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Palladium-Catalyzed Dehydrogenative C-2 Alkenylation of 5-Arylimidazoles and Related Azoles with Styrenes

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Abstract: The construction of carbon–carbon bonds by direct involvement of two unactivated carbon–hydrogen bonds, without any directing group, ensures a high atom economy of the entire process. Here, we describe a simple protocol for the Pd(II)/Cu(II)-promoted intermolecular cross-dehydrogenative coupling (CDC) of 5-arylimidazoles, benzimidazoles, benzoxazole and 4,5-diphenylimidazole at their C-2 position with functionalized styrenes. This specific CDC, known as the Fujiwara–Moritani reaction or oxidative Heck coupling, also allowed the C-4 alkenylation of the imidazole nucleus when both 2 and 5 positions were occupied.

Keywords: C-H activation; imidazoles; Fujiwara–Moritani reaction; dehydrogenative coupling; oxidative Heck coupling; styrenes; palladium catalysis; copper salts

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1. Introduction

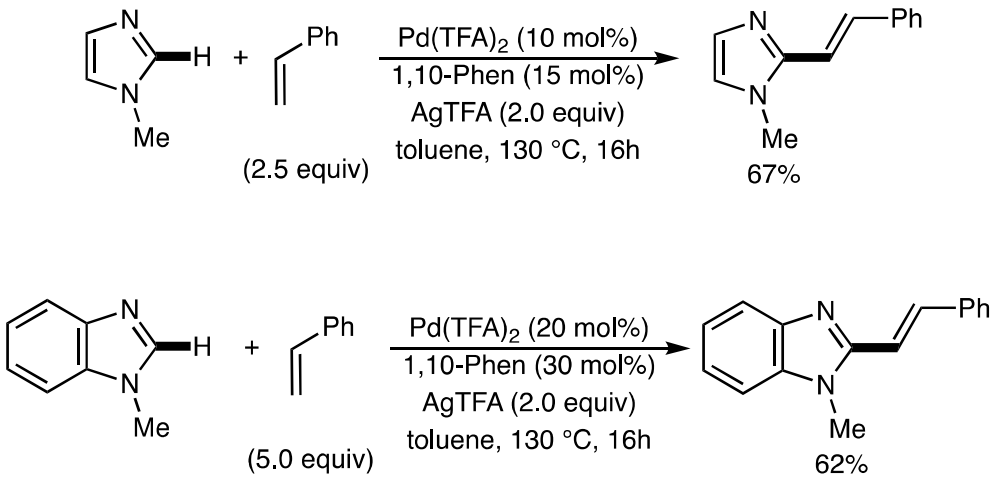
Transition metal-catalyzed carbon–carbon bond-forming reactions that occur by the breaking of carbon–hydrogen bonds are attracting increasing interest in modern synthetic organic chemistry since this approach does not require any pre-activation of the starting materials [1–11]. When compared with conventional cross-coupling methodologies that require the use of organic halides and/or preformed organometallic reagents, this strategy, known as cross dehydrogenative coupling (CDC), allows the obtainment of a high degree of atom economy and structural complexity in the target molecule, while ensuring high chemoselectivity. In addition, unlike traditional cross-couplings, the possibility of avoiding the use of metals and halogens in stoichiometric quantities reduces the production of inorganic waste.

In this context, the palladium-catalyzed cross-coupling between (hetero)arenes and terminal alkenes, known as the Fujiwara–Moritani reaction or even oxidative Heck coupling [12–14],represents one of the most classic CDC reactions for the functionalization of (hetero)arenes [2–4,6,11,15–17].

Although this reaction was first reported in 1967 [12], and thus historically precedes the development of the Mizoroki–Heck alkenylation [18,19], problems related to poor regioselectivity and the need to use oxidants have in the past limited its application in favor of both the aforementioned Mizoroki–Heck alkenylation and the traditional cross-coupling procedures, and also the most recent direct alkenylation of aromatic C-H bonds, also catalyzed by transition metals, involving alkenyl halides [20–26]. If problems associated with the use of oxidants in stoichiometric quantities can be overcome by the latest electrochemical approaches [27–30], the achievement of high regioselectivity is still often an issue to be solved. In this regard, however, it is important to note that when the reaction is conducted using a heteroarene as a partner, the presence of one or more heteroatoms leads to an innate distinction among the different C-H bonds, thus allowing, with appropriate optimization of the reaction conditions, the selective involvement of a specific Csp2-H bond.

Due to our continuous interest in the development of methods for the palladium-catalyzed regioselective C-H functionalization of azoles and in their application to the preparation of new organic materials [31–36], we recently decided to evaluate the Fujiwara–Moritani reaction as an atom economy way to achieve the preparation of styryl-substituted imidazoles. Our interest in this investigation was also given by the fact that while several procedures are reported for the dehydrogenative alkenylation of indoles, pyrroles, and oxazoles [4,11], to the best of our knowledge only two papers reported the synthesis of styryl-substituted imidazoles by dehydrogenative alkenylation, both using only unfunctionalized styrene as the coupling partner.

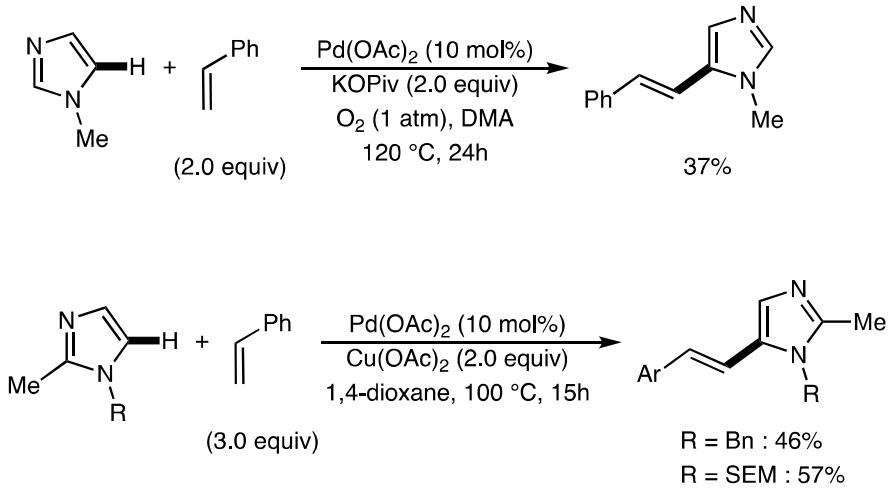
In a study mainly devoted to the dehydrogenative C-2 alkenylation of benzoxazole, in 2014, Ong and coworkers reported the synthesis of 1-methyl-2-styrilimidazole and 1-methyl-2-styrilbenzimidazole starting from the corresponding 1-methylazoles and 2.5–5 equiv of styrene, in the presence of 10–20 mol% palladium(II) trifluoroacetate ($Pd(TFA)_2$) as the pre-catalyst, 15–30 mol% 1,10-phenantroline (1,10-Phen) as the ligand, 1.0–2.0 equiv of silver(I) trifluoroacetate (AgTFA) as the oxidant, in toluene at 130 °C for 16 h (Scheme 1) [37].



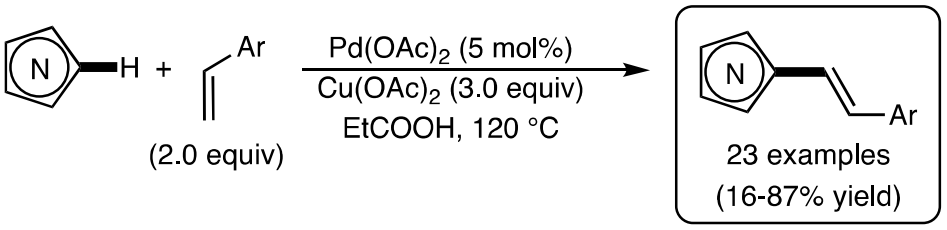
Scheme 1. Cross-dehydrogenative C-2 alkenylation of 1-methylimidazole and 1-methylbenzimidazole with styrene, according to Ong and co-workers [37].

In 2018, Joo and co-workers described a protocol for the regioselective C-5 alkenylation of 1-substituted imidazoles (Scheme 2) [38]. The optimized conditions involved the coupling of 1-methylimidazole with 2.0 equiv of styrene in the presence of 10 mol% palladium(II) acetate ($Pd(OAc)_2$, 2.0 equiv potassium pivalate (KOPiv) in *N*,*N*-dimethylacetamide (DMA) at 120 °C for 24 h under an oxygen atmosphere. When 1,2-disubstituted imidazoles were used as the reaction partners, the authors found it better to perform the coupling using copper (II) acetate ($Cu(OAc)_2$) as the stoichiometric oxidant instead of oxygen, in dioxane at 100 °C for 15 h.

In this paper, we are pleased to summarize our efforts in finding an effective and simple protocol for the dehydrogenative alkenylation of imidazole derivatives, which allowed us to develop a simple procedure for the dehydrogenative alkenylation of 5-aryl-1-methylimidazoles and some related azoles with functionalized styrenes (Scheme 3). The optimized reaction conditions involve the use propanoic acid as the solvent at 120 °C, in the presence $Pd(OAc)_2$ as the pre-catalyst and $Cu(OAc)_2$ as the oxidant.



Scheme 2. Cross-dehydrogenative C-5 alkenylation of 1-substituted imidazoles with styrene, according to Joo and co-workers [38].

