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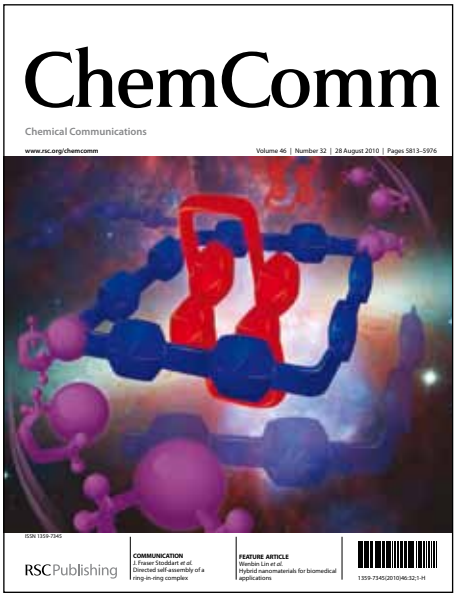

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Ligand Promoted Pd-Catalyzed Dehydrogenative Alkenylation of Hetereoarenes

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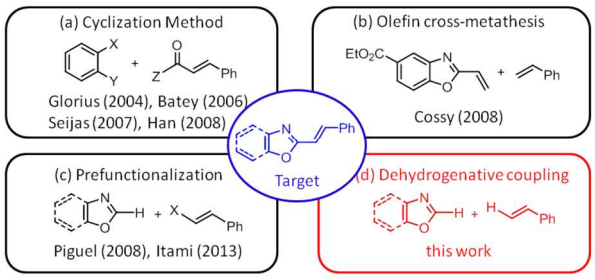
An efficient Pd-catalyzed cross-dehydrogenative coupling of heteroarenes with styrenes and other olefinic substrates has been developed. This alkenylation paradigm encompasses a wide range of substrate scopes and provides a straightforward approach toward C2-*E*-alkenylated azole motifs.

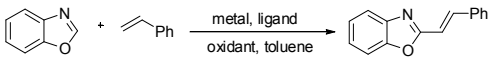
Transition metal mediated C-H bond activation and functionalization are attractive by obviating extra steps associated with prefunctionalized coupling partners.[1] Clearly, cross-dehydrogenative coupling (CDC) reactions[2] provide approaches to construct C-C bonds in an atom- and step-economical fashion. In this context, Fujiwara-Moritani process[3] is one of the most classic CDC reactions regarding alkenylation of arenes. Direct C-H alkenylation of heteroarenes[4-10] has gained great attention mainly because the resulting products are core motifs in natural products, pharmaceuticals, and materials. Representative Pd-mediated C-H/C-H alkenylations of heteroarenes include pyridines,[4] indoles,[5] pyrroles,[6] caffeines,[7] C2-subtituted azoles,[8] furans,[9] and others.[10] However, only few examples involving C-H/C-H coupling between alkenes and C2-position of azoles were discussed, presumably due to undesirable homocoupling and decomposition of azoles.[7,8]



Scheme 1. Selected reports on styrenylation of heteroarenes.

Traditionally, synthetic works toward C2-alkenylated heteroarenes can be achieved through intra- and intermolecular cyclization strategy as shown in Scheme 1(a).[11] Recently, Itami,[12] Piguel,[13] and others[14] expanded the versatility of CH activation toward alkenylation of heteroarenes based on prefunctionalized alkenes (Scheme 1(c)). More encouragingly, You and co-workers reported Pd/Cu-catalyzed C-H/C-H coupling of caffeines with alkenes.[7] Inspired by these pioneering works, we herein disclose an alternative and user-friendly approach to prepare C2-alkenylated heterocyclic motifs based on the Pd-catalyzed CDC reaction of heteroarenes with alkenes.

Table 1. Selected optimization for direct olefination of benzoxazole.[a]



1a 2a 10aa

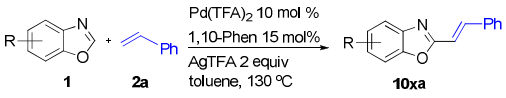
entry	metal	ligand (eq)	oxidant (eq)	yield (%)[b]
1	$Pd(OAc)_2$	---	AgOAc (2)	NR
2	$Pd(OAc)_2$	---	$Cu(OAc)_2$ (2)	9
3	$Pd(OAc)_2$	---	AgTFA (2)	17
4	$Pd(TFA)_2$	---	AgTFA (2)	60
5	$Pd(TFA)_2$	---	[O][c] (2)	NR
6	$Pd(TFA)_2$	IPr (0.1)	AgTFA (2)	49
7	$Pd(TFA)_2$	PCy_3 (0.2)	AgTFA (2)	50
8	$Pd(TFA)_2$	pyridine (1)	AgTFA (2)	68
9	$Pd(TFA)_2$	bipyridine (0.2)	AgTFA (2)	50
10	$Pd(TFA)_2$	1,10-Phen (0.15)	AgTFA (2)	87

[a] Conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), $Pd(TFA)_2$ (0.05 mmol), ligand (0.075 mmol), oxidant (1.0 mmol) in 1 mL toluene at 130 °C for 16 hours. [b] Isolated yield. [c] [O]: $K_2S_2O_8$, AgOAc, BQ-Me_2, or $PhI(OAc)_2$. BQ-Me_2 = 2,6-dimethyl-1,4-benzoquinone. 1,10-Phen = 1,10-phenanthroline.

