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Aerobic Direct C–H Arylation of Nonbiased Olefins

Nicolas Gigant and Jan-E. Bäckvall*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

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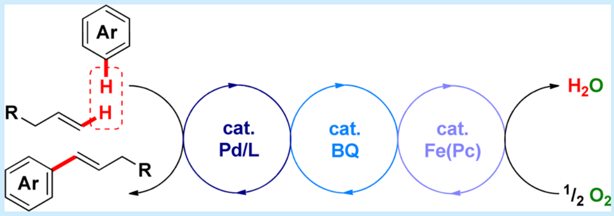
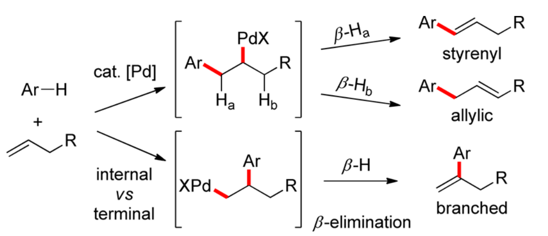
ABSTRACT: An efficient ligand-promoted biomimetic aerobic oxidative dehydrogenative cross-coupling between arenes and nonbiased olefins is presented. Acridine as a ligand was found to significantly enhance the rate, the yield, and the scope of the reaction under ambient oxygen pressure, providing a variety of alkenylarenes via an environmentally friendly procedure.



Direct functionalization of C–H bonds has emerged as a promising tool to create new C–C bonds, and one of the ideal ways is the oxidation of two simple C–H bonds.[1,2] Among these catalytic dehydrogenative cross-couplings, the "dehydrogenative Heck reaction" was originally disclosed by Fujiwara and Moritani.[3] Much progress has been achieved in this field following this pioneering work, and this transformation is now fully recognized as a powerful method for the construction of valuable scaffolds.[4] However, recent developments of this reaction have witnessed several restrictions in the presence of simple arenes. Limitations of these approaches include the requirement of a relatively high palladium loading and the use of various inorganic salts as terminal oxidants that provide stoichiometric amounts of reduced external oxidants as waste. In addition, due to their low reactivity, arenes are usually used in a large excess or even as the solvent, thus making the process less attractive in terms of atom economy.[5] The scope of alkenes is also largely limited to "activated" coupling partners such as acrylates and styrene derivatives. On the contrary, electronically nonbiased olefins are not reactive enough to promote the Pd-catalyzed dehydrogenative reaction.[6] Finally, the control of the selectivity is problematic: a mixture of products can be obtained from the insertion of the alkene into the Pd–Ar bond (internal vs external) and the *β*-hydride elimination (*β*-H_a vs *β*-H_b) (Scheme 1). Consequently a general and efficient protocol solving several of these problems would be desirable.

On the basis of these considerations, we have explored the aerobic direct C–H functionalization of simple arenes using nonbiased olefins. There are several challenges to deal with during the development of this reaction, the two most critical being the use of an environmentally friendly method and the capacity to engage these much less reactive alkenes efficiently in the coupling. Our laboratory is indeed involved in the development of new sustainable transformations for the creation of C–C bonds via a biomimetic approach.[7] With this strategy the electron transfer is facilitated between the organic substrate and O_2 under mild conditions, decreasing the activation energy during the catalytic process.[8] Following this concept, we have shown that acrylates[4d] and allyl esters[7a] efficiently undergo the Heck coupling with arenes; however, nonbiased alkenes, such as protected allylamines, were unfortunately not tolerated by our catalytic systems. Since the beneficial effect of various nitrogen-containing ligands has recently been demonstrated in the intermolecular dehydrogenative Heck reaction,[9] we sought to address the lack of reactivity of unactivated alkenes by enhancing the rate of the reaction through the use of ligands. Our attention was drawn to recent work by Yu[9d] and Sanford,[1j,9e] emphasizing the use of pyridine-type ligands. We now report our study regarding the ligand-promoted aerobic dehydrogenative coupling of arenes and nonbiased olefins via a biomimetic approach.

