RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances

Communication

Palladium-Catalyzed Direct Alkenylation of 4-Hydroxy-2-pyridones

Tania Katsina, Elissavet E. Anagnostaki, Foteini Mitsa, Vasiliki Sarli and Alexandros L. Zografos*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

The first direct C-3 alkenylation of *N*-substituted-4-hydroxy-2-pyridones with unactivated alkenes has been achieved under conventional palladium acetate catalysis. The presented protocol enables the efficient production of functionalized furo[3,2-*c*]-pyridones-2 when terminal alkenes are utilized and 3-alkenyl-4-hydroxy-2-pyridones when more substituted reaction partners are involved. The mild reaction conditions allow easy, scalable access to pyridone derivatives that resemble core structures isolated from natural alkaloids.

The 4-hydroxy-2-pyridone heteroaromatic core is increasingly attracting the attention of scientific community due to its abundance in natural alkaloids and its implication in important biological systems.[1] Its biological action is mainly depended on the molecular decoration presented at 3- and 5-positions of its core. Specific 3-acyl-substituted derivatives were recognized as important neuritogenic compounds targeting the stress pathway kinase MAP4K4.[2] On the other hand, selected 3-alkyl derivatives were documented as potent antibacterials[3] and antimalarials,[4] potentially through their ability to chelate iron.[5] Furthermore, bicyclic analogues of 2-pyridones, utilizing the 4-hydroxy-substituent in cycloetheric rings were also found to possess potent antibacterial activities.[6] Interestingly, aromatic bicyclic pyridones and especially furo[3,2-*c*]-pyridones-2 and their 2- and 4-thio-derivatives were utilized as unnatural base pairs for the *in vivo* expansion of an organism's genetic alphabet and the prophylaxis or the treatment of obesity (Figure 1).[7]

Although pyridone-2 derivatives are increasingly filling the biological active space, still their true biological profile is hampered by the unavailability of simple protocols for their synthesis. The last five years, tremendous efforts have been witnessed in utilizing direct functionalization practices to enrich the synthetic libraries of 2-pyridones and simplify

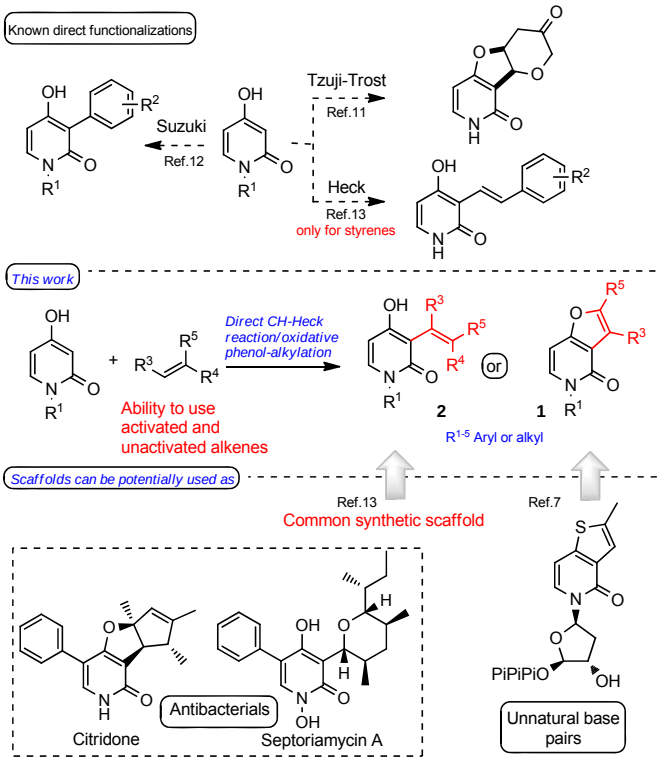


Figure 1. Reported direct functionalizations of 4-hydroxy-2-pyridone heteroaromatic core; Current work which enables the utilization of unactivated alkenes on the synthesis of diverse pyridone scaffolds and their potential biological utility.

