Direct palladium-catalyzed alkenylation, benzylation and alkylation of ethyl oxazole-4-carboxylate with alkenyl-, benzyl- and alkyl halides†

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The ethyl oxazole-4-carboxylate was directly and regioselectively alkenylated, benzylated and alkylated with alkenyl-, benzyl-, allyl- and alkyl halides in the presence of catalytic amounts of palladium acetate with caesium carbonate using Buchwald's JohnPhos ligand.

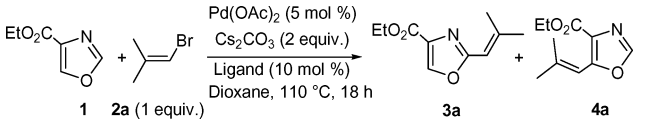
The direct functionalization of arenes proceeding through catalytic transition metal-catalyzed C–H bond activation has raised a lot of interest as an alternative to classical cross-coupling reactions due to its atom-economy, high functional group tolerance, and mild reaction conditions.[1] The direct formation of C–C_{azole} bonds has received particular attention as substituted azoles are architectural units in the design of natural products, pharmaceutics and organic materials. Current developments in the direct vinylation and alkylation of heteroaromatics are mainly centered on Fujiwara–Moritani oxidative Heck coupling and the transition metal-catalyzed hydroheteroarylation of alkenes and alkynes.[1d–j,2] The great feature of these processes based upon direct C–H activation followed by addition to a double or a triple C–C bond lies in the suppression of the pre-functionalization step. To date the literature on direct transition metal-catalyzed alkenylation, alkynylation and allylation of azoles with alkenyl-, alkynyl- and allyl halides or triflates remains sparse although these coupling partners could be more valuable than alkenes and alkynes for controlling both the regio- and stereochemical outcomes of the alkenylation and alkylation processes.[3] In this communication we report the direct C-2 regio- and stereocontrolled palladium-catalyzed alkenylation, benzylation and alkylation with alkenyl-, benzyl- and alkyl halides of the commercially available ethyl oxazole-4-carboxylate **1**. This approach provides novel access to diverse 2-alkenylated and 2-alkylated oxazole-4-carboxylates[4] which are common valuable precursors of increasing occurrence in 2,4-disubstituted oxazole natural products.[5]

Initially, the direct palladium-catalyzed vinylation of **1** was investigated using the combination of $Pd(OAc)_2$ pre-catalyst, Cs_2CO_3 as the base and dioxane as the solvent, which proved effective in the analogous direct (hetero)arylation of **1** with aryl halides[6] (Scheme 1 and Table 1). The performance of the ligand in the direct vinylation of **1** with 1-bromo-2-methylpropene carried out in dioxane in a sealed tube at 110 °C for 18 h is summarized in Table 1 (runs 1–10).

Table 1 Ligand effect on the regioselective direct vinylation of **1** with **2a**[a]

Run	Ligand	**1**, conversion (%)	Yield (%)[b] **3a**	**4a**
1	none	41	34	–
2	PPh_3	68	51	15
3	P(*o*-tol)$_3$	90	63	25
4	PCy_3	66	49	15
5	P^{t}Bu$_3$·HBF_4	95	63	29
6	P(biphen-2-yl)Cy_2	100	92 (100)[c]	–
7	IMes	70	62	–
8	IPr	41	38	–
9	PEPPSI-IPr[e]	60	38	17
10	HBP[d,e]	100[f]	17	51

[a] Reactions were performed using **1** (0.35 mmol), 1-bromo-2-methylpropene (0.35 mmol), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (2 equiv.) and ligand (10 mol%) in 1 ml of dioxane at 110 °C for 18 h. [b] Isolated yield. [c] 1-Bromo-2-methylpropene (0.7 mmol). [d] HBP: Hermann-Beller's palladacycle. [e] Catalyst used without $Pd(OAc)_2$ and ligand added. [f] The 2- and 5-vinylated isomers were accompanied by the 2,5-divinylated isomer, isolated in 23% yield.



Scheme 1 Pd(0)-catalyzed direct vinylation of **1** with **2a**.

It should be noted that the direct vinylation of **1** occurring without any ligand provided exclusively the 2-vinyl oxazole **3a** in poor 34% yield (run 1). By using a ligand, the conversion of **1** was dramatically increased and **3a** was obtained as the major product along with the 5-vinyl oxazole isomer **4a** whilst the divinylated oxazolecarboxylate was not produced (runs 1–8). Among the broad range of trialkylphosphines and carbene ligands examined, excellent conversions of **1** (90–100%) could be obtained using P(*o*-tol)$_3$, P^{t}Bu$_3$ or P(biphenyl-2-yl)Cy_2 but only Buchwald's JohnPhos ligand provided exclusively **3a** in 92% yield (run 6). Most remarkably, **3a** was obtained in quantitative yield, without any trace of 2,5-divinylated oxazole-4-carboxylate, when the direct vinylation was carried out with a two-fold-excess of 1-bromo-2-methylpropene (run 6). Finally, the use of *N*-heterocyclic carbene-based palladium complex PEPPSI-IPr[7] or the Hermann-Beller's HBP palladacycle[8] was examined but these two catalyst systems proved to be less effective than the $Pd(OAc)_2$/JohnPhos ligand system (runs 9,10).[9] The scope and limitations of the optimized direct vinylation reaction of **1** using two vinyl halide equivalents are summarized in Table 2. Notably, the direct vinylation of **1** with 1-chloro-2-methylpropene was successfully accomplished, providing **3a** in excellent 91% yield without any trace of 5-vinyl- or 2,5-divinylisomers. However, the