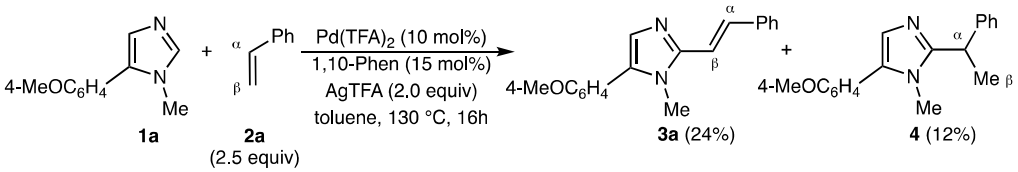


Scheme 3. Our protocol for the cross-dehydrogenative Pd(II)/Cu(II)-mediated alkenylation of imidazoles.

2. Results and Discussion

2.1. Screening of the Reaction Conditions

At the onset of our study, we decided to test the efficiency of the Ong protocol by trying a dehydrogenative alkenylation of 5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (**1a**) with styrene (**2a**), chosen as model reaction partners. Hence, **1a** and 2.5 equiv of **2a** were reacted in the presence of 10 mol% $Pd(TFA)_2$, 15 mol% 1,10-Phen and 2.0 equiv AgTFA (Scheme 4).



Scheme 4. Dehydrogenative alkenylation of imidazole **1a** with styrene (**2a**) using the Ong protocol [37].

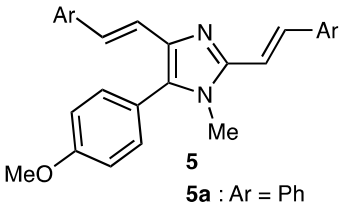
After stirring the reaction mixture for 16 h at 130 °C in toluene, an unsatisfactory 59% GLC conversion of **1a** was observed. Moreover, the required alkenyl-substituted imidazole **3a** was formed in a 58:42 GLC ratio with the 2-alkylimidazole **4**. These derivatives were isolated in 24 and 12% yields, respectively, and their structures confirmed by NMR analyses. The unexpected formation of compound **4** can be explained by admitting that the carbopalladation of styrene by the Pd-imidazole complex (resulting from the activation of the heteroaromatic C2-H bond, see later) occurred with incomplete regioselectivity [11].

An even worse result was observed when **1a** and **2a** were reacted using the Joo protocol [38], i.e., in the presence of 10 mol% $Pd(OAc)_2$ and 2.0 equiv of KOAc in DMA

under an oxygen atmosphere. In fact, the GLC conversion of **1a** after 24 h at 120 °C was less than 15% (result not shown).

These unsatisfactory results prompted us to search for alternative reaction conditions. Considering that classical Fujiwara–Moritani protocols require the use of simple carboxylic acid (such as acetic acid) as the reaction solvent [3,13], and that many of the reported procedures for the dehydrogenative alkenylation of azoles have been carried out in acidic solvents [4,11], we decided to start a screening of the reaction conditions using a carboxylic acid as the solvent and examining the influence of the nature of the solvent, the oxidant, and the palladium pre-catalyst on the reaction outcome.

Due to the fact that no protocols for the dehydrogenative alkenylation of imidazoles using acidic solvents were reported, we started our trial performing the reaction between imidazole **1a** and styrene (**2a**) under reaction conditions very similar to those described by Miura and co-workers in 2010 for the regioselective C-5 dehydrogenative alkenylation of 2-substituted oxazoles and thiazoles [39]. Hence, **1a** and 2.0 equiv of **2a** were stirred at 120 °C in propionic acid (EtCOOH), in the presence of 5 mol% palladium(II) acetate ($Pd(OAc)_2$) and 3.0 equiv of silver(I) acetate (AgOAc) (entry 1, Table 1). After 24 h the expected C-2 alkenylated imidazole **3a** was obtained in 33% GLC yield, along with a higher molecular weight side product, that was preliminarily identified by GLC-MS and UPLC-MS analyses to be the bis-alkenylated imidazole **5a**.



5

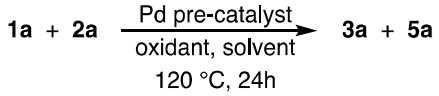
5a : Ar = Ph

Interestingly, under acidic conditions the formation of the 2-alkyimidazole **4** was not observed in the crude reaction mixture, proving that propionic acid as solvent cleanly increases the regioselectivity of the carbopalladation step of the mechanistic pathway (see later).

With the aim of evaluating the influence of the carboxylic acid, we then carried out the Ag(I)-promoted coupling using acetic acid and pivalic acid as the reaction solvent (entries 2 and 3, Table 1). However, both the acidic solvents revealed less effectiveness in promoting the alkenylation when compared with propionic acid, scoring 24 and 23% GLC yields, respectively. As recently reported [40], the efficiency of C-H activation reactions carried out using palladium catalysts with carboxylate ligands strictly depends on the pKa of the carboxylic acid used as the solvent. It is in fact necessary to find a balance between the generation of an active catalyst and the N-3 protonation of the imidazole nucleus with its consequent deactivation. In our case, the pKa of propionic acid (4.87) is intermediate between that of pivalic acid (5.05) and acetic acid (4.76), which means that acetic acid gave a higher percentage of unreactive imidazolium salt, while pivalic acid is not enough acid to generate an active catalyst.

Notably, while the use of silver(I) salts different from AgOAc gave GLC yields ranging from 32 to 38% (entries 4–6, Table 1), when the alkenylation was performed in the presence of 3.0 equiv of copper(II) acetate ($Cu(OAc)_2$), a relevant increase in the GLC yield of **3a** was observed, and the C-2 alkenylated product was isolated in a satisfactory 56% yield (entry 7, Table 1). From the crude reaction mixture, we were also able to isolate the side-product **5a** in a 13% yield.

Table 1. Screening of the reaction conditions for the palladium-catalyzed dehydrogenative alkenylation of 1-methyl-5 (4-methoxyphenyl)imidazole (**1a**) with styrene (**2a**).



Entry [1]	Oxidant	Solvent	1a Conversion (GLC %)	Yield of 3a (%) [2]	3a:5a Ratio (AP%) [3]
1	AgOAc	EtCOOH	90	33	68:32
2	AgOAc	AcOH	69	24	65:35
3	AgOAc	PivOH	64	23	60:40
4	Ag_2cO_3	EtCOOH	93	32	61:39
5	Ag_2O	EtCOOH	79	38	70:30
6	AgTFA	EtCOOH	75	35	66:35
7	$Cu(OAc)_2$	EtCOOH	>95	61(56) [4]	76:24
8 [5]	$Cu(OAc)_2$	EtCOOH	81	39	82:18
9 [6]	$Cu(OAc)_2$	EtCOOH	<5	traces	–
10 [7]	$Cu(OAc)_2$	EtCOOH	<5	traces	–
11	CuO	EtCOOH	>95	31	52:48
12	$CuCl_2$	EtCOOH	<5	traces	–
13	$PhI(OAc)_2$	EtCOOH	<5	traces	–
14	NMO	EtCOOH	<5	traces	–
15 [8]	$Cu(OAc)_2$	EtCOOH	>95	50(42)	74:26
16 [9]	$Cu(OAc)_2$	EtCOOH	94	37	69:31
17	$Cu(OAc)_2$	EtCOOH/DMF	91	44	61:39
18	$Cu(OAc)_2$	EtCOOH/NMP	94	45	56:44

[1] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), oxidant (1.5 mmol), solvent (5.0 mL) for 24 h at 120 °C (oil bath temperature) under an argon atmosphere, unless otherwise reported. [2] GLC yield vs. PPh_3. In parentheses isolated yield. [3] AP% is the area percent of the products in the GLC chromatogram. AP% values are uncorrected for the differences in GLC response factors. [4] Compound **5a** was also isolated in 13% yield. [5] This reaction was carried out using 0.5 mmol of **2a**. [6] This reaction was performed at 80 °C (oil bath temperature). [7] This reaction was carried out under a dioxygen atmosphere. [8] This reaction was carried out using $PdCl_2$ (0.025 mmol) as pre-catalyst. [9] This reaction was carried out using $Pd(acac)_2$ (0.025 mmol) as pre-catalyst.

In an attempt to reduce the amount of undesired double alkenylated imidazole **5a**, we lowered the amount of styrene to 1.0 equiv, but a parallel lowering of the **3a** yield without a significant increase in the selectivity was observed (entry 8, Table 1).

Lowering the reaction temperature from 120 °C to 80 °C led to a complete recovery of the reactants (entry 9, Table 1), and a similar negative result was observed when the coupling was performed under a dioxygen atmosphere (entry 10, Table 1).

None of the other typical copper(II) salts tested gave results comparable with that obtained when $Cu(OAc)_2$ was used. CuO gave **3a** in 31% GLC yield (entry 11, Table 1), while no reaction was observed when $CuCl_2$ was employed as the oxidant (entry 12, Table 1). The use of two typical organic oxidants, i.e., NMO and $PhI(OAc)_2$ gave unsatisfactory results (entries 13 and 14, Table 1).

As regards the palladium pre-catalyst, replacing $Pd(OAc)_2$ with $PdCl_2$ gave **3a** in a 50% GLC yield (entry 15, Table 1), while a lower 37% GLC yield was obtained when $Pd(acac)_2$ was employed (entry 16, Table 1).