synthetic protocols. Following these efforts, pyridone-2 core and heteroaromatic analogues have been able to be functionalized selectively in 5- and 3-positions by utilizing mainly electrophilic palladation[8] or radical initiated SOMO/HOMO interaction[9] and in the 6-position by nucleophilic metal addition.[10] On the other hand, the literature is particularly poor when describing the direct functionalization of 4-hydroxy-2-pyridones. To the best of our knowledge, only couple of references exist describing their direct 3-alkylation,[11] 3-arylation[12] and very recently their 3-alkenylation with a limited number of activated styrenes[13] by

Aristotle University of Thessaloniki, Department of Chemistry, Laboratory of Organic Chemistry, University Campus 54124, Thessaloniki, Greece. Email: alzograf@chem.auth.gr
Electronic Supplementary Information (ESI) available: Characterization data, experimental procedures and copies of spectra see DOI: 10.1039/x0xx00000x

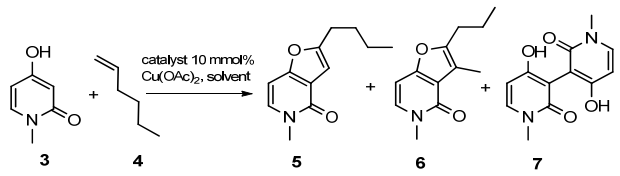
utilizing modified palladium-catalyzed Tzuji-Trost, Suzuki and Heck-type reactions respectively (Figure 1). Surprisingly, none of the reported direct alkenylation methods either on the 4-hydroxy-2-pyridone,[13b] analogous heteroaromatics[13a] or pyridone-2 rings[8a] have manage to utilize an unactivated alkene as reaction partner of the requisite Heck reaction, precluding the utilization of such methods on the preparation of useful alkylated substrates as those shown in Figure 1.

Recently, we were involved into the synthesis of 4-hydroxy-2-pyridone alkaloids[14] and during this endeavour we discovered that we were able to selectively direct metalate the 3-position of *N*-alkylated-4-hydroxy-2-pyridone moiety, even at ambient temperature with the aid of palladium acetate.[12]

Based on this success, we challenged ourselves whether it would be possible to target directly the underexplored alkylated 4-hydroxy-2-pyridone derivatives, especially those resembling our previously discovered common synthetic intermediate **2** for the synthesis of citridone and septoriamycin A antibacterials[15] or the biological intriguing bicyclic compounds **1** (Figure 1).

In order to test this working hypothesis, a palladium-catalyzed direct Heck type reaction of 4-hydroxy-2-pyridone ring with unactivated alkenes was envisioned.[16] *N*-Methyl-4-hydroxy-2-pyridone (**3**) and 1-hexene (**4**) were chosen as starting materials for this survey. In our first attempts, when **3** was allowed to react with **4** in DMF at 90 °C, in the presence of palladium acetate, mixtures of 3-alkylated products were isolated along with unreacted pyridone **3**. Pufication and characterization of the reaction mixture revealed not the expected simply 3-alkylated product but instead the coupled products **5-6** along with high ratio of the previously described methyl-dipyridone (**7**)[12] (Table 1).

Table 1. Palladium-Catalyzed Reaction of *N*-Methyl-4-hydroxy-2-pyridone and unactivated-alkene, hexene-1: Optimization of Reaction Parameters.[a]



Entry	Catalyst (10 mol %)	Solvent	Conversion (%)	Combined Yield (%)	Ratio[b] **5:6:7**
1	$Pd(OAc)_2$	DMF	76	66	0.6:0.1:1
2	$Pd(OAc)_2$	Dioxane	73	68	3:5:1
3	**$Pd(OAc)_2$**	**CH_3CN**	**80**	**76**	**2:1:1**
4	$Pd(OAc)_2$	AcOEt	50	42	2:1:1
5	$Pd(OAc)_2$	Toluene	-	0	NR
6	-	CH_3CN	-	0	NR
7	$Pd(OAc)_2$[c]	CH_3CN	10	8	2:1:1
8	$FeCl_3$	Dioxane	-	0	NR
9	CuI	DMF	-	0	NR
10	$PdCl_2$	CH_3CN	71	69	1:1:1
11	$PdCl_2$[d]	CH_3CN	60	57	0.5:0:1
12	$Pd(PPh_3)_4$	CH_3CN	-	0	NR

[a] Reaction conditions: **3** (0.08 mmoles), **4** (0.32 mmoles), solvent (1 mL), catalyst (10 mmol%), $Cu(OAc)_2$ (0.16 mmoles), 90 °C, 12h. [b] Ratio was determined by ^1H NMR spectroscopy. [c] Benzoquinone (2 equiv) was used as oxidant. [d] Silver carbonate (0.08 mmoles) was used as an additive.

