), KOAc (10 mol %), and Et₃N (1.3 equiv) were used (Table 1, entry 3). When the catalyst loading was decreased to 2.5 mol %, the yield of **3a** dropped to 47% (Table 1, entry 4), and an excess of

Table 1. Preliminary Investigations^a



entry	1a/2a	solvent	y (mol %)	ligand	3a (yield)
1	1.0:1.1	THF	10	dppf	$37\%^b$
2	1.0:1.1	toluene/EG	10	dppf	$30\%^b$
3	1.0:1.1	THF	10	S-Phos	0%
4	1.0:1.1	THF	10	XantPhos	$97\%^c$
5^d	1.0:1.1	THF	2.5	XantPhos	$47\%^c$
$6^{d,e}$	1.5:1.0	THF	2.5	XantPhos	$80\%^c$

^{*a*} Conditions: Pd(OAc)₂ (*y* mol %), ligand (2*y* mol %), Et₃N (1.3 equiv), 10 mol % KOAc in THF (0.06 M), reflux, 15 min, then **1a** and **2a** were added in a minimum of THF. Refluxed until total consumption of the limiting reagent, determined by TLC. ^{*b*} Determined by ¹H NMR of the crude mixture, using DMF as the internal standard. ^{*c*} Isolated yield. ^{*d*} Reaction concentration: 0.25 M. ^{*e*} 1.8 equiv of Et₃N were used.

1a (1.5 equiv) was required to obtain the cross-coupled product **3a** in good yield (80%).

For 5-bromo-pyrazole **1b**, compound **3a** was formed in 75% yield by using 1.5 equiv of **1b** and 10 mol % of Pd(OAc)₂ (Table 2, entry 1). However, when the catalyst loading was decreased to 5 mol %, **3a** was only formed in 5% yield, and **1b** was almost entirely recovered (Table 2, entry 2). The replacement of XantPhos by dppf was detrimental as **3a** was isolated in 55% yield (Table 2, entry 3), and more electron-rich phosphines such as dtpf and dcpf were found to be poor ligands in this coupling reaction (Table 2, entries 4 and 5).



entry	y (mol %)	ligand	3a (yield)
1	10	XantPhos	$75\%^b$
2^d	5	XantPhos	$5\%^b$
3	10	dppf	$55\%^b$
4	10	dtpf	$12\%^c$
5	10	dcpf	$9\%^c$

^{*a*}Conditions: Pd(OAc)₂ (y mol %), ligand (2y mol %), Et₃N (1.8 equiv), 10 mol % KOAc in THF (0.06 M), reflux, 15 min, then **1a** and **2a** were added in the minimum of THF. Refluxed until total consumption of **2a**, determined by TLC. ^{*b*}Determined by ¹H NMR of the crude mixture, using DMF as the internal standard. ^{*c*} Isolated yield. ^{*d*}Reaction concentration: 0.25 M.

Under the best conditions determined for 1a (conditions A) and 1b (conditions B), the coupling reaction of halopyrazoles with H-phosphonate esters 2a-2e appeared to be general, as the corresponding C5-phosphonylated compounds were isolated in modest to good yields (11–86%). In general, the use of conditions B rather than conditions A resulted in significantly higher yields in the cross-coupled products, even with the less reactive 5-bromo-pyrazole 1b. Not surprisingly, the coupling attempt with diallylphosphite 2f led to a complex mixture, and the cross-coupled product could not be isolated (Table 3, entry 11).

Secondary phosphine oxides 2g-j as well as H-phosphinates 2k-m can also engage in the cross-coupling with 1a and 1b to produce the corresponding phosphonylated derivatives, as illustrated in Table 4. Modest to excellent yields were obtained (19–94%), and once again conditions **B** were found to be significantly superior to conditions **A**. Most notably, we demonstrated that phosphonylidenes directly substituted by an alkyl chain were suitable substrates for this reaction (Table 4, entries 6–9 and 12–13), despite their lower stability compared to aryl-substituted phosphonylidenes.¹⁰ It is worth noting that, in the case of

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 Table 3. Scope of the Pd-Catalyzed Cross-Coupling of

 H-Phosphonates with 5-Halo-pyrazoles 1a and 1b



entry	Х	2	conditions ^a	product (yield) ^b
1 2	I Br	O H EtO ^{-/2} H EtO 2a	A B	3a (80%) 3a (75%)
3 ^c 4 ^c	I Br	O H MeO [∽] P MeO 2b	A B	3b (9%) 3b (47%)
5^d 6^d	I Br	0 Ⅱ PhO [∽] /, PhO 2c	A B	3c (20%) 3c (46%)
7^d 8^d	I Br	$\begin{array}{c} & O \\ F_3C & -P \\ F_3C & O \\ & O \\ & O \\ & O \\ & 2d \end{array}$	A B	3d (35%) 3d (40%)
9^d 10^d	I Br		A B	3e (11%) 3e (86%)
11	Br		В	3f (0%)

