Letter

Pd-Catalyzed Regioselective Decarboxylative / C-H #-Alkoxyalkenylation of Heterocycles using #-Carboxyvinylethers

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Pd-Catalyzed Regioselective Decarboxylative / C–H α-Alkoxyalkenylation of Heterocycles using α-Carboxyvinylethers

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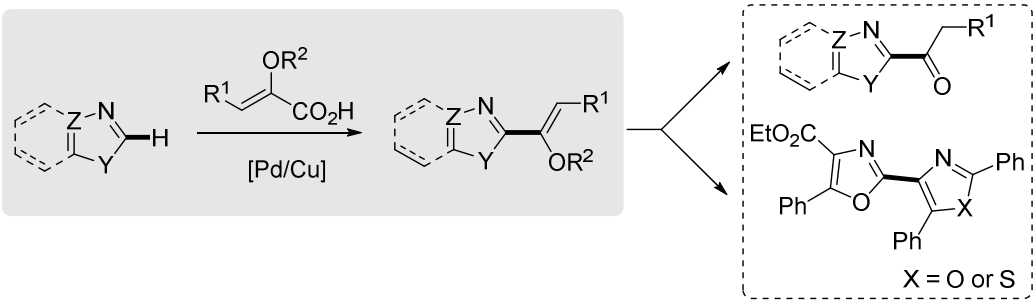
Keywords: α-Alkoxyalkenylation, Enol ether, C-H Functionalization, Azoles, Decarboxylative cross-coupling, Pd-catalysis, α-Carboxyvinylethers



Abstract: A direct introduction of vinyl ethers into C–H bond of heterocycles is reported. For this purpose, decarboxylative direct C–H cross-coupling of 1,3-diazoles with α-carboxyvinyl ethers as coupling partners was achieved under Pd(0)/Cu(I) cooperative catalysis to produce various α-heteroarylated vinylethers. This methodology was applied to the innovative production of heteroarylated enolizable ketones and naturally-occurring bis-oxa(thia)zoles.

Vinyl ethers are found in many natural products and biologically active molecules. They represent one of the most reactive and synthetically-valuable class of hetero-substituted alkenes for the synthesis of complex organic molecules. Employed as masked-ketones and activated alkenes, vinyl ethers might be involved in number of chemical transformations such as hydrolysis, reduction, cycloaddition reactions, Heck and related cross-coupling reactions to produce poly-functionalized ketones, alcohols, heterocycles and alkenes.[1-2]In particular, the, transition-metal catalyzed heteroarylation of enol ethers has drawn lot of attention. The Heck reaction of non- prefunctionalized vinyl ethers with halides is currently the most step-economical developed strategy. [3,4] However, this reaction is fraught with difficulties associated with selectivity issues (α/β and *Z*/*E*). Therefore, others traditional cross-coupling approaches have been considered using pre-metalated vinyl ethers in order to control the regio- and the stereochemistry (Figure 1).[2,5] In this context, straightforward, atom-economic, and environmentally benign method for direct heteroarylation of vinyl ethers with a full control of the *E*/*Z* stereochemistry and α/β regiochemistry are highly demanded.

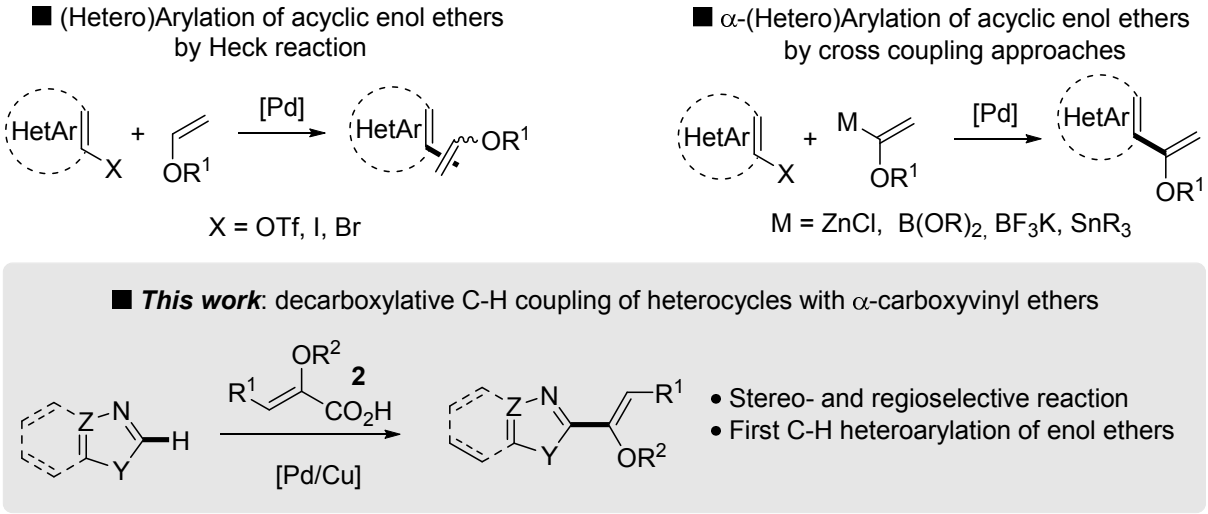
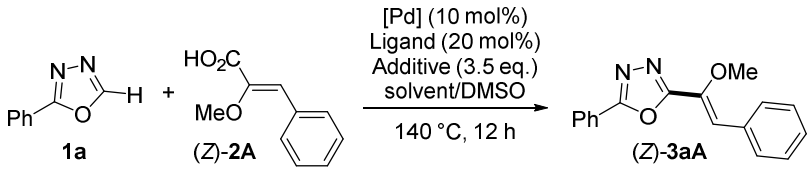