The ratio of these products was highly dependent on the polarity of the solvent as evidenced by their yields when the reaction was screened in a window from DMF to toluene. The reaction remained slugish in all attempts providing high yields of unreacted starting materials, even at long reaction times (20-100% for 12h reaction; Table 1). More polar solvents promote the coupling reaction (DMF *vs* toluene entries 1 and 5; Table 1), but produce higher ratio of dipyridone byproduct, compared to less polar solvents, something that was also observed in the arylation of 4-hydroxy-2-pyridones.[12]

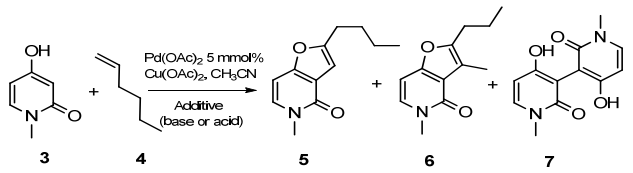
Acetonitrile was recognized as the solvent of choice not only by producing the lowest yields of unreacted starting pyridone **3** but also by minimizing the ratio of the produced isomeric compound **6** (entry 3; Table 1). Interestingly dioxane produce an inverse ratio of the two alkylated products changing the **5**:**6** = 40:20 acetonitrile ratio to **5**:**6** = 26:39 (entries 2 and 3; Table 1). Entries 6, 8 and 9 support that the reaction proceeds only with the aid of a palladium complex as catalyst, except in cases where styrene is used as coupling partner, where $FeCl_3$ was found to be an efficient radical activator,[17] something that additionally corroborates for the effectiveness of styrenes as reaction substrates. Finally, palladium acetate is superior to other palladium catalytic systems as $PdCl_2$, $PdCl_2/Ag_2CO_3$ and $Pd(PPh_3)_4$ (entries 10-12; Table 1).

Trying to explain the persistent production of the isomeric compound **6** in the reaction mixture, we attributed part of its formation on the prior isomerization of the terminal alkene in the presence of palladium catalysis. Literature survey suggests that these isomeric mixtures can be attributed to palladium cationic intermediates.[18] Having this in mind, we wanted to evaluate the reaction profile when basic or acidic additives are utilized (Table 2).

Addition of a base accelerates the reaction that now proceeds at lower temperature but still without driving it to completion (entries 1-6; Table 2). Unfortunately, although the use of basic conditions minimizes isomeric product **6**, it enhances the production of dipyridone **7**. Potassium carbonate is superior to other bases, with Et_3N being the worse producing undefined mixture of products (entry 1; Table 2).