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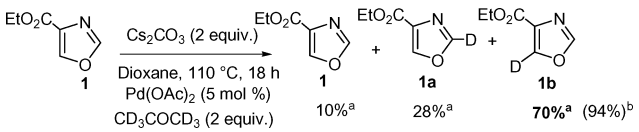
Table 2 Pd-catalyzed direct alkenylation of **1** with various vinyl halides **2**[a]

Run	**2**, R-X	X	Product	**3**	Yield (%)
1	**2b**	Cl		**3a**	91
2	**2c**	Br		**3b**	55[b]
3	**2d**	Br		(*E*)-**3c**	97
4	**2e**[c]	Br		(*Z*)-**3d**	60[d]

[a] **1** (0.35 mmol) was reacted with 2 equiv. of vinyl halide **2** with $Pd(OAc)_2$/P(biphenyl-2-yl)Cy_2 (5:10 mol%), Cs_2CO_3 (2 equiv.) in dioxane at 110 °C. [b] The 2,5-divinylated product was isolated in 28% yield. [c] 5:1 mixture of *Z*- and *E*- isomers. [d] The *E*-isomer was isolated in 13% yield.

direct vinylation reaction using 2-bromopropene led to a mixture of 2- and 5-vinyl isomers which were isolated in 55% and 28% yields respectively (runs 2,3). We then focused on the stereochemical behaviour of the direct palladium-catalyzed vinylation process of **1**. In the first experiment, the commercially available (*E*)-2-bromobut-2-ene was reacted with **1** leading exclusively to the single stereoisomer (*E*)-**3c** in an excellent 97% yield (run 3). A direct vinylation reaction using the bromostyrene **2e** as a 5:1 mixture of *Z*- and *E*-isomers was then carried out with **1**, providing a 4.8:1 mixture of styrenyloxazole conformers (*Z*)-**3d** and (*E*)-**3d** isolated in 60% and 13% yields (run 4). The applicability of the optimized catalyst system (5 mol% $Pd(OAc)_2$, 10 mol% JohnPhos ligand and Cs_2CO_3) in the direct vinylation with vinyl halides encouraged us to further explore novel functionalizations of **1** at the C-2 position, such as direct allylation, benzylation and alkylation using allyl-, benzyl- and alkyl halides (Table 3). The palladium-catalyzed direct benzylation of **1** with benzyl halides **2f,g** was first carried out (runs 1–4). Although the direct benzylations of **1** using one or two equivalents of benzyl bromide were fully regioselective for the 2-position, surprisingly both reactions proceeded very smoothly affording the 2-benzyloxazole-4-carboxylate **3e** in 15% and 39% yields respectively. In fact the benzyl chloride proved a much more efficient coupling partner than benzyl bromide in the direct benzylation leading to the expected 2-benzyloxazole-4-carboxylate in 86% yield when two equivalents of electrophile were used. Substrates bearing an electron-withdrawing group such as 4-fluorobenzyl chloride **2h** as well as those with electron-releasing groups such as 4-methoxybenzyl chlorides **2i** or 2-(chloromethyl)naphthalene **2j** were also successfully engaged in direct benzylation of **1** affording the corresponding 2-substituted oxazole-4-carboxylates in good 82%, 91% and 80% yields (runs 5–7). It should be noted that two equivalents of electrophiles were used to complete the conversion of **1** and 5-arylmethyl isomers appeared to be the exclusive side-compounds, which were ready isolated from the 2-arylmethyl isomers **3f–h**. Thus, contrary to the direct vinylation of **1** , no trace of dibenzylated oxazole-4-carboxylate was observed. At this stage direct allylation of **1** with allyl halides was evaluated. Allyl bromide immediately proved to be an ineffective coupling partner since the direct allylation of **1** using indifferently one or two equivalents of allyl bromide failed. As previously observed in vinylating and benzylating experiments, the chlorinated coupling partner showed excellent reactivity with **1** (runs 8–10) but only the 2-vinylated oxazole-4-carboxylates **3i** and **3a** arising from subsequent palladium-catalyzed side-isomerization of the 2-allyloxazole-4-carboxylate were obtained in almost quantitative yields using 2 equivalents of allyl chloride (runs 9,10).