Figure 1. Pd-catalyzed heteroarylation of enol ethers

Faced with the necessity to do '*better with less*', the direct C–H functionalization of heterocycles has emerged as powerful and complementary approach avoiding the generation of metalated heteroarenes, sometimes air-moisture sensitive and unstable.[6] Since the past decades, explosive achievements have been made in direct C-C bonds formation including arylation, alkenylation, alkylation, carbonylation and acylation. As a complementary approach to dramatically increase the functional diversity, the direct C–H introduction of valuable functions, which offers several options for chemical-modulation and/or reactivity, is of great synthetic interest. While remarkable advances have been made in direct C–H alkenylation of heterocycles,[7] the transition-metal catalyzed direct C–H α-alkoxyalkenylation of heterocycles with vinyl ethers has not been reported so far.[8] In line with our ongoing interest in the direct introduction of hetero-substituted alkenes into C–H bond of heterocycles,[9] and knowing that carboxylic acids are regarded as potential air-stable and easy to handle masked catalytic organometallic building blocks by transition-metal-mediated extrusion of CO_2,[10-13] we turned our attention to the α-alkoxylated acrylic acids (**2**) as coupling partners for palladium-catalyzed hetero-substituted alkenylation of heterocycles (Figure 1). Herein, Pd(0)-catalyzed and Cu(I)-mediated decarboxylative / C–H α-alkoxyalkenylation of (hetero)arenes using challenging α-alkoxylated acrylic acids (**2**) is reported. This methodology gives access to stereocontrolled *gem*-heteroarylated vinyl ethers, and offers a rational and step-economical route to attractive polysubstituted heteroarylated enol ethers. As an application, the decarboxylative / C–H α-alkoxyalkenylation reaction was applied to afford a novel and convenient entry point into α,β-enolizable α-ketoazole structures[14] and biologically active C2-C4' linked azoles.[15]

Table 1. Decarboxylative coupling: Reaction optimization



Entry	[Pd]	Ligand	[Additive]	Ratio **2A**/**1a**	Solvent/DMSO (8/3)/[Conc.]	Yield [%][a,b]
1	$Pd(OAc)_2$	dcpe	$CuCO_3$•$Cu(OH)_2$	1.5:1	1,4-Diox./0.2M	n.r.
2	$Pd(OAc)_2$	dcpe	$CuCO_3$•$Cu(OH)_2$	1.5:1	DMAc/0.2M	23
3	$PdBr_2$	dcpe	$CuCO_3$•$Cu(OH)_2$	1.5:1	DMAc/0.2M	34
4	$Pd(acac)_2$	dcpe	$CuCO_3$•$Cu(OH)_2$	1.5:1	DMAc/ 0.2M	41
5	$Pd(acac)_2$	dppe	$CuCO_3$•$Cu(OH)_2$	1.5:1	DMAc/ 0.2M	62
6	$Pd(acac)_2$	dppe	Cu_2O	1.5:1	DMAc/ 0.2M	55
7	$Pd(acac)_2$	dppe	$Cu(OAc)_2$	1.5:1	DMAc/ 0.2M	29
8	$Pd(acac)_2$	dppe	Ag_2CO_3	1.5:1	DMAc/ 0.2M	29
9	$Pd(acac)_2$	dcpe	$CuCO_3$•$Cu(OH)_2$	2/1	DMAc/0.2M	78
10	$Pd(acac)_2$	dppe	$CuCO_3$•$Cu(OH)_2$	2/1	DMAc/0.1M	96
11	--	--	$CuCO_3$•$Cu(OH)_2$	2/1	DMAc/0.1M	n.r.