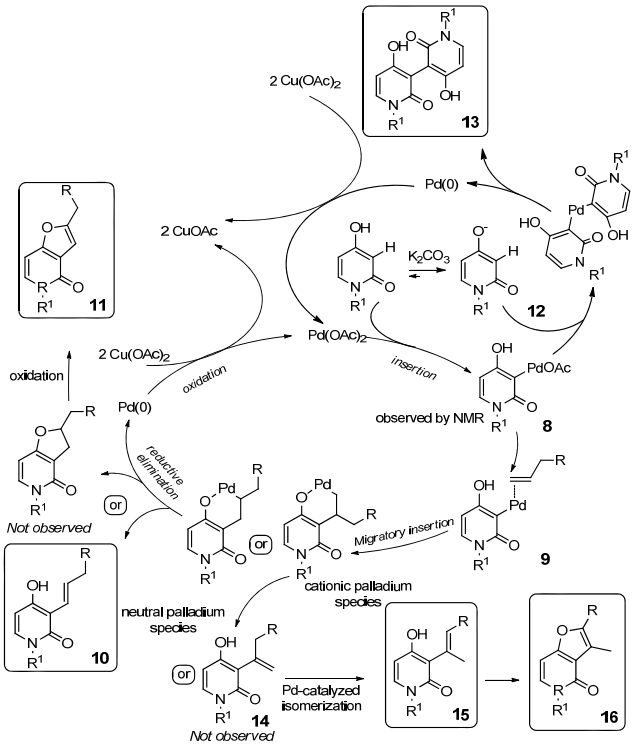
On the other hand, utilization of acidic conditions accelerate the reaction to completion, even at low temperatures (entry 7-14; Table 2) and provides a simpler reaction mixture profile as observed by ^1H NMR spectroscopy. Acidic conditions prohibited the formation of dipyridone **7**, while minimized the production of isomer **6**, majorly due to the milder reaction conditions that can be employed (Table 2). Formic acid leads to minimization of isomer **6** (with the exception of dioxane) compared to other acids, like acetic and pivaloic acid. It has to be pointed out that higher temperature and prolonged reaction times, still with the aid of formic acid, can produce low yields of the isomer **6**. Based on these results, optimized reaction conditions include the utilization of CH_3CN as the solvent, with acidic conditions provided by 2 eq of formic acid, at 40 °C. Commonly, depending on the alkene substrate (Scheme 2), the reaction does not require more than 3h at 40 °C to be completed.

Table 2. Involvement of Basic and Acidic Conditions on Palladium Catalyzed Reaction of *N*-Methyl-4-hydroxy-2-pyridones with Hexene-1.[a]



Entry	Additive	Solvent	Temp (°C)	Time (h)	Conv (%)	Yields (%)[b] 5:6:7
1	Et_3N	CH_3CN	90	12	-	-
2	K_2CO_3	CH_3CN	90	12	62	25:5:32
3	$NaHCO_3$	CH_3CN	90	12	72	45:9:18
4	K_2CO_3	CH_3CN	60	12	64	20:0:44
5	K_2CO_3	CH_3CN	25	24	40	10:0:30
6	K_2CO_3	Dioxane	60	12	68	17:17:34
7	CH_3COOH	None	90	4	100	71:29:0
8	CH_3COOH	CH_3CN	90	4	100	59:38:0
9	PivOH	CH_3CN	90	4	100	48:40:12
10	HCOOH	CH_3CN	90	4	100	76:10:0
11	HCOOH	Dioxane	90	4	100	36:63:0
12	HCOOH	CH_3CN	60	3	100	82:0:0
13	**HCOOH**	**CH_3CN**	**40**	**3**	**100**	**80:0:0**
14	HCOOH	Dioxane	40	3	100	59:41:0

[a]Reaction conditions: Reaction conditions: **3** (0.24 mmoles), **4** (0.72 mmoles), solvent (3 mL), catalyst (5 mmol%), $Cu(OAc)_2$ (0.24 mmoles), additive (0.48 mmoles), at indicative temperature and time. [b] Yields correspond to isolated compounds.