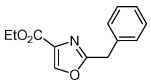
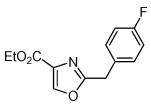
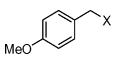
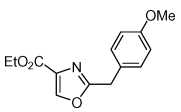
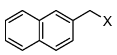
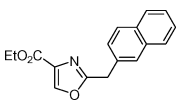
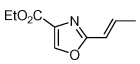
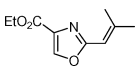
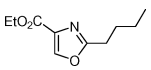
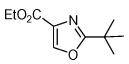
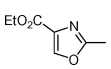
In the final part of this study we turned to the challenging direct alkylation of **1** using alkyl halides (runs 11–14). Interestingly, a first assay of direct alkylation of **1** using 1 equivalent of butyl bromide was successfully achieved providing exclusively the 2-butyloxazole-4-carboxylate **3j** in modest 32% yield (run 11). However, the yield could be dramatically improved (60%) using 2 equivalents of electrophile (run 12) and notably occurs without any trace of 5-mono- or 2,5-dialkylated oxazole. It should be noted that the butyl chloride proved an ineffective coupling partner even when other ligands were used such as Buchwald's SPhos and XPhos ligands, IMes, IPr as well as P^tBu_3 which were originally designed for the crucial oxidative step of C–Cl bonds. Moreover, the reaction with the highly sterically hindered *tert*-butyl bromide failed (runs 13). However, interestingly the direct C-2 methylation of **1** with methyl iodide was successfully achieved (run 14) affording a mixture of 2-methyloxazole-4-carboxylate **3l** and starting material **1** which could be separated only by using preparative HPLC on silica gel (Li-chrosorb 10 μm). To our knowledge there is no literature precedent of the direct Pd(0)-catalyzed C–H alkylation of heteroaromatics using alkyl halides and here we have reported the first two examples. It should be noted that the direct C–H benzylation and alkylation of **1** with benzyl- and alkyl bromides and iodides could not be regarded as being a simple nucleophilic displacement of the halogen by a C-2 carbanionic intermediate arising from a deprotonative pathway at the 2-position of **1** since direct alkylations of **1** carried out without the $Pd(OAc)_2$ precatalyst failed. Moreover, when acetone-d_6 was used as a cosolvent as a source of deuterium, the H/D exchange occurred predominantly at the C-5 position (Scheme 2).



Scheme 2 C-2 *vs* C-5 H/D exchange experiments.[a] Percentage of **1**, **1a–b** was determined by ^{1}H NMR analysis.[10] [b] Isolated yield of the mixture of **1**, **1a** and **1b** based on the amount of **1** used.

In conclusion we succeeded in carrying out the C-2 regioselective palladium-catalyzed direct alkenylation, benzylation and alkylation of the commercially available ethyl oxazole-4-carboxylate with alkenyl-, benzyl- and alkyl halides. The methodology provides new routes towards highly valuable oxazole-4-carboxylate precursors and can be directly used for an innovative synthetic approach towards 2,4-disubstituted oxazole natural product synthesis. Furthermore, in the recent context of research into novel coupling partners for the direct palladium-catalyzed coupling of heteroaromatics *via* C–H bond activation, the first examples of palladium-catalyzed direct C–H benzylation and alkylation of heteroaromatics with benzyl- and alkyl halides are

Table 3 Pd-catalyzed direct alkylation of **1** with benzyl-, allyl- and alkyl halides **2**[a]

Run	**2**, R-X		X	Equiv.	Product	**3**	Yield (%)
1	**2f**		Br	1		**3e**	15
2	**2f**		Br	2			39
3	**2g**		Cl	1			51
4	**2g**		Cl	2			86[b]
5	**2h**		Cl	2		**3f**	82[c]
6	**2i**		Cl	2		**3g**	91
7	**2j**		Cl	2		**3h**	80[d]
8	**2k**		Cl	1		**3i**	41
9	**2k**		Cl	2			97
10	**2l**		Cl	2		**3a**	98
11	**2m**		Br	1		**3j**	32
12	**2m**		Br	2			60
13	**2n**		Br	2		**3k**	n.r.
14	**2o**		I	2		**3l**	41

[a] **1** (0.35 mmol) was reacted with 1 or 2 equiv. of alkyl halide with $Pd(OAc)_2$/P(biphenyl-2-yl)Cy_2 (5:10 mol%), Cs_2CO_3 (2 equiv.) in dioxane at 110 °C. [b] The 5-benzylated product was also isolated in 14% yield. [c] The 5-benzylated product was also isolated in 11% yield. [d] The 5-benzylated product was also isolated in 17%.

described here. Further investigations to highlight in detail the mechanism of the direct regioselective C-2 functionalizations of **1** including the previously reported direct C-2 (hetero)arylation[6] are being undertaken. The anionic cross-coupling mechanism involving deprotonation at the C-2 position of **1** is ruled out on the basis of the H/D exchange study (Scheme 2).[1,10] The other palladium-catalyzed pathways, concerted metallation-deprotonation (CMD), oxidative C–H insertion, electrophilic substitution (S_EAr), and Heck–like are now considered.[11]

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