Scheme 1. Competitive Pathways in the Heck Reaction



We evaluated the feasibility of the proposed strategy in the reaction of alkene **1a** (1 equiv) with 1,4-dimethoxybenzene **2a** (6 equiv) using $Pd(OAc)_2$ (2.5 mol %), *p*-benzoquinone (BQ) (10 mol %), and iron phthalocyanine [Fe(Pc), 2.5 mol %] in a mixture of acetic acid/dioxane (1:1, v:v) for 24 h at 90 °C under ambient oxygen pressure (Scheme 2). In this reaction BQ and Fe(Pc) serve as electron-transfer mediators. These reaction conditions provided the desired product **3aa** in low yield. As noted above, this unactivated alkene exhibited poor reactivity, and the protocol was further optimized by examining the effect of pyridine (**L1**) as a ligand. The reaction was very dependent on the palladium/pyridine ratio, and it was found that a 1:1 ratio is optimal.[10] Lower yields were observed with different ratios, and a 20:1 ratio in favor of pyridine (50 mol %)

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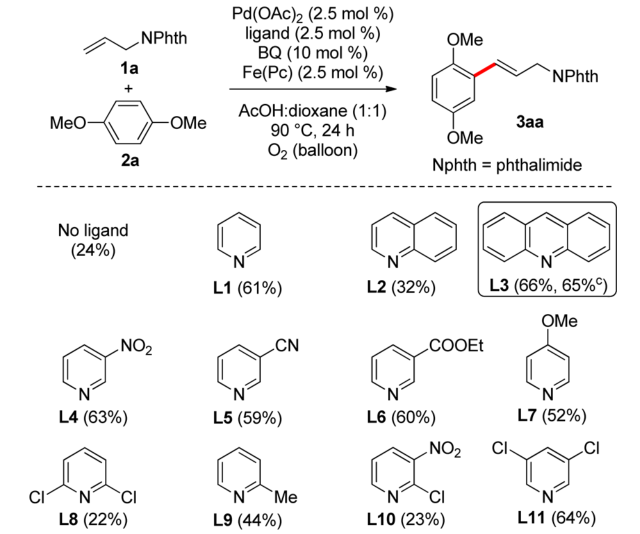
Scheme 2. Ligand Screening[a,b]

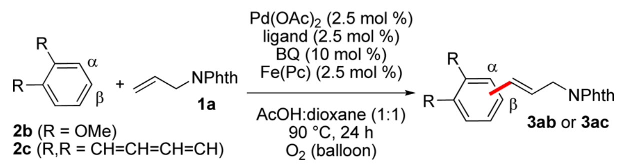


[a]Unless otherwise noted the reactions were carried out at 90 °C using **1a** (0.30 mmol), **2a** (1.80 mmol, 6 equiv), $Pd(OAc)_2$ (2.5 mol %), ligand (2.5 mol %), BQ (10 mol %), and Fe(Pc) (2.5 mol %) in AcOH/dioxane (0.5 mL/0.5 mL) for 24 h under O_2 (balloon). The use of air in place of O_2 gave low yields and poor reproducibility. [b]NMR yield using an internal standard. [c]Isolated yield.

totally inhibited the reaction. A number of both electronically and sterically different pyridine-type ligands (**L2**−**L11**) were tested in combination with this catalytic system. Systematic variation of the pyridine moiety revealed that acridine (**L3**) provided the highest yield. It is interesting to note that no correlation between either the electronic nature or the steric encumbrance of the ligand was observed.[10] Importantly, **3aa** was isolated with high levels of selectivity (E:Z = 18:1, L:B > 40:1).