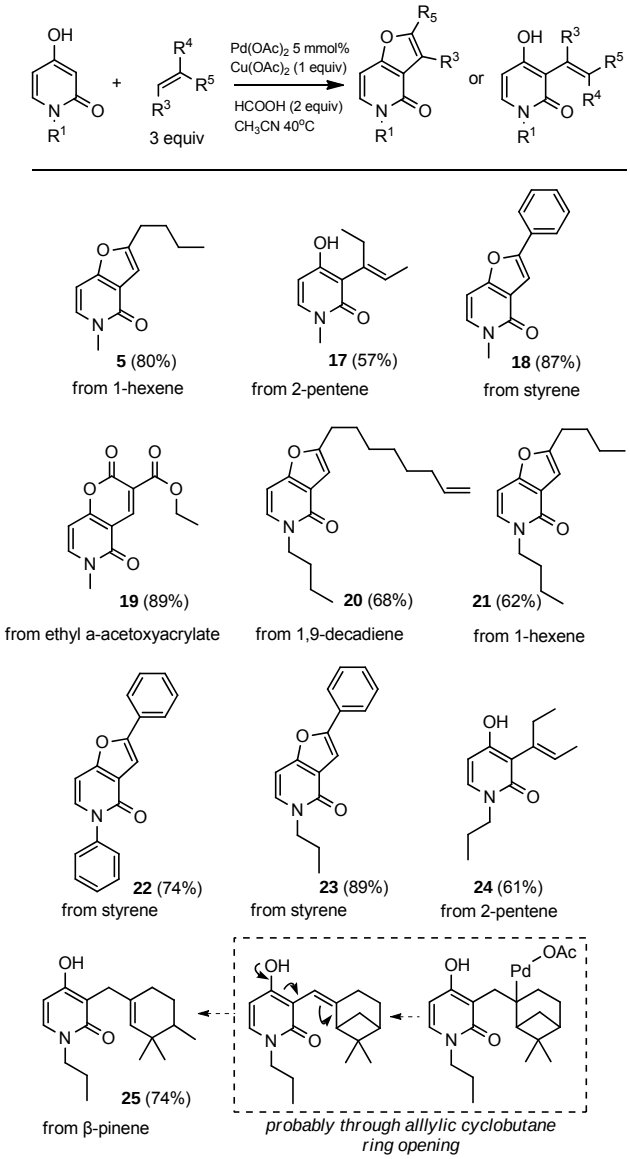
Scheme 1. Postulated Reaction Mechanism

Preliminary studies on the reaction mechanism suggests a catalytic cycle that starts with the direct activation of 4-hydroxy-2-pyridone by Pd(II) (Scheme 1).[19] Migratory insertion of pyridone-palladium species **8** to alkenes, followed by reductive elimination produces products **10** or **11** after further oxidation, depending on the substrate and releases Pd(0). Pd(0) is re-entered the catalytic cycle after its oxidation by copper acetate (Scheme 1).

Apart from the main catalytic pathway, anion of 4-hydroxy-2-pyridone (**12**), formed under basic conditions, becomes a competing substrate to alkene for palladium species **8** to produce dipyridone (**13**). On the other hand, the formation of the observed isomeric compound **16** is much less obvious and can be attributed potentially either to the direct isomerization of the starting terminal alkene under the applied reaction conditions and its later reaction with complex **8** or due to the poor regioselectivity of the migratory insertion of palladium-complex **8** directly to the alkene (intermediate **9**), isomerization of the resulting **14** and further elaboration to the final products **15** and **16**. Interestingly, such alkenes isomerizations are known to be enhanced in the presence of free phenols something that corroborates to the validity of the later pathway.[20]

Wishing to investigate further these pathways, we checked the ability of 1-hexene to isomerize independently by palladium, omitting the use of 4-hydroxy-2-pyridone in reaction conditions. Interestingly, 1-hexene produces its isomer, 2-hexene in 5-10 % yield when is heated in dioxane overnight at high temperatures (100-120 °C). No evidence of such isomerization has been witnessed at lower temperatures and shorter reaction times. This of course does not exclude isomerization of the alkene from complex **8**, but so far no evidence of even traces of isomerized alkene have been identified by GC. What is more, utilization of similar compounds to the potential isomerized alkene, like 2-pentene, as reaction partners did not provide the furo-cyclized product **16** or the regioisomeric compound **15** but rather leads to a regioselective addition to form compound **17** (Scheme 2). Inductively, the latter suggests the direct dependence of regioselectivity of migratory insertion of intermediate **9** on the reaction outcome, which is diverted in the cases of acetonitrile and dioxane media. Several studies, related to the Heck reaction, correlate the regioselectivities observed on the insertion of terminal electron rich alkenes to the nature of the palladium species applied in the Heck reaction.[21] Based on these studies, our case, as indicated from the regioselectivities presented above, indicates a neutral-type mechanism in acetonitrile which changes to cationic when reaction is conducted in dioxane.[21] Although this interesting behavior is important and it seeks of further investigation it does not meet the purpose of the current study.