[a]Reaction conditions: [Pd] (10 mol%), ligand (20 mol%), **1a** (0.1 mmol), (*Z*)-**2a** (0.2 mmol), $CuCO_3$•$Cu(OH)_2$ (3.5 equiv), solvent/DMSO (8:3), MS 4Å, 140 °C, 12 h. [b]Yield based on isolated product after flash chromatography. 1,4-Diox = 1,4-Dioxane. n.r. = no reaction

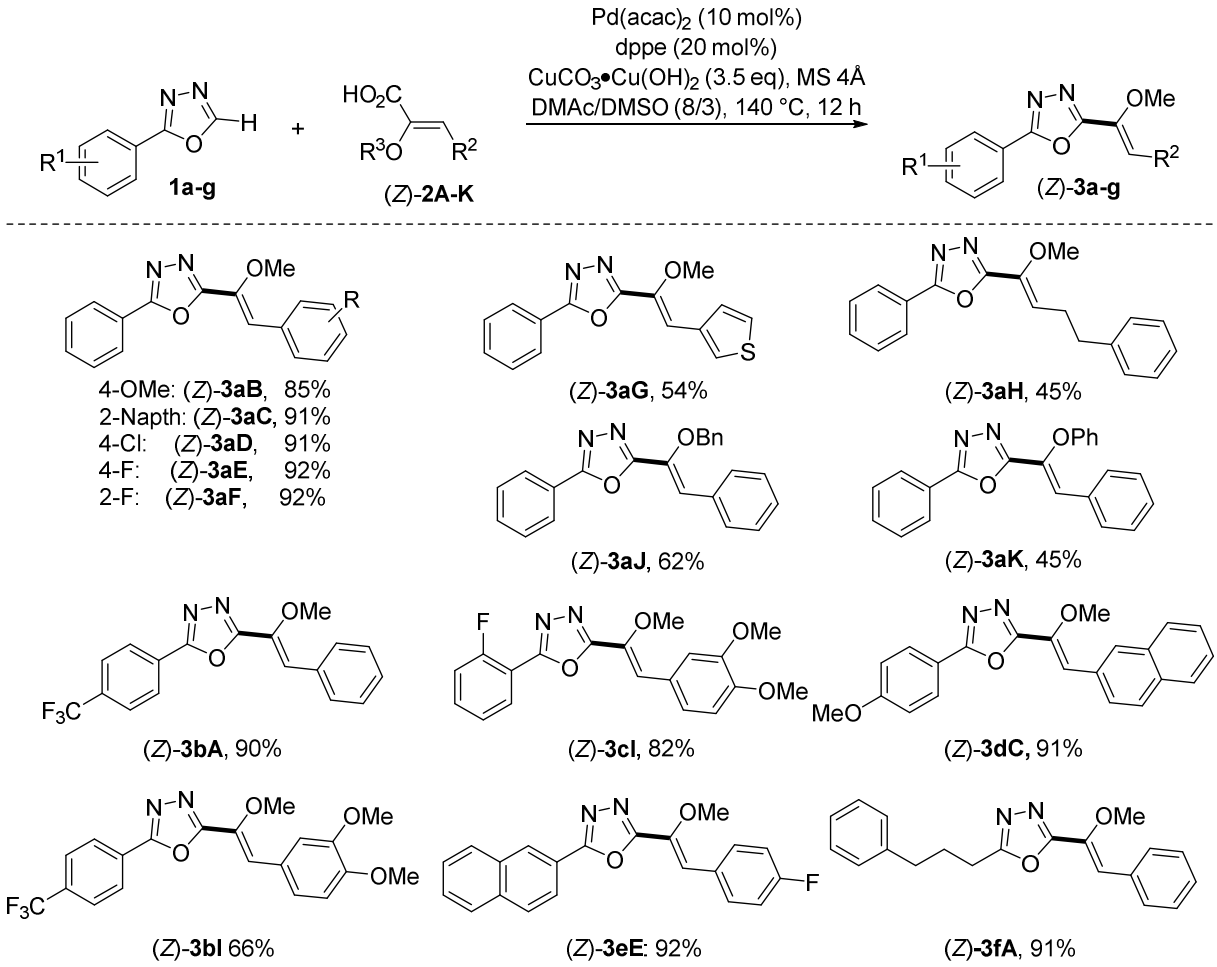
We first established reaction conditions to operate the decarboxylative C–H coupling of 1,3,4-oxadiazole **1a** with β-arylated *α*-methoxyacrylic acid **2A** prepared as pure (*Z*)-isomer through an aldol reaction followed by a dehydroxylation and hydrolysis of the resulting ester[16] (Table 1). We observed that the heteroarylated enol ether **3Aa** was not produced using strictly the Greaney's conditions.[11a] However, by switching the 1,4-dioxane/DMSO mixture of solvents for DMAc/DMSO, the reaction occurred leading to the expected enol ether **3Aa** in 23% yield.