In order to reduce the amount of propionic acid, we tried also the alkenylation involving **1a** and **2a** using 1:1 (*v*:*v*) mixtures of propionic acid with, respectively, DMF or NMP (entries 17–18, Table 1), but the presence of an organic solvent depletes the formation of the required alkenylimidazole **3a**.

2.2. Scope of the Pd-Catalyzed Dehydrogenative Alkenylation of Imidazoles and Related Azoles

Considering the results of the preliminary screening, the scope and limitations of this regioselective C-2 dehydrogenative alkenylation under the experimental conditions of entry 7, Table 1, were then evaluated by us. Hence, 5-aryl-1-methylimidazoles **1a**–**f** and styrenes **2a**–**g** (Figure 1) were reacted in the presence of 5 mol% $Pd(OAc)_2$ and 3.0 equiv of $Cu(OAc)_2$ in EtCOOH at 120 °C (Table 2).

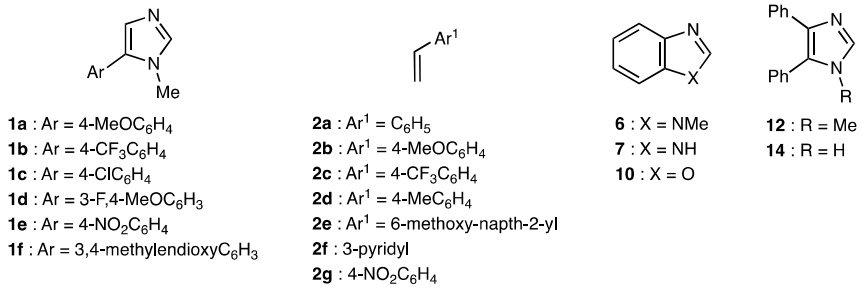
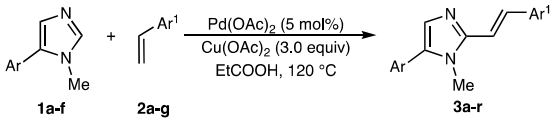


Figure 1. Chemical structures of imidazole derivatives **1a**–**f**, **6**, **7**, **10**, **12**, **14**, and of styrenes **2a**–**g**.

Table 2. Pd-catalyzed, Cu(II)-promoted synthesis of 2-alkenyl-5-aryl-1-methylimidazoles **3a**–**r** by intermolecular dehydrogenative alkenylation of imidazoles **1a**–**f** with styrenes **2a**–**g**.



1a-f **2a-g** **3a-r**

Entry [1]	Product 3	Ar	Ar [1]	Yield of 3 (%) [2,3]	3:5 Ratio (AP%) [4]
1	a	4-MeOC$_6$H$_4$	C$_6$H$_5$	56	76:24
2	b	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	41	77:23
3	c	4-MeOC$_6$H$_4$	4-CF$_3$C$_6$H$_4$	61	85:15
4	d	4-MeOC$_6$H$_4$	4-MeC$_6$H$_4$	49	79:21
5	e	4-MeOC$_6$H$_4$	6-MeO-naphth-2-yl	51	77:23
6	f	4-MeOC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	44	82:18
7	g	4-CF$_3$C$_6$H$_4$	C$_6$H$_5$	43	78:22
8	h	4-CF$_3$C$_6$H$_4$	4-MeOC$_6$H$_4$	41	75:25
9	i	4-CF$_3$C$_6$H$_4$	4-MeC$_6$H$_4$	44	75:25
10	j	4-CF$_3$C$_6$H$_4$	4-CF$_3$C$_6$H$_4$	50	79:21
11	k	4-ClC$_6$H$_4$	C$_6$H$_5$	45	78:22
12	l	4-ClC$_6$H$_4$	4-MeOC$_6$H$_4$	28 [5]	nd
13	m	4-ClC$_6$H$_4$	4-CF$_3$C$_6$H$_4$	46	93:7
14	n	4-ClC$_6$H$_4$	4-pyridyl	16 [6,7]	nd
15	o	4-ClC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	27 [6,8]	nd
16	p	3-F,4-MeOC$_6$H$_3$	4-MeOC$_6$H$_4$	56	78:22
17	q	4-NO$_2$C$_6$H$_4$	4-MeOC$_6$H$_4$	30 [9]	nd
18	r	3,4-MethylendioxyC$_6$H$_3$	4-MeOC$_6$H$_4$	52	76:24

[1] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), Pd(OAc)$_2$ (0.025 mmol), Cu(OAc)$_2$ (1.5 mmol), EtCOOH (5.0 mL) for 24 h at 120 °C (oil bath temperature) under an argon atmosphere, unless otherwise reported. [2] Isolated yield. [3] After 24 h the GLC conversion of **1** was >95% unless otherwise noted. [4] AP% is the area percent of the products in the GLC chromatogram. AP% values are uncorrected for the differences in GLC response factors. [5] The GLC conversion of **1c** was 49%. [6] The coupling was carried out for 72 h. [7] The GLC conversion of **1c** was 45%. [8] The GLC conversion of **1c** was 56%. [9] The GLC conversion of **1e** was 53%.

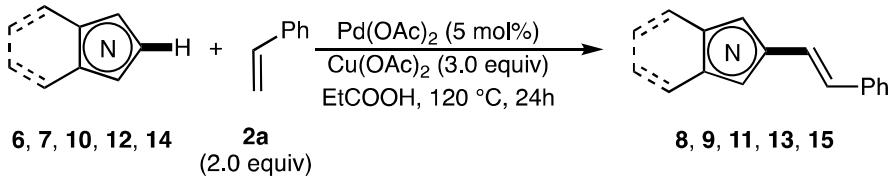
As summarized in Table 2, all the 5-arylimidazoles **1a**–**f** gave the required 2-alkenyl substituted analogues in moderate to good yields. In details, 5-arylimidazoles **1a**, **1d**, and **1f**, bearing electron-rich aryl rings at their 5-position gave slightly better results, giving the alkenylated products **3a**–**f**, **3p** and **3r** in 41–61% isolated yield (entries 1–6, 16, and 18, Table 2). In contrast, 5-(4-trifluoromethylphenyl) imidazole **1b**, 5-(4-chlorophenyl)imidazole **1c**, and 5-(4-nitrophenyl)imidazole **1e** gave lower yields and sometimes incomplete GLC conversions when reacted with styrenes **2a**–**d** (entries 7–13, and 17, Table 2), confirming that the efficiency of this dehydrogenative coupling is related to the electronic nature of the C-5 aromatic substituent.

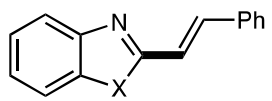
That electron-poor substituents negatively influence the coupling is evidenced also when styrenes **2f** and **2g** were employed as reaction partners, and it seems synergic with the effect exerted by electron-withdrawing groups at C-5 on the imidazole counterpart. Actually, while an acceptable 44% isolate yield was observed when imidazole **1a** was reacted with 4-nitrostyrene **2g** (entry 6, Table 2), a more significant reduction in the chemical

yield was recorded when the 4-chlorophenyl substituted imidazole **1c** reacted with the electron-poor styrenes **2f** and **2g** (entries 14 and 15, Table 2).

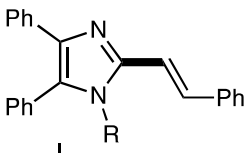
Regarding the results summarized in Table 2, it is also important to note that the efficiency of the coupling strongly depends also on the relative stability of the substituted styrenes **2** in the acid medium. It is in fact well known that electron-rich styrenes, such as 4-methoxystyrene **2b**, are highly susceptible to polymerization in an acidic environment, while electron-poor analogues such as 4-nitrostyrene **2g** are almost inert under the same conditions [41]. For this reason, it is not possible to make a clear correlation between the nature of the coupling partners **1** and **2** and the observed isolated yields of compounds **3**.

We were pleased to find that the reaction conditions summarized in Table 1, entry 7, are also well suited for the C-2 dehydrogenative alkenylation of 1-methyl-1*H*-benzimidazole (**6**) and 1*H*-benzimidazole (**7**). As summarized in Scheme 5, 1-methyl-2-styrylbenzimidazole **8** and 2-styrylbenzimidazole **9** were isolated in a satisfactory 87 and 64% yield, respectively. In contrast, the reaction involving benzoxazole **10** with styrene gave the required 2-styrylbenzoxazole **11** in a lower isolated yield (30%) (Scheme 5), while no product was observed when benzothiazole was submitted to the dehydrogenative alkenylation (result not shown).





	8	9	11
X	NMe	NH	O
Yield (%)	87	64	30

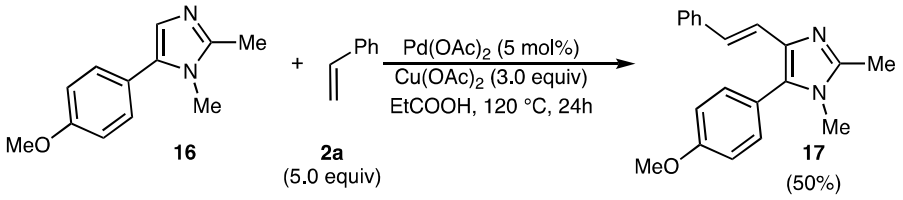


	13	15
R	Me	H
Yield (%)	55	36

Scheme 5. Pd-catalyzed, Cu(II)-promoted dehydrogenative alkenylation of azoles **6**, **7**, **10**, **12**, and **14** with styrene (**2a**).