Having in our hands the optimized protocol for the alkenylation of 4-hydroxy-2-pyridones, we seeked to explore its ability on different substrates including terminal and internal alkenes but also activated partners as styrenes and acrylates (Scheme 2). As shown in Scheme 2, *N*-substituted 4-hydroxy-2-pyridones were able to react under the optimized reaction conditions with electron rich and electron deficient alkenes providing moderate to excellent yields on the final



Scheme 2. Substrate Scope and a Potential Mechanism for the Formation of Compound **25**

products (57-96%) by applying low temperature and short reaction times (2.5-4.5h). Electron rich, unactivated, terminal alkenes are providing the lowest yields compared to styrene and acrylates. On the contrary, the utilization of unactivated, internal alkenes produce 3-alkylated products in moderate yields which do not proceed further to elaborate etherocyclization or furan formation. The latter is potentially attributed to the high sterics invoked in the transition state of the final cyclization step. This was further supported by the reaction of 2,2-disubstituted alkenes to produce also uncyclized 3-alkylated products due to sterics (compound **25** from β-pinene).

Interestingly, in all cases, cyclized and non-cyclized, the regioisomeric product has not been observed in higher than 10% yield. What is more, an unproblematic scale-up was feasible under the optimized reaction conditions. Thus, when 2 mmoles of *N*-methyl-4-hydroxy-2-pyridone and styrene were reacted a similar yield of compound **19** was isolated (90%), even at lower loadings of palladium acetate catalyst (2%).

In conclusion, the first direct 3-alkenylation of *N*-substituted 4-hydroxy-2-pyridones with unactivated alkenes is reported through a palladium acetate catalyzed, oxidative coupling. Compared to the other alkenylation methods, our protocol enables the utilization of both activated and unactivated alkenes as reaction partners. It solves the highly challenging issue of migratory regioselectivity allowing an easy and scalable access to highly functionalized 4-hydroxy-2-pyridones that can be readily used to access an array of biological intriguing compounds.

Notes and references

1 H. J. Jessen and K. Gademann, *Nat. Prod. Rep.* 2010, **27**, 1168.
2 (a) P. Schöder, T. Förster, S. Kleine, C. Becker, A. Richters, S. Ziegler, D. Rauh, K. Kumar and H. Waldmann, *Angew. Chem. Int. Ed.* 2015, **54**, 12398; (b) K. Schmidt, W. Günther, S. Stoyanova, B. Schubert, Z. Li and M. Hamburger, *Org. Lett.* 2002, **4**, 197.
3 M. M. Wagenaar, D. M. Gibson and J. Clardy, *Org. Lett.* 2002, **4**, 671.
4 M. Isaka and M. Tanticharoen, *J. Org. Chem.* 2001, **66**, 4803.
5 A. Jegorov, V. Matha, M. Husak, B. Kratochvil, J. Stuchilik, P. Sedmera and V. Havlicek, *J. Chem. Soc, Dalton Trans.* 1993, 1287.
6 (a) M. R. TePaske, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *Tetrahedron Lett*. 1991, **32**, 5687; (b) B. B. Snider and Q. Lu, *Synth. Commun.* 2001, **31**, 2667; (c) T. Fukuda, H. Tomoda and S. Omura, *J. Antibiot.* 2005, **58**, 315.
7 For their use as unnatural base pairs please refer to: (a) A. A. Henry, C. Yu and F. E. Romesberg, *J. Am. Chem. Soc.* 2003, **125**, 9638; (b) L. Li, M. Degardin, T. Lavergne, D. A. Malyshev, K. Dhami, P. Ordoukhanian and F. E. Romesberg, *J. Am. Chem. Soc.* 2014, **136**, 826. For prophylaxis from obesity please refer to patents: WO 2013/168760 and EP 2 848 622 A1 from Takeda Pharmaceutical Company Limited.
8 (a) Y. Chen, F. Wang, A. Jia and X. Li, *Chem. Sci.* 2012, **3**, 3231; (b) D. Cheng and T. Gallagher, *Org. Lett.* 2009, **11**, 2639; (c) V. Ortiz-de-Elguea, N. Sotomayor, E. Lette, *Adv. Synth. Catal.* 2015, **357**, 463.
9 A. Nakatani, K. Hirano, T. Satoh and M. Miura, Chem. Eur. J. 2013, **19**, 7691; (b) A. Modak, S. Rana and D. Maiti, *J. Org. Chem.* 2015, **80**, 296; (c) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.* 2014, **79**, 1377.
10 (a) R. Tamura, Y. Yamada, Y. Nakao and T. Hiyama, *Angew. Chem. Int. Ed.* 2012, **51**, 5679; (b) Y. Nakao, H. Idei, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.* 2009, **131**, 15996; (c) R. Odani, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.* 2014, **53**, 10784; (d) P. A. Donets and N. Cramer, *Angew. Chem. Int. Ed.* 2015, **54**, 633; (e) J. G. Sośnicki, P. Dzitkowski and L. Struk, *Eur. J. Org. Chem.* 2015, 5089.
11 (a) A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Angew. Chem., Int. Ed.* 2003, **42**, 5361; (b) A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Tetrahedron* 2004, 9543.
12 (a) E. E. Anagnostaki, V. P. Demertzidou and A. L. Zografos, *Chem. Commun.* 2014, **50**, 6879; (b) L. M. Pardo, A. M. Prendergast, M.-T. Nolan, E. O. Muinhneachain, G. P. McGlacken, *Eur. J. Org. Chem.* 2015, 3540.
13 (a) Similar protocols utilized coumarin heteroaromatic core by X.-c. Tan, H.-y. Zhao, Y.-m. Pan, N. Wu, H.-s. Wang, Z.-f. Chen *RSC Adv.* 2015, **5**, 4972 and (b) its expansion in pyrones and 4-hydroxy-2-pyridones by H. U. Lah, F. Rasool, S. K.