Interestingly, the enol ether **3aA** was only isolated as pure (*Z*)-isomer (Table 1, entries 1 and 2) and the stereochemistry was confirmed by single crystal X-ray structure determination.[17a,b] After an additional screening of palladium sources and phosphine ligands,[17c] enol ether **3aA** was isolated in a fair 62% yield using $Pd(acac)_2$ catalyst and dppe as ligand. However, the use of other copper sources or silver carbonate as oxidants was detrimental (Table 1, entries 6-8) leading predominantly to protodecarboxylative side product **4** (Figure 2). Full conversion of 1,3,4-oxadiazole **1a** as well as quantitative production of (*Z*)-**3aA** were finally reached by reacting 2 equivalents of α-methoxyacrylic acid (Z)-**2A** along with reducing of the (*Z*)-**3aA** concentration from 0.2 to 0.1 M (Table 1, entries 9-10). When lowering the amount of [Pd]-charge (from 10 to 5 mol%) and removing the molecular sieve, the efficiency of the Pd(0)-catalyzed and Cu(I)-mediated decarboxylative process is significantly affected.[17c] Moreover the decarboxylative coupling failed without palladium and ligand[18] (Table 1, Entry 11).

With the optimized conditions in hands, we turned our attention to the scope and limitations of the Pd-catalyzed and Cu-mediated decarboxylative C–H alkenylation methodology. We first performed the C-2 alkenylation of 1,3,4-oxadiazoles **1a-g** with a broad panel of substituted β-arylated *α*-methoxyacrylic acids **2A-I**. Overall, the cross-coupling was successfully achieved whatever the electronic effect and the position of substituents on both aromatic units of coupling partners **1** and **2** affording *α*-methoxyoxadiazolylalkenes (*Z*)-**3** in fair to excellent yields (Scheme 1). The β–heteroarylated α-methoxyacrylic acid **2G** led also to the desired product (*Z*)-**3aG** in 54% isolated yield. We were pleased to find that alkyl groups on both coupling partners **1** and **2** are also tolerated under our optimized experimental conditions. The corresponding 1,2-trisubstituted methoxylated alkenes (*Z*)-**3aH** and (*Z*)-**3fA** were obtained in moderate to good yields. Interestingly, the methodology remains efficient with α-benzyloxy- and

α-phenoxyacrylic acids (*Z*)-2**J**-**K** leading to corresponding enol ethers **(Z)-3aJ** and **(Z)-3aK** in moderate 45-62% isolated yields.