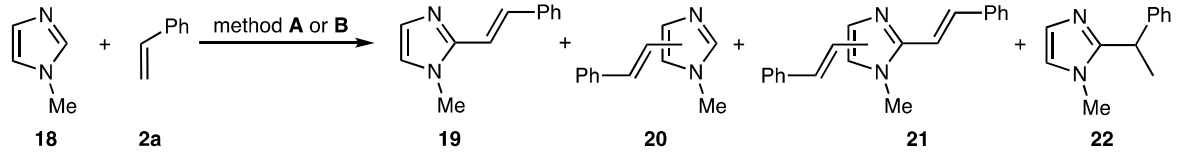
A positive result was instead obtained in the C-2 alkenylation of 4,5-diphenyl-1-methyl-1*H*-imidazole (**12**) with styrene (**2a**). In fact, the expected 2-styryl-substituted derivative **13** was isolated in a satisfactory 55% yield (Scheme 5). However, when the coupling was carried out using the analogue NH-free imidazole **14** the expected 4,5-diphenyl-2-styrylimidazole **15** was recovered in 36% isolated yield (Scheme 5).

Considering also that the C4-H bond seems to be reactive when the other two positions on the imidazole ring are occupied due to the formation of side-products **5**, we also tried to force the C-4 alkenylation by using 5-(4-methoxyphenyl)-1,2-dimethyl-1*H*-imidazole (**16**) as a typical 2,5-disubstituted imidazole. Fortunately, when the reaction was carried out using 2-methyl substituted imidazole **16** and 5.0 equiv of **2a**, the expected C4-alkenylated imidazole **17** was recovered in a 50% isolated yield (Scheme 6).



Scheme 6. Pd-catalyzed, Cu(II)-promoted dehydrogenative alkenylation of 5-(4-methoxyphenyl)-1,2-dimethyl-1*H*-imidazole (**16**) with styrene (**2a**).

With the intention of verifying the regioselectivity of our new Pd/Cu-mediated dehydrogenative alkenylation protocol, we set up a model reaction involving 1-methylimidazole **18** and styrene (**2a**) the experimental conditions of entry 7, Table 1. Hence, **18** and 2.0 equiv of **2a** were reacted in the presence of 5 mol% $Pd(OAc)_2$ and 3.0 equiv of $Cu(OAc)_2$ in EtCOOH (Method **A**, Scheme 7). To our delight, after stirring at 120 °C for 24 h, the GLC conversion of **18** was 83%, and we were able to isolate (*E*)-1-methyl-2-styryl-1*H*-imidazole (**19**) in 45% yield confirming the expected C-2 selectivity.



Method **A** : **2a** (2.0 equiv), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (3.0 equiv), EtCOOH, 120 °C, 24h, air (45%)
Method **B** : **2a** (2.5 equiv), $Pd(TFA)_2$ (5 mol%), AgTFA (1.0 equiv), 1,10-Phen (7.5 mol%), toluene, 130 °C, 16h in a closed vessel under Ar (33%)

	AP GLC%			
Compound	**19**	**20**	**21**	**22**
Method **A**	93	3	4	0
Method **B**	73	6	4	17

Scheme 7. Pd-catalyzed dehydrogenative alkenylation of 1-methyl-1*H*-imidazole (**18**) with styrene (**2a**) according to our new protocol (Method **A**), or to Ong procedure (Method **B**) [37].

In contrast, when the same coupling was carried out using the Ong protocol [37], i.e., reacting **16** and 2.5 equiv of **2a** in a closed vessel for 16 h at 130 °C in toluene in the presence of 10 mol% $Pd(TFA)_2$, 15 mol% 1,10-Phen and 2.0 equiv AgTFA, the GLC conversion of **16** was lower (70%), and the required imidazole **19** was observed in only 33% isolated yield (vs. a reported 67% yield [37]) (Method **B**, Scheme 7). It is worth mentioning that also in this case GLC-MS analysis of the crude reaction mixture evidences the presence of the side-product **22**, a structural analogue to imidazole **4** already observed when the same reaction was performed with 1-methylbenzimidazole **1a** (Scheme 4), in a 77:23 GLC ratio with **19**.

As already noted for Pd/Cu-mediated direct arylation reactions of 1,3-azoles with aryl halides [44–46], it is thought that an initial N-3 protonation or complexation with copper enhances the acidity of the C2-H bond, allowing a fast and regioselective palladation to give the imidazole intermediate **A**. The subsequent regioselective carbopalladation yields the intermediate **B**, which decomposes through β-elimination to generate the desired product **3** and Pd(0). Finally, the reoxidation of Pd(0) to Pd(II) by Cu(II) closed the catalytic cycle.

Based on previous reports [2,11,13,42,43] and according to the results described here, a plausible reaction mechanism is summarized in Figure 2.

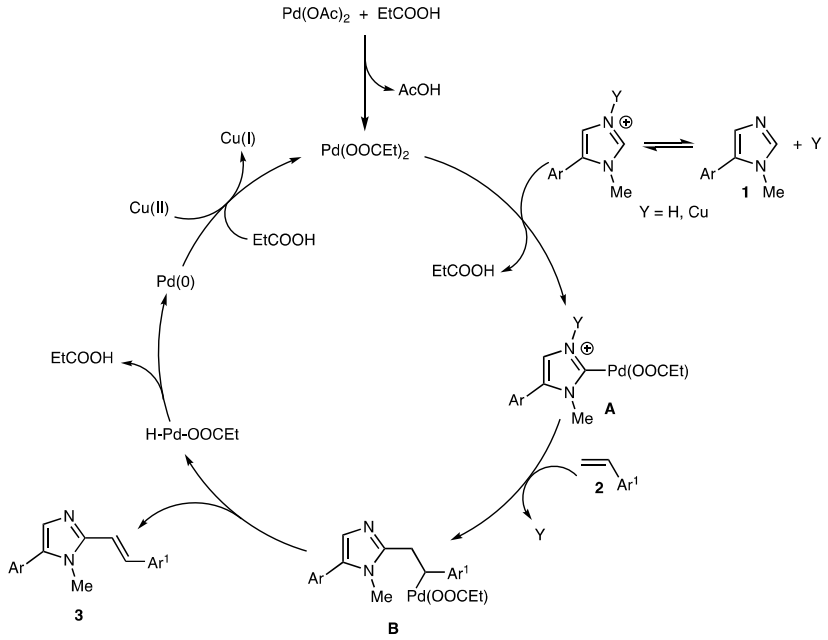


Figure 2. Suggested mechanistic pathway for the Pd/Cu-mediated dehydrogenative alkenylation of imidazoles.

3. Materials and Methods

Melting points were recorded on a hot-stage microscope (Reichert Thermovar). Precoated silica gel PET foils (Sigma-Aldrich, St. Louis, MO, USA) were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument equipped with a PTV injector and recorded with a Dani DDS 1000 data station. Three types of capillary columns were used: an Agilent J&W HP-5 ms column (30 m × 0.25 mm i.d. × 0.25 μm), an Agilent J&W DB-5 column (30 m × 0.25 mm i.d. × 1 μm) and an Alltech AT-35 FSOT column (30 m × 0.25 mm i.d. × 0.25 μm). EI-MS spectra were recorded at 70 eV by GLC-MS, performed on an Agilent 6890N gas-chromatograph interfaced with an Agilent 5973N mass detector. The ESI spectra were acquired on an Acquity QDa Water spectrometer (Temperature Probe: 600 °C; ESI capillary voltage 1.5 V; Cone voltage 15 V; mass range 200–1000) coupled with an Acquity HUPLC Water (Phase A 95/5 H_2O/ACN + 0.1% Formic Acid, Phase B 5/95 H_2O/ACN + 0.1% Formic Acid; Column Acquity UPLC 2.1 × 100 mm, BEH C18, 1.7 μm; Flow 0.6 mL/min). Elementar analyses were acquired with an Elementar Vario Micro Cube in CHNS mode. ^{1}H NMR spectra were recorded on a Varian Gemini 200 or on a Bruker 400 MHz spectrometer using TMS as an internal standard. The following notation was used in order to report NMR spectra: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quadruplet. The ^{13}C NMR spectra were recorded at 50 or 100 MHz, using Varian Gemini or Bruker instrument respectively, and the spectra were referred to as the signal of the solvent. Copies of ^{1}H and ^{13}C NMR spectra of all the new compounds are provided as Supplementary Materials. Unless otherwise stated all the reactions were performed under a positive atmosphere of argon by standard syringe, cannula and septa techniques. All the liquid styrenes **2a**–**d**,**f** were purified by distillation at reduced pressure over CaH_2. Propionic acid was distilled at atmospheric pressure. 5-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (**1a**), 1-methyl-5-(4-(trifluoromethyl)phenyl)-1*H*-imidazole (**1b**) 1-methyl-5-(4-chlorophenyl)-1*H*-imidazole (**1c**), 5-(3-fluoro-4-methoxyphenyl)-1-methyl-1*H*-imidazole (**1d**), 5-(4-nitrophenyl)-1-methyl-1*H*-imidazole (**1e**), 5-(benzo[d][1,3]dioxol-5-yl)-1-methyl-1*H*-imidazole (**1f**) were synthesized according to literature procedure previously developed by us [47]. The following compounds were prepared according to reported procedures: 1-Methyl-4,5-diphenyl-1*H*-imidazole (**12**) (yield: 80%) [48], 5-(4-methoxyphenyl)-1,2-

dimethyl-1*H*-imidazole (**16**) (yield: 66%) [49], 1-nitro-4-vinylbenzene (**2g**) (yield: 61%) [50]. All the other commercially available reagents and solvents were used as received.