Yousuf, *RCS Adv.* 2015**, 5**, 78958 came to our attention during the preparation of our manuscript, describing the 3-alkenylation of heteroaromatics by activated styrene derivatives.
14 (a) A. D. Fotiadou and A. L. Zografos, *Org. Lett.* 2011, **13**, 4592; (b) A. D. Fotiadou and A. L. Zografos, *Org. Lett.* 2012, **14**, 5664.
15 E. E. Anagnostaki and A. L. Zografos, *Chem. Soc. Rev.* 2012, **41**, 5613.
16 J. Le Bras and J. Muzart, *Chem. Rev.* 2011, **111**, 1170; For selected direct dehydrogenative Heck reactions with unactivated alkenes please see: (a) Z. Wang, B. J. Reinus and G. Dong, *J. Am. Chem. Soc.* 2012, **134**, 13954; (b) A. Deb, S. Bag, R. Kancherla and D. Maiti *J. Am. Chem. Soc.* 2014, **136**, 13602; (c) S. Yu, S. Liu, Y. Lan, B. Wan, and X. Li, *J. Am. Chem. Soc.* 2015, **137**, 1623.
17 Preliminary results show that Fe(III) are efficient catalysts for the 3-selective alkenylation of 4-hydroxy-2-pyridones with styrene dervatives. Studies are under way and will be communicated elsewhere.
18 (a) A. Sen and T.-W. Lai, *Inorg. Chem.* 1981, **20**, 4036; (b) A. Sen and T.-W. Lai, *Inorg. Chem.* 1984, **23**, 3257.
19 Please refer to the supporting information of reference 12 for spectroscopic studies.
20 J. Fan, C. Wan, Q. Wang, L. Gao, Z. Zheng, Z. Wang, *Org, Biomol. Chem.* **2009**, *7*, 3168; For selected related couplings with phenols please see: (a) U, Sharma, T. Naveen, A. Maji, S. Manna, D. Maiti, *Angew. Chem. Int. Ed.* 2013, 52, 12669; (b) S. Agasti, S. Maiti, K. J. Szabo, D. Maiti *Adv. Synth. Catal.*2015, 357, 2331.
21 (a) *The Mizoroki-Heck Reaction* Editor: Martin Oestreich, Wiley 2009; (b) P. Fristup, S. Le Quement, D. Tanner and P.-O. Norrby, *Organometallics* 2004, **23**, 6160; (c) P. Wucher, L. Caporaso, P. Roesle, F. Ragone, L. Cavallo, S. Macking and I. Göttker-Schnetmann, *Proceed. Nat. Acad. Sci.* (USA) 2011, **108**, 8955.