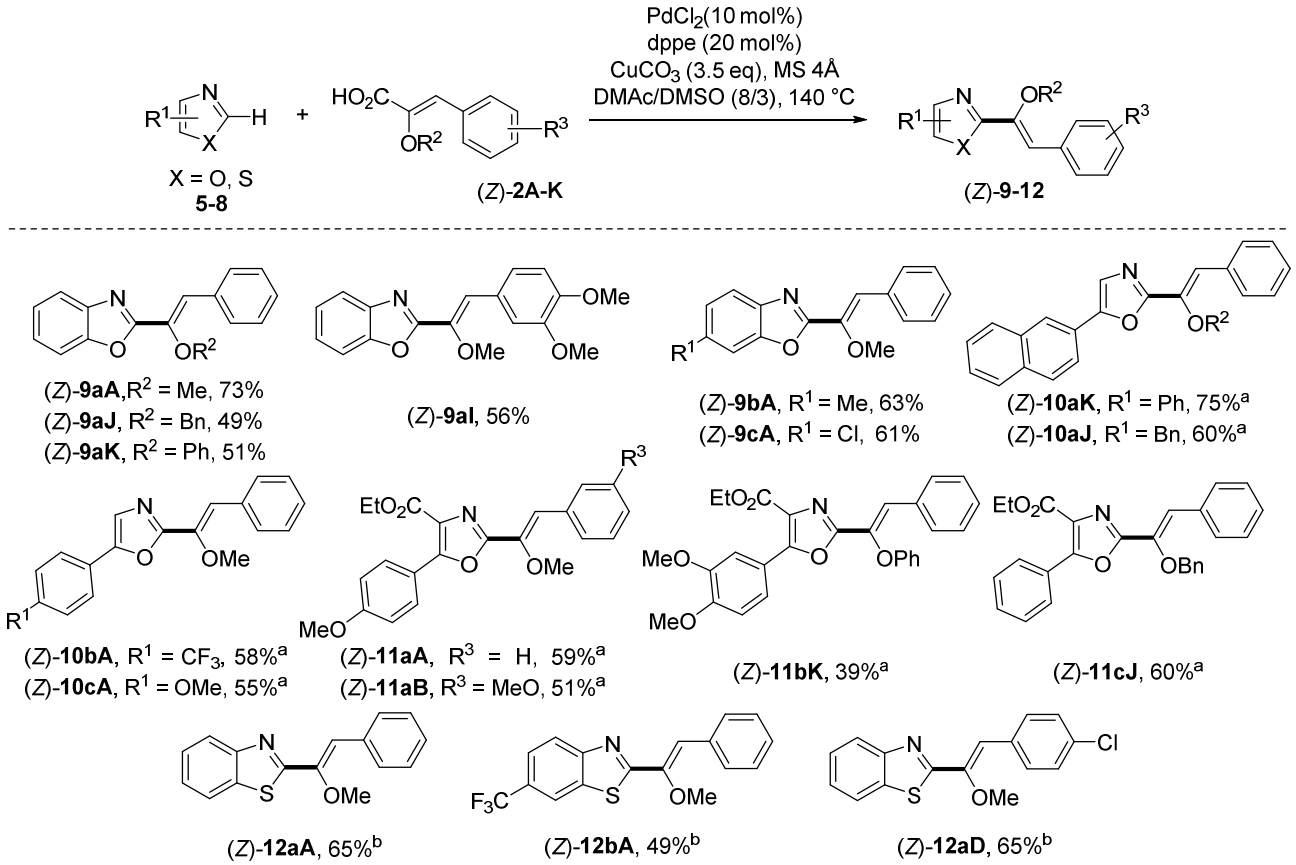
Scheme 1. Scope of decarboxylative / direct C–H α-methoxyalkenylation of 1,3,4-oxadiazoles with various α–alkoxyacrylic acids **2A**-**K**



We next sought to investigate the scope of heterocycles (Scheme 2). Interestingly, electronically different heterocycles displayed a good reactivity with α-methoxyacrylic acids (Z)-**2A-I.** The α-phenoxy and α-benzyloxy (Z)-**2J**-**K** also proved to be reactive by switching the

palladium source $Pd(acac)_2$ to $PdCl_2$ to provide a broad set of heteroarylated enol ethers (*Z*)-**9-11**in fair to excellent yields (Scheme 2).