*3.1. (E)-5-(4-Methoxyphenyl)-1-methyl-2-styryl-1H-imidazole (**3a**) and 5-(4-methoxyphenyl)-1-methyl-2-(1-phenylethyl)-1H-imidazole (**4**)*

As summarized in Scheme 4, a mixture of 5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (**1a**) (94.0 mg, 0.5 mmol), styrene (**2a**) (0.14 mL, 130 mg, 1.25 mmol), $Pd(TFA)_2$, (16.6 mg, 0.05 mmol), 1,10-phenantroline (13.5 mg, 0.075 mmol), and AgTFA (27.3 mg 1.0 mmol) in toluene (2 mL) was stirred in a Paar Microwave 50® reactor for 16 h at 130 °C. After cooling to room temperature, the mixture was diluted with AcOEt (20 mL) then filtered on celite and the filter was washed with 15 mL AcOEt and 20 mL CH_2Cl_2. The crude reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (50:50) as eluent. Concentration of the first eluted chromatographic fractions allowed the isolation of compound **3a** (34.8 mg, 24 %) light-pink solid: m.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, 1H, *J* = 15.85 Hz), 7.54 (d, 2H, *J* = 7.54), 7.40–7.22 (m, 5H), 7.09 (s, 1H), 7.00–6.92 (m, 3H), 3.84 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.39, 146.26, 136.69, 134.34, 132.12, 130.06 (2C), 128.68 (2C), 128.07, 127.49, 126.66 (2C), 122.23, 114.15(2C), 113.86, 55.24, 30.95. EI-MS *m*/*z* (%): 290 (31), 289 (100), 274 (6), 245 (10), 144 (5). $C_{19}H_{18}N_2O$ (290.37): calcd. C, 78.59; H, 6.25; N, 9.65; found C 78.64, H 6.26, N 9.67.

Concentration of the last eluted chromatographic fractions with AcOEt allowed the isolation of compound **4** (17.5 mg, 12% yield) as a light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (m, 3H), 7.26–7.18 (m, 4H), 7.02 (s, 1H), 6.95–6.90 (m, 2H), 4.16 (q, 1H, *J* = 7 Hz), 3.82 (s, 3H), 3.26 (s, 3H), 1.77 (d, 3H, *J* = 7Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.30, 150.65, 143.87, 133.72, 130.24 (2C), 128.80 (2C), 127.30 (2C), 126.59, 125.50, 122.83, 114.07 (2C), 55.33, 38.91, 30.91, 21.86. EI-MS *m*/*z* (%): 292 (100), 277 (90), 262 (10), 233 (20), 215 (12), 201 (40). $C_{19}H_{20}N_2O$ (292.38): calcd. C, 78.05; H, 6.90; N, 9.58; found C 77.98, H 6.89, N 9.56.

Compound **3a** was also obtained in a 56% isolated yield from the $Pd(OAc)_2$-catalyzed reactions of **1a** and **2a** carried out using Ag_2O, AgTFA, or $Cu(OAc)_2$ as oxidant (entry 7, Table 1), and in 42% isolated yield when the alkenylation was performed using $PdCl_2/Cu(OAc)_2$ as pre-catalyst/oxidant (entry 15, Table 1).

*3.2. Procedure for the Screening of the Reaction Conditions for the Pd-Catalyzed Dehydrogenative C2-Alkenylation of 5-(4-Methoxyphenyl)-1-Methyl-1H-Imidazole (**1a**) with Styrene (**2a**) Using Carboxylic Acids as Reaction Solvents*

A mixture of 5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (**1a**) (94 mg, 0.5 mmol), styrene (**2a**) (0.12 mL, 104 mg, 1.0 mmol), palladium pre-catalyst (0.025 mmol), oxidant (1.5 mmol), in the selected solvent (5 mL) was stirred for 24 h at 120 °C. After cooling to room temperature, when an Ag(I) oxidant was used the crude reaction mixture was diluted with AcOEt, and PPh_3 was added as internal standard. When a Cu(II) salt was used as oxidant, the crude reaction mixture was diluted with AcOEt and poured into a saturated aqueous NH_4Cl solution. The resulting mixture was basified with a few drops of aqueous NH_4OH, stirred in the open air for 0.5 h, and then extracted with AcOEt and with CH_2Cl_2. The organic extract was washed with water, dried, filtered, and PPh_3 was added as internal standard.

All the resulting mixtures were analyzed by GLC, GC–MS, and UPLC-MS. Table 1 summarizes the results of this screening.

(*E*)-5-(4-methoxyphenyl)-1-methyl-2-styryl-1*H*-imidazole (**3a**) and 5-(4-methoxyphenyl)-1-methyl-2,4-di((*E*)-styryl)-1*H*-imidazole (**5a**)

The crude reaction mixture (entry 7, Table 1) was concentrated at reduced pressure and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent. Concentration of the first eluted chromatographic fractions allowed the isolation of compound **5a** (25.5 mg, 13%) as a yellow solid: m.p 57–58 °C. ^{1}H NMR (400

MHz, $CDCl_3$): δ 7.75 (d, *J* = 15.8 Hz, 1H), 7.59–7.57 (m, 2H), 7.47–7.43 (m, 2H), 7.39–7.36 (m, 2H), 7.31–7.24 (m, 5H), 7.18–7.15 (m, 2H), 7.04–7.03 (m, 2H), 6.98 (d, *J* = 15.8 Hz, 1H), 6.89 (d, *J* = 15.8 Hz, 1H), 3.90 (s, 3H), 3.55 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 159.8, 145.9, 138.2, 137.2, 136.8, 133.3, 132.5, 131.9 (2C), 128.8 (2C), 128.5 (2C), 128.3, 127.2, 126.9 (2C), 126.8, 126.3 (2C), 121.6, 119.6, 114.4 (2C), 113.7, 55.4, 31.1. EI-MS *m*/*z* (%): 392 (90), 391 (100), 207 (6), 157 (10), 144 (13) 115 (6). $C_{27}H_{24}N_2O$ (262.35): calcd. C, 82.62; H, 6.16; N, 7.14; found C 82.57, H 6.12, N 7.16.

The concentration of the last fractions, eluted with a mixture of toluene and AcOEt (50:50) allowed the isolation of compound **3a** (81.1 mg, 56%) as a light-pink solid, m.p. 151–152 °C. The physical and spectral properties of this compound are in agreement with those reported in Section 3.1.

3.3. General Procedure for the Pd(II)/Cu(II)-Promoted Dehydrogenative Alkenylation of Azoles with Styrenes

To a suspension of the appropriate azole **1a**–**f**, **6**, **7**, **10**, **12** or **14** (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $Cu(OAc)_2$ (272.5 mg, 1.5 mmol) in EtCOOH (5 mL), the appropriate styrene **2a**–**g** (1.0 mmol) was added under vigorous stirring. The resulting mixture was heated for 24 h at 120 °C. After cooling to room temperature, the crude reaction mixture was diluted with AcOEt (50 mL) and sequentially washed with a 2:1 (*v*:*v*) solution of saturated aqueous NH_4Cl and aqueous NH_4OH (2 × 20 mL), H_2O (1 × 20 mL), and brine (1 × 20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with water, dried, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. This procedure was used to prepare compounds **3b**–**r** (Table 2), **8**, **9**, **11**, **13**, **15** (Scheme 5) and **17** (Scheme 6).

3.3.1. (*E*)-5-(4-Methoxyphenyl)-2-(4-methoxystyryl)-1-methyl-1*H*-imidazole (**3b**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1a** with **2b** (entry 2, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (97:3) as eluent to give **3b** (65.7 mg, 41%) as a light-orange solid: m.p. = 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 1H, *J* = 15.9 Hz), 7.48 (d, 2H, *J* = 8.5 Hz), 7.30 (d, 2H, *J* = 8.7), 7.07 (s, 1H), 6.97 (d, 2H, *J* = 8.6 Hz), 6.90 (d, 2H, *J* = 8.5 Hz), 6.82 (d, 1H, *J* = 15.9 Hz), 3.84 (s, 3H), 3.82 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.87, 159.54, 146.81, 134.21, 132.20, 130.27 (2C), 129.69, 128.17 (2C), 127.45, 122.58, 114.31 (4C), 111.88, 55.46, 55.43, 31.14. EI-MS *m*/*z* (%): 320 (39), 319 (100), 304 (7), 276 (5),160 (5). ESI-MS (+): *m*/*z* (%) = 321 (100) $[M+H]^+$. $C_{20}H_{20}N_2O_2$ (320.39): calcd. C, 74.98; H, 6.29; N, 8.74; found C, 75.05, H, 6.31, N, 8.76.