First, we examined alkenylation of benzoxazole (**1a**) with styrene (**2a**) in the presence of 10 mol% of $Pd(OAc)_2$ and different oxidants in toluene upon heating at 130 °C (entries 1-3 in Table 1).[15] Utilization of $Cu(OAc)_2$ gave 9% of **10aa** accompanied by formation of azole homocoupling product (50-60%).[16] Silver trifluoroacetate (AgTFA) had increased the yield to 17% without any homocoupling product, while other oxidants were completely ineffective. Replacement of $Pd(OAc)_2$ with $Pd(TFA)_2$ remarkably improved the yield to 60 % (entry 4). Addition of ligand like IPr, PCy_3, pyridine, and bipyridine did not enhance the catalytic activity (entries 6-9) in respect to the ligand-free condition. Gratifyingly, as 1,10-phenanthroline was introduced, the yield was elevated to 87% (entry 10). It is worth mentioning that *E*-isomer was exclusively obtained for **10aa**.

Under the optimal reaction condition, the scope of benzoxazole derivatives was investigated with results listed in Table 2. High yields (entries 2-4) were observed for 4-methyl- (**1b**), 5-methyl- (**1c**) and 6-methylbenzoxazoles (**1d**), illustrating the non-sensitivity of the reaction toward methyl substituents at different position. Likewise, the presence of electron-withdrawing group like 5-phenyl (**1e**) and 6-ester (**1g**) substituents also gave good yields (entries 5 and 7). Moderate yield was witnessed in the 5-chloro derivative (**1f**) (entry 6) with a chloride functionality staying intact, which provides further manipulation possibility.

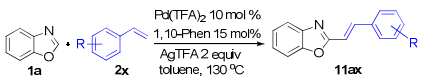
Table 2. Scope of various benzoxazole derivatives.[a]



entry	1		major product	yield (%)[b]
1	R = H	**1a**		87
2	R = 4-Me	**1b**		86
3	R = 5-Me	**1c**		79
4	R = 6-Me	**1d**		87
5	R = 5-Ph	**1e**		85
6	R = 5-Cl	**1f**		56
7	R = 6-CO_2Me	**1g**		70

[a] Conditions: **1** (0.5 mmol), **2a** (2.5 mmol), $Pd(TFA)_2$ (0.05 mmol), 1,10-phen (0.075 mmol) and AgTFA (1.0 mmol) in toluene (1 mL) at 130 °C for 16 hours unless otherwise noted. [b] Isolated yield.

Table 3. Scope of various styrene & olefin derivatives.[a]



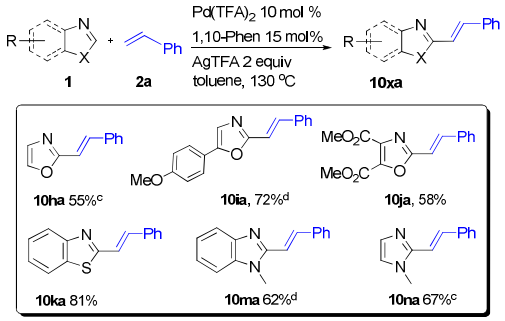
entry	2x		major product	yield (%)[b]
1	R = H	**2a**		87
2	R = 2-Me	**2b**		71
3	R = 3-Me	**2c**		68
4	R = 4-Me	**2d**		87
5	R = 3-Ph	**2e**		78
6	R = 4-F	**2f**		91
7	R = 4-Cl	**2g**		94
8	R = 2,4,6-Me_3	**2h**		62[c]
9		**2i**		64
10	Ph	**2j**		75
11		**2k**		67
12		**2l**		53
13		**2m**		71[c]
14		**2n**		66[c]
15		**2o**		56[c]
16		**2p**		32[c]
17		**2q**		55

[a] Conditions: **1a** (0.5 mmol), **2x** (2.5 mmol), $Pd(TFA)_2$ (0.05 mmol), 1,10-phen (0.075 mmol) and AgTFA (1.0 mmol) in toluene (1 mL) at 130 °C for 16 hours unless otherwise noted. [b] Isolated yield. [c] $Pd(TFA)_2$ (0.1 mmol), 1,10-phen (0.15 mmol).