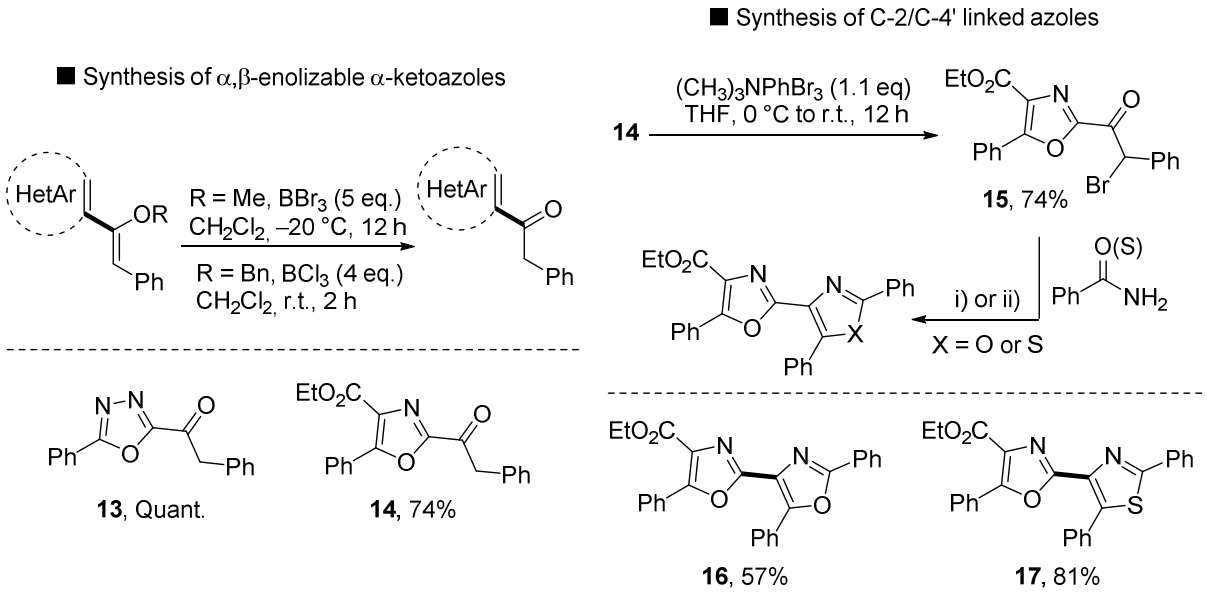
Scheme 2. Scope of decarboxylative / direct C-H alkenylation of azoles using various α–alkoxyacrylic acids **2A**-**L** as coupling partners. [a] dcpe instead of dppe. [b] Addition of CuI (10 mol%).



The decarboxylative / C–H α-alkoxyalkenylation of variously substituted benzoxazoles **5a-c** as well as oxazole derivatives, such as 5-arylated oxazoles **6a-c** and 5-arylated ethyl oxazole-4-carboxylates **7a-d**, were successfully achieved using either dppe or dcpe ligands to produce the heteroarylated enol ethers **9-11** in 50-73% yields while limiting the main homocoupling side reaction. α–Phenoxy and benzyloxyalkoxyacrylic acids **2J-K** were also reactive with

(benzo)oxazole derivatives **5-7** leading to the corresponding heteroarylated enol ethers **9-11J-K** in moderate 35% to good 75% isolated yields. To complete the scope of heterocycles, we found that the cross-coupling of α-methoxyacrylic acid (*Z*)-**2A** with less acidic benzothiazole **8a** under the optimized protocol provided the heteroarylated **12aA** in only 25% isolated yield. However, the reaction could be improved by using CuI as additive. Indeed, this latter is supposed to facilitate the catalytic metalation key-step of less-acidic and more-electron-rich 1,3-diazoles, such as thiazole and imidazole, through the formation of [Cu]-heterocycle pre-complex in order to increase the C2-H acidity.[19, 20] In that case, the benzothiazolyl enol ether **12aA**, as well as two additional benzothiazolyl enol ethers **12bA** and **12aD**, have been produced in 49% and 65% isolated yields (Scheme 2).

Scheme 3. Synthesis of biologically active structures. Reaction conditions: i) X = O, $AgSbF_6$ (1 eq), CH_2Cl_2, -20 °C, 12 h; ii) X = S, $CaCO_3$ (1 eq), EtOH, reflux, 6 h.