3.3.2. (*E*)-5-(4-Methoxyphenyl)-1-methyl-2-(4-(trifluoromethyl)styryl)-1*H*-imidazole (**3c**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1a** with **2c** (entry 3, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (65/35) as eluent to give **3c** (109.2 mg, 61% yield) as yellow solid: m.p. = 174–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.47 (m, 5H), 7.26–7.23 (m, 2H), 7.05 (s, 1H), 6.97 (d, 1H, *J* = 15.09 Hz), 6.94–6.90 (m, 2H), 3.79 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.77, 145.86, 140.41, 135.05, 130.53, 130.38(2C), 129.80 (q, *J* = 32.4 Hz), 128.18, 126.92 (2C), 125.82 (q, 2C, *J* = 3.8 Hz), 124.29 (q, *J* = 271.9 Hz), 122.26, 116.29, 114.42 (2C), 55.51, 31.23. EI-MS *m*/*z* (%): 358 (30), 357 (100), 342 (5), 313 (10). ESI-MS (+): *m*/*z* (%) = 359 (100) $[M+H]^+$. $C_{20}H_{17}F_3N_2O$ (358.36): calcd. C, 67.03; H, 4.78; N, 7.82; found C, 66.97, H, 4.79, N, 7.80.

3.3.3. (*E*)-5-(4-Methoxyphenyl)-1-methyl-2-(4-methylstyryl)-1*H*-imidazole (**3d**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1a** with **2d** (entry 4, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (20/80) as eluent to give **3d** (74.5 mg, 49% yield) as dark orange solid: m.p. = 124–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 1H, *J* = 15.9 Hz), 7.46–7.42 (m, 2H), 7.32–7.26 (m, 2H), 7.18–7.14 (m, 2H), 7.09 (s, 1H), 6.99–6.95 (m, 2H), 6.89 (d, 1H, *J* = 15.9 Hz),

3.84 (s, 3H), 3.62 (s, 3H), 2.35 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 159.56, 146.67, 138.28, 134.35, 134.14, 132.46, 130.29 (2C), 129.56 (2C), 127.63, 126.79 (2C), 122.56, 114.32 (2C), 113.05, 55.45, 31.15, 21.41. EI-MS *m*/*z* (%): 304 (30), 303 (100), 288 (5), 259 (10), 144 (5). ESI-MS (+): *m*/*z* (%) = 305 (100) $[M+H]^+$. $C_{20}H_{20}N_2O$ (304.39): calcd. C, 78.92; H, 6.62; N, 9.20; found C, 79.02; H, 6.63; N, 9.22.

3.3.4. (*E*)-2-(2-(6-Methoxynaphthalen-2-yl)vinyl)-5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (**3e**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1a** with **2e** (entry 5, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60/40) as eluent to give **3e** (94.5 mg, 51% yield) as brown solid: m.p. = 184–186 °C.^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83–7.70 (m, 5H), 7.33–6.96 (m, 8H), 3.90–3.83 (m, 6H), 3.66 (s, 3H).^{13}C NMR (50 MHz, $CDCl_3$): δ 159.36, 157.89, 134.43, 133.11, 131.82, 131.73, 130.08 (2C), 129.62, 128.85, 127.24, 127.10, 126.62, 123.80 (2C), 121.93, 119.03 (2C), 114.11, 113.83, 112.37, 105.80 (2C), 55.28 (2C), 31.17. EI-MS *m*/*z* (%): 370 (52), 369 (100), 326(8), 281 (7), 207 (60). ESI-MS (+): *m*/*z* (%) = 371 (100) $[M+H]^+$ $C_{24}H_{22}N_2O_2$ (370.45): calcd. C, 77.81; H, 5.99; N, 7.56; found: C, 77.96; H, 6.00; N, 7.55.

3.3.5. (*E*)-5-(4-Methoxyphenyl)-1-methyl-2-(4-nitrostyryl)-1*H*-imidazole (**3f**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1a** with **2g** (entry 6, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60/40) as eluent to give **3f** (73.5 mg, 44% yield) as red solid: m.p. = 195–197 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24–8.20 (m, 2H,), 7.71–7.62 (m, 3H), 7.35–7.26 (m, 2H), 7.16 (s, 1H), 7.08–6.95 (m, 3H), 3.87 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.66, 146.88, 145.33, 143.26, 135.39, 130.23 (2C), 129.16 128.43, 127.04 (2C), 124.20 (2C), 121.83, 117.86, 114.31 (2C), 55.46, 31.25. EI-MS *m*/*z* (%): 335 (28), 334 (100), 304(14), 288 (38), 207 (13). ESI-MS (+): *m*/*z* (%) = 336 (100) $[M+H]^+$. $C_{19}H_{17}N_3O_3$ (335.36): calcd. C, 68.05; H, 5.11; N, 12.53; found C, 68.18; H, 5.12; N, 12.52.

3.3.6. (*E*)-1-Methyl-2-styryl-5-(4-(trifluoromethyl)phenyl)-1*H*-imidazole (**3g**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1b** with **2a** (entry 7, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80/20) as eluent to give **3g** (70.6 mg, 43% yield) as yellow solid: m.p. = 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.65 (m, 3H), 7.58–7.47 (m, 4H), 7.40–7.35 (m, 2H), 7.32–7.28 (m, 1H), 7.22 (s, 1H), 6.97 (d, 1H, *J* = 15.9 Hz), 3.71 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 147.91, 133.74, 133.70, 133.68, 133.26, 129.85 (q, 1C, *J* = 32.6 Hz), 129.26, 128.92 (2C), 128.72 (2C), 128.59, 126.99 (2C), 125.91 (q, 2C, *J* = 3,75 Hz), 124.14 (q, 1C, *J* = 272.2 Hz), 113.49, 31.51. EI-MS *m*/*z* (%): 328 (30), 327 (100), 312 (10), 128 (5). ESI-MS (+): *m*/*z* (%) = 329 (100) $[M+H]^+$.$C_{19}H_{15}F_3N_2$ (328.34): calcd. C, 69.50; H, 4.61; N, 8.53; found C, 69.60; H, 4.62; N, 8.52.

3.3.7. (*E*)-2-(4-Methoxystyryl)-1-methyl-5-(4-(trifluoro-methyl)phenyl)-1*H*-imidazole (**3h**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1b** with **2b** (entry 8, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60/40) as eluent to give **3h** (73.4 mg, 41% yield) as yellow solid: m.p. = 193–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71–7.67 (m, 2H), 7.63 (d, 1H, *J* = 15.8 Hz), 7.54–7.46 (m, 4H), 7.21 (s, 1H), 6.93–6.89 (m, 2H), 6.83 (d, 1H, *J* = 15.9 Hz), 3.83(s, 3H), 3.69 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 160.13, 148.34, 133.81, 133.43, 133.00, 129.75 (q, 1C, *J* = 32.9 Hz), 129.40, 129.12, 128.70 (2C), 128.41 (2C), 125.87 (q, 2C, *J* = 3.7 Hz), 124.16(q, 1C, *J* = 271.8 Hz), 114.39 (2C), 111.36, 55.45, 31.49. EI-MS *m*/*z* (%): 358 (30), 357 (100), 342 (8), 314 (15), 299 (8). ESI-MS (+): *m*/*z* (%) = 359 (100) $[M+H]^+$. $C_{20}H_{17}F_3N_2O$ (358.36): calcd. C, 67.03; H, 4.78; N, 7.82; found C, 67.16; H, 4.79; N, 7.81.

3.3.8. (*E*)-1-Methyl-2-(4-methylstyryl)-5-(4-(trifluoro-methyl)phenyl)-1*H*-imidazole (**3i**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1b** with **2d** (entry 9, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (40/60) as eluent to give **3i** (75.3 mg, 44% yield) as yellow solid: m.p. = 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71–7.67 (m, 2H), 7.65 (d, 1H, *J* = 15.9 Hz), 7.52–7.48 (m, 2H), 7.47–7.43 (m, 2H), 7.21 (s, 1H), 7.20–7.16 (m, 2H), 6.91 (d, 1H, *J* = 15.8 Hz), 3.69 (s, 3H), 2.36 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 148.13, 138.70, 133.83, 133.75, 133.12, 129.75 (q, 1C, *J* = 32.7 Hz), 129.64 (2C), 129.19 (2C), 128.67 (2C), 126.94 (2C), 125.87(q, 2C, *J* = 3,70 Hz), 124.23 (q, 1C, *J* = 272.0 Hz), 112.50, 31.50, 21.44. EI-MS *m*/*z* (%): 342 (30), 341 (100), 326 (5), 170 (5). ESI-MS (+): *m*/*z* (%) = 343 (100) $[M+H]^+$. $C_{20}H_{17}F_3N_2$ (342.37): calcd. C, 70.16; H, 5.01; N, 8.18; found C, 70.20; H, 5.02; N, 8.17.

3.3.9. (*E*)-1-methyl-5-(4-Trifluoromethyl)phenyl)-2-(4-(trifluoromethyl)-styryl)-1H-imidazole (**3j**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1b** with **2c** (entry 10, Table 2), was purified by flash chromatography on silica gel with a mixture of petroleum ether and AcOEt (70/30) as eluent to give **3j** (82.7 mg, 50% yield) as yellow solid: m.p. = 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.61 (m, 7H), 7.55–7.51 (m, 2H), 7.25 (s, 1H), 7.06 (d, 1H, *J* = 15.8 Hz), 3.75. (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.24, 140.07, 133.75, 133.48, 131.87, 130.12 (q, 2C, *J* = 32.7 Hz), 129.57, 128.86 (2C), 127.07 (2C), 125.99 (q, 2C, *J* = 3.8 Hz), 125.89 (q, 2C, *J* = 3.8 Hz), 124.24 (q, 1C, *J* = 271.8 Hz), 124.14 (q, 1C, *J* = 271.8 Hz), 115.77, 31.55. EI-MS *m*/*z* (%): 396 (30), 395 (100), 380 (10), 378 (10), 327 (5), 196 (5). ESI-MS (+): *m*/*z* (%) = 397 (100) $[M+H]^+$. $C_{20}H_{14}F_6N_2$ (396.34): calcd. C, 60.61; H, 3.56; N, 7.07; found C, 60.55; H, 3.57; N, 7.06.