^{*a*} Conditions A: Pd(OAc)₂ (2.5 mol %), XantPhos (5 mol %), Et₃N (1.8 equiv), KOAc (10 mol %) in THF (0.25 M), reflux, 15 min, then **1** and **2** were added in the minimum of THF, refluxed until total consumption of **2**, determined by TLC. Conditions **B**: Pd(OAc)₂ (10 mol %), XantPhos (20 mol %), Et₃N (1.8 equiv), KOAc (10 mol %) in THF (0.06 M), reflux, 15 min, then **1** and **2** were added in the minimum of THF, refluxed until total consumption of **2**, determined by TLC. ^{*b*} Isolated yield. ^{*c*} *i*Pr₂NEt was used instead of Et₃N. ^{*d*} Temperature was increased to 100 °C (sealed tube) to reach complete consumption of **2**.

the sterically hindered di-*tert*-butyl phosphine oxide **2h**, no coupling product was observed (Table 4, entries 4-5). Also, as reported by Montchamp et al.,¹¹ the use of H-phosphinate **2m** instead of **2k** led to an increase of the yield of the cross-coupled product **3** (Table 4, entries 12-13 vs entries 14-15).

Having demonstrated the generality of this method for the phosphonylation of 5-halo-pyrazoles, 3- and 4-iodo-pyrazoles were examined. These latter compounds appeared to be suitable substrates for the cross-coupling, as the corresponding 3- and 4-phosphonyl pyrazoles were isolated in good yields (Table 5, entries 1-3).

 Table 4. Scope of the Pd-Catalyzed Cross-Coupling of

 Secondary Phosphine Oxides and H-Phosphinates with

 5-Halo-pyrazoles 1a and 1b



entry	Х	2	conditions ^a	product (yield) ^b
1 2 3	I I Br	O Ph ⁻ P- Ph 2g O	A B B	3 g (32%) 3 g (75%) 3 g (66%)
$\frac{4^c}{5^c}$	I Br	t-Bu [∽] ⊢H <i>t</i> -Bu 2h	B B	2h (0%) 2h (0%)
6 7	I Br	O Ph´ ' H Me 2i	B B	3i (92%) ^d 3i (48%)
8 9	I Br	Ph [−] P [−] H ∠ 2j	B B	3j (88%) ^d 3j (27%)
10 11	I Br	O P P OEt 2k	A B	3k (87%) 3k (77%)
12 ^e 13 ^e	I Br	O = Et ⁻ H OEt 21	A B	3l (19%) 3l (58%)
14 15	I Br	O Ph ⁻ P- OCy 2m	A B	3m (90%) 3m (94%)

^{*a*} Conditions A: Pd(OAc)₂ (2.5 mol %), XantPhos (5 mol %), Et₃N (1.8 equiv), KOAc (10 mol %) in THF (0.25 M), reflux, 15 min, then **1** and **2** were added in the minimum of THF, refluxed until total consumption of **2**, determined by TLC. Conditions **B**: Pd(OAc)₂ (10 mol %), XantPhos (20 mol %), Et₃N (1.8 equiv), KOAc (10 mol %) in THF (0.06 M), reflux, 15 min, then **1** and **2** were added in the minimum of THF, refluxed until total consumption of **2**, determined by TLC. ^{*b*} Solated yield. ^{*c*} Temperature was increased to 100 °C (sealed tube) to reach complete consumption of **2**. ^{*d*} Reaction concentration: 0.25 M. ^{*e*} *i*Pr₂NEt was used instead of Et₃N.

Functionalization of the pyrazole ring at the C3-position is a difficult transformation, owing to its low nucleophilicity and electrophilicity.¹² Recently, Sames et al. proposed an elegant solution to this problem by transposing the SEM-protecting group from one nitrogen to the other one in a one-step procedure, thus transforming the unreactive C3-position to a more acidic C5-position.¹³

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^{*a*} Conditions: Pd(OAc)₂ (2.5 mol %), ligand (5 mol %), Et₃N (1.8 equiv), KOAc (10 mol %) in THF (0.25 M), reflux, 15 min, then **1** and **2a** were added in the minimum of THF, refluxed until total consumption of **2a**, determined by TLC. ^{*b*} Isolated yield.

However, they only established the generality of this method for pyrazoles substituted by an aryl group. Herein, we demonstrated that this method can be used to transform C5-phosphonylated pyrazoles **3** into C3-phosphonylated pyrazoles 7-10 in yields ranging from 82% to 87% (Table 6).

Finally, the cleavage of the *N*-SEM group in 3 could be realized by using TFA in CH_2Cl_2 to produce the corresponding pyrazoles 11-12 in yields ranging from 71% to 73% (Table 7).

In conclusion, a general palladium-catalyzed cross-coupling between 3-, 4-, and 5-halo-pyrazoles and H-phosphonates, H-phosphinates, and secondary phosphine oxides was developed. The present reaction provides a highly general access to phosphonylated pyrazoles in one step from an easily accessible halogenated precursor. Future work will be devoted to demonstrate the feasibility of the coupling reaction using more functionalized pyrazoles. Table 6. N-SEM Group Transposition



Table 7. N-SEM Group Cleavage





^{*a*}Isolated yield. ^{*b*}TFA (15 equiv), no additive. ^{*c*}TFA (30 equiv), EtOH (2 equiv) added as additive. ^{*d*}Obtained as a single tautomer. ^{*e*}Obtained as a mixture of tautomers.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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