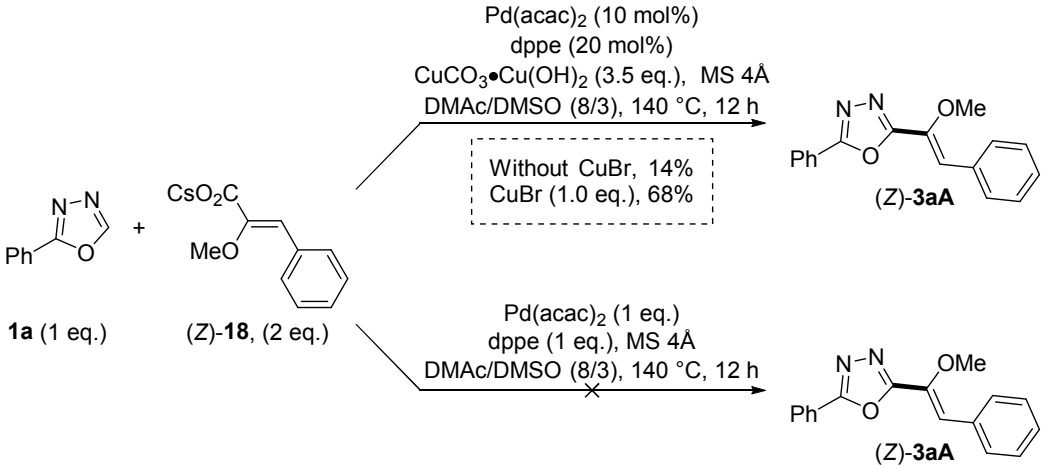
To illustrate the potential usefulness of this novel regio- and stereo-controlled access to heteroarylated enol ethers, two synthetic applications were investigated (Scheme 3). To date and to the best of our knowledge, while the palladium-catalyzed direct C-H aroylation of 1,3-diazoles have been already reported,[21-23] the direct production of valuable 2-(2-oxoxalkyl)-1,3-diazoles[24] through direct C2-H functionalization of 1,3-diazoles remain highly challenging. In this context, the first application of this methodology was directed towards the challenging synthesis of α,β-enolizable α-keto-1,3-diazoles which are immediately available by adding a deprotection step of the enol ether function. Selected as inhibitors of fatty acid amide hydrolase,[14] the heteroarylated ketones **13** and **14** were produced by treatment of methylated enol ethers (*Z*)-**3aA** and benzylated (*Z*)-**11cJ** with BBr_3 and BCl_3 respectively, according to the nature of the enol ether.[25, 26] As an additional application, the α,β-enolizable α-ketoazoles **14** was used as a building block for the synthesis of naturally-occurring C2-C4' linked bis-oxa(thia)zole.[15] In particular, the α,β-enolizable α-ketoazole **14** was used both to prepare the C2-C4' linked bis-oxazole **16** applying the Blümlein-Lewis reaction[27] and the C2-C4' linked oxazole-thiazole **17** *via* the Hantzsch's condensation.[28]

To gain insight into the mechanism, we carried out several control experiments (Scheme 4). First, the decarboxylative cross-coupling was executed with cesium (*Z*)-α-methoxycinnamate salt **18** (Scheme 4, eq 1). Interestingly, the addition of CuBr used as electrophile to generate the methoxycinnamate copper salt was required to generate the desired product (*Z*)-**3aA** in good yield. Moreover, under stoichiometric amount of $Pd(acac)_2$ and dppe as ligand, no cross-coupling product was obtained. Importantly, the Heck coupling reaction of cesium (Z)-α-methoxycinnamate salt **18** with phenyl bromide followed by CuBr-mediated protodecarboxylation[29] led to the exclusive production of the β-diphenylated vinyl ether **19**

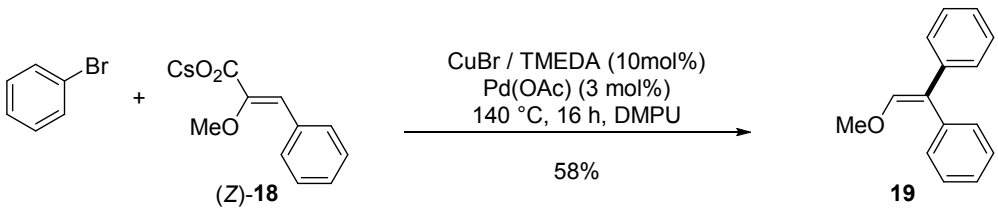
(Scheme 4, eq 2).[17c] Therefore, the oxidative Heck-type / protodecarboxylative sequence for the synthesis of (Z)-**3aA** can be discarded. All these data highlighted the importance of $CuCO_3$•$Cu(OH)_2$ both in the oxidation step of Pd(0) to Pd(II) and in the crucial generation of copper carboxylate intermediate that may lead to the generation of alkenyl copper intermediate (**II**) through the *ipso*-decarboxylative cupratation process. (Figure 2)

Scheme 4. Additional experiments for mechanism study

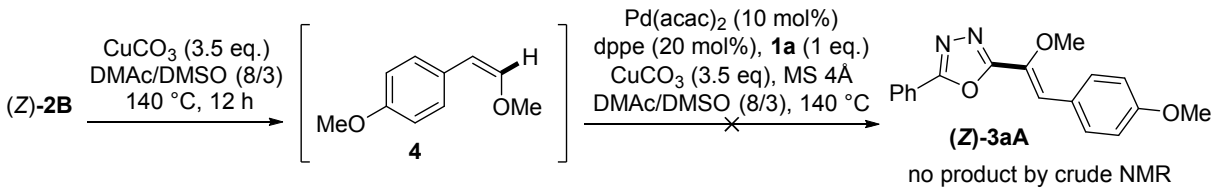
(1) *Role of [Cu] in the decarboxylative step*