3.3.10. (*E*)-5-(4-Chlorophenyl)-1-methyl-2-styryl-1*H*-imidazole (**3k**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1c** with **2a** (entry 11, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (97/3) as eluent to give **3k** (70.5 mg, 45% yield) as yellow solid: m.p. = 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, 1H, *J* = 15.9 Hz), 7.56–7.52 (m, 2H), 7.45–7.27 (m, 7H), 7.15 (s, 1H), 6.95 (d, 1H, *J* = 15.9 Hz), 3.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.28, 136.70, 134.07, 133.48, 133.17, 129.99 (2C), 129.14 (2C), 128.88 (2C), 128.51, 128.44, 126.92 (2C), 113.67, 31.31. EI-MS *m*/*z* (%): 296 (10), 295 (30), 294 (28), 293 (100), 278 (10), 128 (10). ESI-MS (+): *m*/*z* (%) = 295 (100), 297 (39) $[M+H]^+$. $C_{18}H_{15}ClN_2$ (294.78): calcd. C, 73.34; H, 5.13; N, 9.50; found C, 73.15; H, 5.14; N, 9.49.

3.3.11. (*E*)-5-(4-Chlorophenyl)-2-(4-methoxystyryl)-1-methyl-1*H*-imidazole (**3l**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1c** with **2b** (entry 12, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70/30) to give **3l** (45.4 mg, 28% yield) as yellow solid: m.p. = 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H, *J* = 15.8 Hz), 7.50–7.46 (m, 2H), 7.42–7.38 (m, 2H), 7.31–7.27 (m, 2H), 7.12 (s, 1H), 6.91–687 (m, 2H), 6.80 (d, 1H, *J* = 15.9 Hz), 3.81(s, 3H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.96, 147.62, 133.88, 133.17, 132.83, 129.88 (2C), 129.44, 129.06 (2C), 128.62, 128.25, 128.23, 114.30 (2C), 111.51, 55.39, 31.25. EI-MS *m*/*z* (%): 326 (10), 325 (34), 324 (32), 323 (100), 308 (7), 280 (10). ESI-MS (+): *m*/*z* (%) = 325 (100), 327 (36) $[M+H]^+$. $C_{19}H_{17}ClN_2O$ (324.81): calcd. C, 70.26; H, 5.28; N, 8.62; found C, 70.41; H, 5.27; N, 8.63.

3.3.12. (*E*)-5-(4-Chlorophenyl)-1-methyl-2-(4-(trifluoromethyl)styryl)-1*H*-imidazole (**3m**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1c** with **2c** (entry 13, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (99/1) to give **3m** (83.3 mg, 46% yield) as an orange solid: m.p. = 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.58 (m, 5H), 7.47–7.43 (m, 2H), 7.35–7.31 (m, 2H), 7.18 (s, 1H), 7.05 (d, 1H, *J* = 15.9 Hz), 3.70 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 146.68, 140.22, 134.41, 134.04, 131.37, 130.13 (2C), 130.05 (q, 1C, *J* = 32.7 Hz), 129.27 (2C), 128.93, 128.39, 127.03 (2C), 125.90 (q, 2C, *J* = 3.8 Hz), 124,.92 (q, 1C, *J* = 271.9 Hz), 115.98, 31.40. EI-MS *m*/*z* (%): 364 (10), 363 (35), 362 (30), 361 (100), 346 (10), 196 (5). ESI-MS (+): *m*/*z* (%) = 363 (100), 365 (38) $[M+H]^+$. $C_{19}H_{14}ClF_3N_2$ (362.78): calcd. C, 62.91; H, 3.89; N, 7.72; found C, 62.89; H, 3.90; N, 7.71.

3.3.13. (*E*)-4-(2-(5-(4-Chlorophenyl)-1-methyl-1*H*-imidazol-2-yl)vinyl)-pyridine (**3n**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1c** with **2f** (entry 14, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (97/3) to give **3n** (23.8 mg, 16% yield) as pale brown wax. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60–6.98 (m, 9H), 3.71 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.99, 143.7, 134.22 (2C), 131.32, 129.86 (2C), 129.75 (2C), 129.18, 129.01 (2C), 128.80 (2C), 127.87, 117.58, 31.29. EI-MS *m*/*z* (%): 297 (9), 296 (36), 295 (27), 294 (100), 279 (6), 242 (4). ESI-MS (+): *m*/*z* (%) = 296 (100), 298 (35) $[M+H]^+$. $C_{17}H_{14}ClN_3$ (295.77): calcd. C, 69.04; H, 4.77; N, 14.21; found C, 69.01; H, 4.78; N, 14.20.

3.3.14. (*E*)-5-(4-Chlorophenyl)-1-methyl-2-(4-nitrostyryl)-1*H*-imidazole (**3o**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1c** with **2g** (entry 15, Table 2), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70/30) to give **3o** (45.8 mg, 27% yield) as pale red solid: m.p. = 187–189 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24–8.20 (m, 2H), 7.74–7.60 (m, 3H), 7.49–7.06 (m, 6H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.01, 146.07, 142.99, 134.34 (2C), 131.64, 129.95 (2C), 129.12 (2C), 128.18, 127.94, 127.13 (2C), 124.19 (2C), 117.50, 31.36. EI-MS *m*/*z* (%): 341 (10), 340 (37), 339 (35), 338 (100), 308 (15), 292 (40). ESI-MS (+): *m*/*z* (%) = 340 (100), 342 (37) $[M+H]^+$. $C_{18}H_{14}ClN_3O_2$ (339.78): calcd. C, 63.63; H, 4.15; N, 12.37; found C, 63.65; H, 4.14; N, 12.38.

3.3.15. (*E*)-5-(3-Fluoro-4-methoxyphenyl)-2-(4-methoxystyryl)-1-methyl-1*H*-imidazole (**3p**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1d** with **2b** (entry 16, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (97/3) to give **3p** (94.7 mg, 56% yield) as beige solid: m.p. = 70 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (d, 1H, *J* = 15.6 Hz), 7.53–7.49 (m, 2H), 7.27 (s, 1H), 7.14–6.76 (m, 7H), 3.94(s, 3H), 3.84(s, 3H), 3.65 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.11, 150.73 (d, 1C, *J* = 393.0 Hz), 147.90 (d, 1C, *J* = 10.6 Hz), 133.82, 133.11, 129.29, 128.43 (2C), 126.82, 125.09 (d, 1C, *J* = 3.3 Hz), 122.63 (d, 1C, *J* = 7.2 Hz), 116.69 (d, 1C, *J* = 19.03 Hz), 114.48 (2C), 113.77 (d, 1C, *J* = 2.42 Hz), 110.77, 56.51, 55.52, 31.44. EI-MS *m*/*z* (%): 338 (38), 337 (100), 322 (10), 169 (5). ESI-MS (+): *m*/*z* (%) = 339 (100) $[M+H]^+$. $C_{20}H_{19}FN_2O_2$ (338.38): calcd. C, 70.99; H, 5.66; N, 8.28; found C, 70.89; H, 5.67; N, 8.29.

3.3.16. (*E*)-2-(4-Methoxystyryl)-1-methyl-5-(4-nitrophenyl)-1*H*-imidazole (**3q**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1e** with **2b** (entry 17, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (97/3) to give **3q** (54.5 mg, 30% yield) as red solid: m.p. = 190–192 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.33–8.29 (m, 2H), 7.65 (d, 1H, *J* = 15.8 Hz), 7.60–7.45 (m,4H), 7.30–7.26 (m, 2H), 6.94–6.90 (m, 2H), 6.83 (d, 1H, *J* = 15.8 Hz), 3.84(s, 3H), 3.75 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.20, 149.27, 146.74, 136.53, 134.23, 132.26, 130.28, 129.11, 128.43 (2C), 128.34 (2C), 124.34 (2C), 114.37 (2C), 110.91, 55.51, 31.86. EI-MS *m*/*z* (%): 335 (33), 334 (100), 304 (22), 288 (32). ESI-MS (+): *m*/*z* (%) = 336 (100) $[M+H]^+C_{19}H_{17}N_3O_3$ (335.36): calcd. C, 68.05; H, 5.11; N, 12.53; found C, 68.11; H, 5.12; N, 12.55.