To further demonstrate its catalytic utility, we expanded the scope of this protocol to other styrene derivatives and olefins (Table 3). Substrates bearing an electron-donating methyl group at *ortho*, *meta* and *para* positions gave the corresponding products in high yields (entries 2-4). Similarly, such method can be extended effectively to other electron-poor styrenes containing 3-phenyl (**2e**), 4-flouro (**2f**), 4-chloro (**2g**) and 4-phenyl (**2j**) group (entries 5-7 & 10). 2-Vinylnaphthalene (**2i**) was reactive to afford the coupling product in a moderate yield (64%, entry 9). More importantly, methyl substitution at α (**2k**) or β (**2l**) position did not seem to have dramatically adverse effect on the styrenylation process. Introduction of acrylate moieties (**2m** and **2n**) resulted in chemically versatile α,β-unsaturated carbonyl compounds (entries 13 and 14), raising the practicality of this methodology. Reactivities of 1,5-cyclooctadiene (**2o**) and indene (**2p**) were demonstrated to give the corresponding adducts **11ao** and **11ap** (entries 15 and 16). In addition, 1-phenyl-1,3-butadiene (**2q**) reacted exclusively at its terminal double bond to give the olefinated product **11aq** (entry 17).

The current catalytic system was also effective for other heteroarenes with results summarized in Table 4. A C4- or C5-substituted oxazole underwent the dehydrogenative coupling to afford the corresponding products **10ia** and **10ja**. Notably, oxazole and N-methylimidazole participated regioselectively in the C2-alkenylation to afforded **10ha** and **10na**. In addition, benzothiazole and N-methylbenzimidazole were applicable in this methodology to give **10ka** and **10ma**.

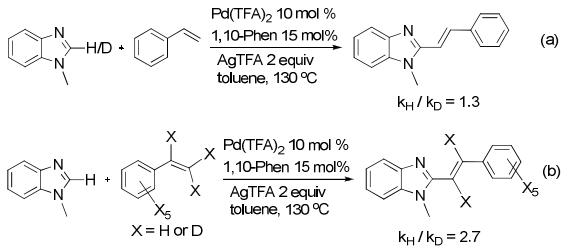
Table 4. Scope of various heteroarenes.[a,b]



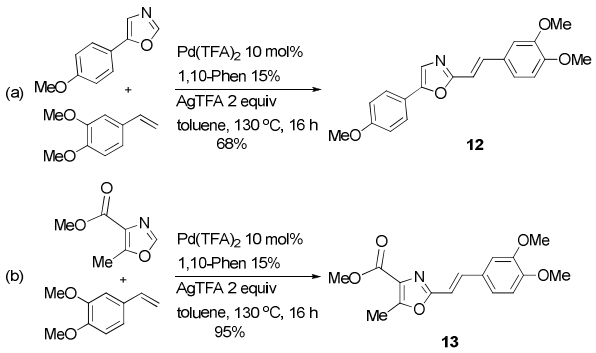
[a] Conditions: heteroarene (0.5 mmol), **2a** (2.5 mmol), $Pd(TFA)_2$ (0.05 mmol), 1,10-phen (0.075 mmol) and AgTFA (1.0 mmol) in toluene (1 mL) at 130 °C for 16 hours unless otherwise noted. [b] Isolated yield. [c] Azole (1.0 mmol). [d] $Pd(TFA)_2$ (0.1 mmol), 1,10-phen (0.15 mmol).

To gain insights of the present catalytic system, we conducted the kinetic isotope effect (KIE) experiments[17] for both coupling partners (Scheme 2). An intermolecular competition reaction between N-methylbenzimidazole and its C2-deuterated derivative did not show a kinetic isotope effect (k_H/k_D = 1.3), revealing C-H bond cleavage of N-methylbenzimidazole was not involved in the rate-determining step. Interestingly, a notable primary KIE value of 2.7 was observed between styrene and d_8-styrene. These results indicated that olefinic C-H bond cleavage of styrene is significant with respect to the rate-determining step. Nevertheless, further kinetic studies are necessary to investigate the mechanistic details.

Practical feasibility of this approach was further demonstrated in the total syntheses of naturally-occurring Annuloline (**12**)[13,18] and Siphonazole (**13**).[19] Dehydrogenative alkenylations to make **12** and Siphonazole precursor (**13**) were performed using commercially available 3,4-dimethoxystyrene and the corresponding oxazoles in 68% and 95% yields, respectively (Scheme 3), which provide a direct and efficient synthetic method compared to recent reports through prefunctionalized styrenes.[12,13]



Scheme 2. Kinetic isotope effect (KIE) experiments.



Scheme 3. Synthesis of compounds **12** (a) and **13** (b).

In summary, we present a straightforward approach toward C2-*E*-alkenylated azoles by cross-dehydrogenative coupling of azoles with a vinyl moiety without using prefunctionalized substrates. Successful preparations of **12** and **13** demonstrate practical implementation of this methodology toward valuable synthetic targets featuring C2-*E*-alkenylated azole motifs. Efforts are now underway to investigate the mechanistic details, in which the C-H activation of styrene is believed to be the rate-determining step based on KIE studies.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectral data for all compounds. See DOI: 10.1039/c000000x/

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