(2) *Heck reaction followed by protodecarboxylative process*



(3) *In situ protodecarboxylation then Fujiwara-Moritani reaction:*



This latter may be facilitated by the electron-withdrawing inductive effect of the methoxy group [30] since we noted that the decarboxylative cross-coupling of 1,3,4-oxadiazole **1a** with cinnamic acid failed under the optimized conditions.[13, 17c] We then investigated the cross-coupling of the protodecarboxylative enol ether **4** with **1a** under optimal experimental conditions (Scheme 4, eq 3).[31] The reaction failed precluding a two-steps mechanism involving initially a protodecarboxylation followed by a Fujiwara-Moritani oxidative Heck-type coupling. Finally, the effect of radical scavenger was examined, and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) did not inhibit the reaction.[17b] Thus a radical process is unlikely involved.

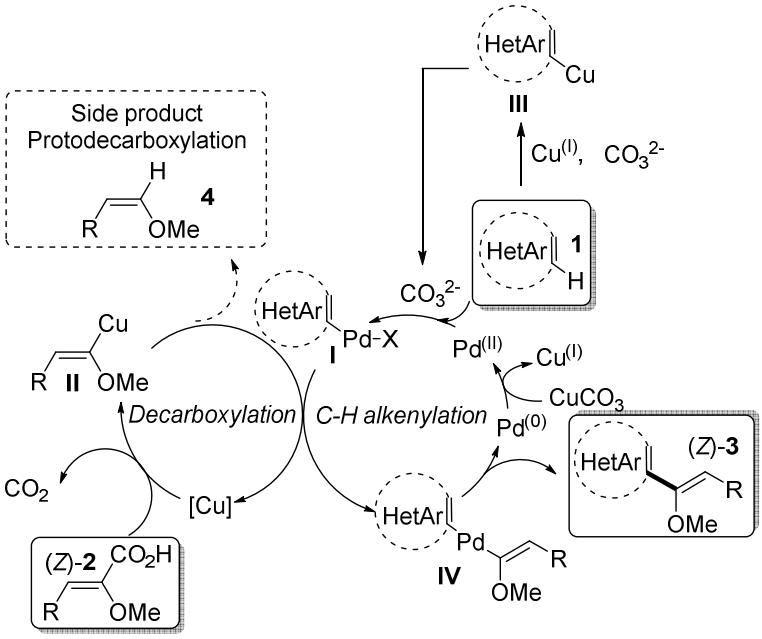


Figure 2. Proposed catalytic pathways.

Based on previous reports [10-12] and our control experiments, a plausible reaction pathway is delineated in Figure 2. The success of this coupling depends on the interception of the generated alkenyl copper intermediate (**II**) produced by copper-catalyzed extrusion of CO_2, and the C-2-palladated heterocycle **(I)** through a transmetalation step. The generation of the C-2-palladated key-intermediate (**I**) is highly dependent both on the intrinsic acidity and nucleophilicity of C2-H

site of 1,3-(oxa)diazoles and may be considered according to two pathways, (i) the catalytic palladation of heterocycles with $Pd(OAc)_2$ through base-assisted concerted[34] or none-concerted (carbanionic-type) process,[35] or (ii) the transmetalation of the *in situ* generated heteroarylcopper intermediate (**III)** to $Pd(OAc)_2$.[19] Base on our experimental observations, we presume that most acidic oxazole derivatives are appropriate for direct palladation with or without [Cu]-assistance.[19e] By contrast, the use of CuI as additive for the success of the coupling with benzothiazoles indicates a copper-assisted pre-activation of the heterocycle leading probably to the generation of benzothiazolylcopper intermediate **III**.[19-20]

In conclusion, we have reported a practical, straightforward, and unprecedented regio- and stereoselective direct introduction of enol ethers onto C–H bonds of heterocycles by decarboxylative/ direct C–H alkenylation of various azoles under palladium catalysis using α-carboxyenol ether as new hetero-substituted alkenylating agent. This procedure offer a rational and step-economical route to attractive regio- and stereocontrolled 1,2-polyheteroarylated enol ethers in moderate to good yield. Moreover, this methodology constitutes a novel and convenient entry point into the synthesis of α,β-enolizable α-ketoazoles and C2-C4' linked bis-azoles.

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Supporting information: Experimental procedures, characterization data, details on the X-ray analyses of compound (*Z*)-**3aA**, and ^{1}H and ^{13}C NMR spectra for compounds.

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