3.3.17. (*E*)-5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxystyryl)-1-methyl-1*H*-imidazole (**3r**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **1f** with **2b** (entry 18, Table 2), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (98/2) to give **3r** (54.5 mg, 52% yield) as pale red wax. ^{1}H NMR

(200 MHz, $CDCl_3$): δ 7.58 (d, 1H, *J* = 15.8 Hz), 7.51–7.47 (m, 2H), 7.07 (s, 1H), 6.93–6.76 (m, 8H), 6.01 (s, 2H), 3.83(s, 3H), 3.63 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.04, 148.09, 147.75, 146.84, 134.18, 133.10, 129.55, 128.37 (2C), 127.11, 123.69, 122.93, 114.40 (2C), 111.38,109.47, 108.82, 101.55, 55.56, 31.42. EI-MS *m*/*z* (%): 334 (38), 333 (100), 318 (4), 290 (6). ESI-MS (+): *m*/*z* (%) = 335 (100) $[M+H]^+$. $C_{20}H_{18}N_2O_3$ (334.38): calcd. C, 71.84; H, 5.43; N, 8.38; found C, 71.88; H, 5.44; N, 8.37.

3.3.18. (*E*)-1-Methyl-2-styryl-1*H*-benzo[*d*]imidazole (**8**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **6** with **2a** (Scheme 5), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and AcOEt (99/1) to give **8** (101.8 mg, 87% yield) as beige solid: m.p. 118–120 °C, lit [51]. mp 119–121 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 15.9 Hz), 7.83–7.72 (m, 1H), 7.65–7.58 (m, 2H) 7.47–7.19 (m, 6H), 7.09 (d, 1H, *J* = 15.9 Hz), 3.83(s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.91, 143.02, 137.02, 135.91, 128.97, 128.78 (2C), 127.17 (2C), 122.52 (2C), 119.12, 112.90 (2C), 109.17, 29.52. EI-MS *m*/*z* (%): 234 (36), 233 (100), 219 (7), 218 (19), 117 (7). ESI-MS (+): *m*/*z* (%) = 235 (100) $[M+H]^+$. $C_{16}H_{14}N_2$ (234.30): calcd. C, 82.02; H, 6.02; N, 11.96; found C, 82.11; H, 6.03; N, 12.00.

3.3.19. (*E*)-2-Styryl-1*H*-benzo[*d*]imidazole (**9**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **7** with **2a** (Scheme 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (50/50) to give **9** (70.0 mg, 64% yield) as white solid: m.p. 195–197 °C; lit.[52] mp 195 °C. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-*d6*): δ 7.71 (d, 1H, *J* = 16.5 Hz), 7.60 (br, 2H), 7.51–7.47 (m, 2H), 7.36–7.25 (m, 4H), 7.24–7.15 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-*d6*): δ 151.37, 135.89, 134.96, 128.71 (3C), 128.67 (2C), 126.88 (3C), 122.39 (3C), 117.21. EI-MS *m*/*z* (%): 220 (32), 219 (100), 218 (14), 109 (7). ESI-MS (+): *m*/*z* (%) = 221 (100) $[M+H]^+$. $C_{15}H_{12}N_2$ (220.28): calcd. C, 81.79; H, 5.49; N, 12.72; found C, 81.84; H, 5.50; N, 12.75. The NMR spectroscopic data of this compound were in agreement with those previously reported [52].

3.3.20. (*E*)-2-Styrylbenzo[*d*]oxazole (**11**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **10** with **2a** (Scheme 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (95/5) to give **11** (33.2 mg, 30% yield) as brown solid: m.p. 84–86 °C, lit.[53] mp 86–88 °C.^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 1H, *J* = 16.4 Hz), 7.73–7.65 (m, 1H), 7.62–7.48 (m, 3H), 7.45–7.28 (m, 6H), 7.07 (d, 1H, *J* = 16.4 Hz).^{13}C NMR (50 MHz, $CDCl_3$) δ 162.79, 150.42, 142.23, 139.54, 135.20, 129.86, 129.81, 129.05, 128.19, 127.64, 125.30, 124.59, 119.95, 114.02, 110.42. EI-MS *m*/*z* (%): 221 (33), 220 (100), 191 (7), 165 (3). ESI-MS (+): *m*/*z* (%) = 222 (100) $[M+H]^+$. $C_{15}H_{11}NO$ (221.26): calcd. C, 81.43; H, 5.01; N, 6.33; found C, 81.35; H, 5.02; N, 6.35. The NMR spectroscopic data of this compound were in agreement with those previously reported [53].

3.3.21. (*E*)-1-Methyl-4,5-diphenyl-2-styryl-1*H*-imidazole (**13**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **2a** (Scheme 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (93/7) to give **13** (89.0 mg, 55% yield) as orange glassy solid: m.p. 65–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 1H, *J* = 15.9 Hz), 7.60–7.56 (m, 2H), 7.54–7.50 (m, 2H), 7.48–7.41 (m, 3H), 7.40–7.26 (m, 5H), 7.24–7.16 (m, 2H), 7.00 (d, 1H, *J* = 15.9 Hz), 3.53 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 145.50, 138.56, 136.96, 134.75, 133.00, 131.02 (2C), 130.22, 129.10 (2C), 128.87 (2C), 128.68, 128.29, 128.22(2C), 127.22 (2C), 126.94 (2C), 126.54, 113.86, 31.13. EI-MS *m*/*z* (%): 336 (50), 335 (100), 319 (10), 165 (5). ESI-MS (+): *m*/*z* (%) = 337 (100) $[M+H]^+$. $C_{24}H_{20}N_2$ (336.44): calcd. C, 85.68; H, 5.99; N, 8.33; found C, 85.76; H, 6.01; N, 8.35. The NMR spectroscopic data of this compound were in agreement with those previously reported [54].

3.3.22. (*E*)-4,5-Diphenyl-2-styryl-1*H*-imidazole (**15**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **14** with **2a** (Scheme 5), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (95/5) to give **15** (59.6 mg, 36% yield) as orange solid: m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.40 (m, 4H), 7.38–7.32 (m, 2H), 7.30–7.20 (m, 10H), 7.00 (d, 1H, *J* = 16.6 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 145.10, 135.93, 133.64, 132.02, 131.34, 128.92, 128.89 (2C), 128.81, 128.76 (5C), 128.07 (6C), 127.06 (2C), 114.44. EI-MS *m*/*z* (%): 322 (50), 321 (100), 165 (10), 115 (5). ESI-MS (+): *m*/*z* (%) = 323 (100) $[M+H]^+$. $C_{23}H_{18}N_2$ (322.41) calcd. C, 85.68; H, 5.63; N, 8.69; found C, 85.78; H, 5.62; N, 8.70. The NMR spectroscopic data of this compound were in agreement with those previously reported [55].

3.3.23. (*E*)-5-(4-Methoxyphenyl)-1,2-dimethyl-4-styryl-1*H*-imidazole (**17**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **16** with **2a** (Scheme 6), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (96/4) to give **17** (76.0 mg, 50% yield) as orange solid: m.p. 39–40 °C. ^{1}HNMR (400 MHz, C_6D_6): δ 8.00 (d, *J* = 15.8 Hz, 1H), 7.38–7.39 (m, 2H), 7.25 (d, *J* = 15.8 Hz, 1H), 7.05–7.10 (m, 4H), 6.95–6.99 (m, 1H), 6.81–6.84 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.08 (s, 3H). ^{13}CNMR (400 MHz, C_6D_6): δ 159.93, 144.93, 139.15, 136.43, 131.91 (2C), 131.02, 128.77 (2C), 126.99, 126.64, 126.55 (2C); 123.16, 120.90, 114.53 (2C), 54.90, 30.33, 13.49. EI-MS (*m*/*z*): 304 (100), 303 (95), 288 (5), 249 (15), 152 (6), 56 (11). ESI-MS (+): *m*/*z* (%) = 305 (100) $[M+H]^+$. $C_{20}H_{20}N_2O$ (304.39): calcd. C, 78.92; H, 6.62; N, 9.20; found C, 79.01; H, 6.63; N, 9.22.

3.3.24. (*E*)-1-Methyl-2-styryl-1*H*-imidazole (**19**)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **18** with **2a** (Scheme 7), was purified by flash chromatography on silica gel with a mixture of CH_2Cl_2 and MeOH (93:7) as eluent to give Y (83 mg, 45%) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 1H, *J* = 16.08 Hz), 7.42–7.26 (m, 5H), 7.11 (s, 1H), 6.90 (s,1H), 6.85 (d, 1H, *J* = 16.06), 3.68 (s, 3H). EI-MS *m*/*z* (%) =184 (25), 183 (100), 168 (12), 128 (5), 115 (7). ESI-MS (+): *m*/*z* (%) = 185 (100) $[M+H]^+$. The NMR spectroscopic data of this compound were in agreement with those previously reported [37].

4. Conclusions

In this work, we developed a simple and efficient Pd(II)/Cu(II)-promoted dehydrogenative alkenylation of 5-arylimidazoles, 4,5-diphenylimidazole, benzimidazoles and benzoxazole with functionalized styrenes. Starting from a preliminary screening of the role of oxidant, catalyst precursors, solvents, and reaction temperature on the efficiency and selectivity of the alkenylation of 5-(4-methoxyphenyl)-1,2-dimethyl-1*H*-imidazole (**1a**) with styrene (**2a**) we were able to identify reaction conditions suitable for the simple preparation of several 2-alkenyl-substituted azoles. We believe that our findings may represent an important clue for late-stage functionalization protocols [56–58] involving imidazoles, because no pre-activation of the reactive bonds is required. Further studies on the application of this interesting methodology to the synthesis of new heteroaromatic organic fluorophores are underway.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11070762/s1: ^{1}H and ^{13}C NMR spectra of all the new compounds.

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