Encouraged by these results, we sought to investigate the regioselectivity of the reaction by examining the influence of our previous best ligands on the site selectivity of the coupling (Table 1). Indeed a mixture of isomers is usually formed during the Pd-catalyzed alkenylation of simple arenes, the site

Table 1. Effect of Ligand on Site Selectivity[a]



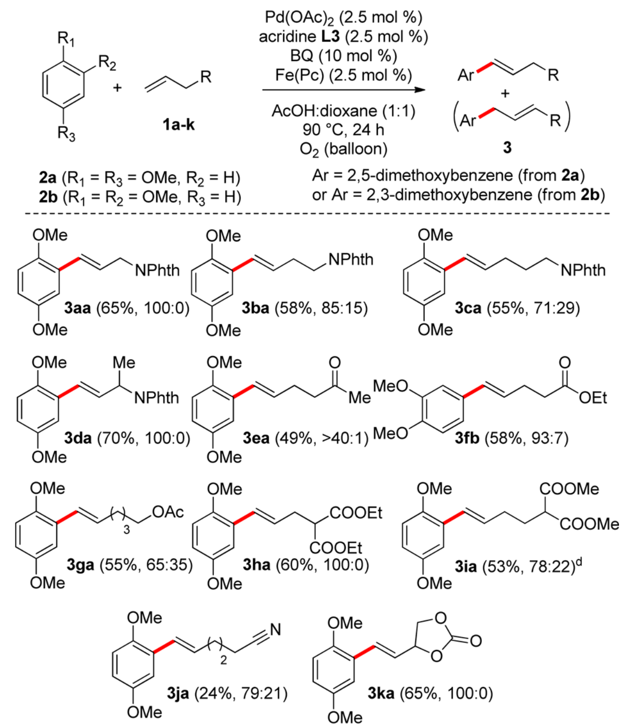
		3ab (from 2b)[b]		3ac (from 2c)	
entry	ligand	selectivity (α:β)[c]	yield (%)[d]	selectivity (α:β)[c]	yield (%)[d]
1	none	>5:95	14	46:54	33
2	**L1**	19:81	19	47:53	80
3	**L3**	>1:99	53 (49)[e]	44:56	82 (56)[e]
4	**L4**	25:75	23	53:47	36
5	**L5**	29:71	25	56:44	27
6	**L6**	30:70	23	55:45	73
7	**L11**	21:79	36	57:43	37

[a]For reaction conditions, see Scheme 1. [b]**2b** (2 equiv). [c]Ratio of regioisomers determined by NMR spectroscopy of crude mixture. [d]NMR yield using an internal standard. [e]Isolated yield.

selectivity being mainly directed by electronic factors with a preference for the most electron-rich carbon. Gratifyingly, starting from veratrole **2b**, acridine (**L3**) was not only the best ligand to promote the reaction but also the best ligand to form product **3ab** as a single regioisomer. Other ligands gave a mixture of isomers in 2:8 or 3:7 ratios in lower yields in favor of the 3-alkenylated scaffold. The high site selectivity with ligand **L3** may be due to steric effects leading to reaction at the less sterically hindered C−H bond. When the coupling was performed in the presence of naphthalene **2c**, a low selectivity was obtained (**3ac**). However, we noticed some variations in the site selectivity of the coupling depending on the ligand.

The arylation of other nonbiased olefins was next studied (Scheme 3).[11] Several alkenes bearing a doubly protected

Scheme 3. Substrate Scope of Alkenes[a,b,c]



[a]For reaction conditions, see Scheme 1. [b]Isolated yield. [c]Ratio of isomers (styrenyl:allylic) determined by NMR spectroscopy of isolated product. [d]**2a** (10 equiv).

terminal amine performed well in the present reaction with satisfying to excellent selectivity (**3aa**−**3da**). Generally, the selectivity decreases with an increased length of the alkyl chain. The source of the loss in the selectivity can be rationalized by a more complicated chelation between the metal and the imide oxygen in the presence of longer alkyl chains.[12] Other functional groups on simple alkenes were suitable coupling partners, including a ketone, an ester, an acetate, and protected malonates (**3ea**, **3fb**, and **3ga**−**3ia**). Unfortunately 5-hexenenitrile **1j** was functionalized in a low yield (**3ja**), probably due to the low stability of the starting material in the reaction medium. We were pleased to find that even a cyclic carbonate can be accommodated under our conditions, giving **3ka** in good yield and complete selectivity. The use of purely aliphatic olefins such as 1-octene or 1-undecene gave low yields and poor selectivity.

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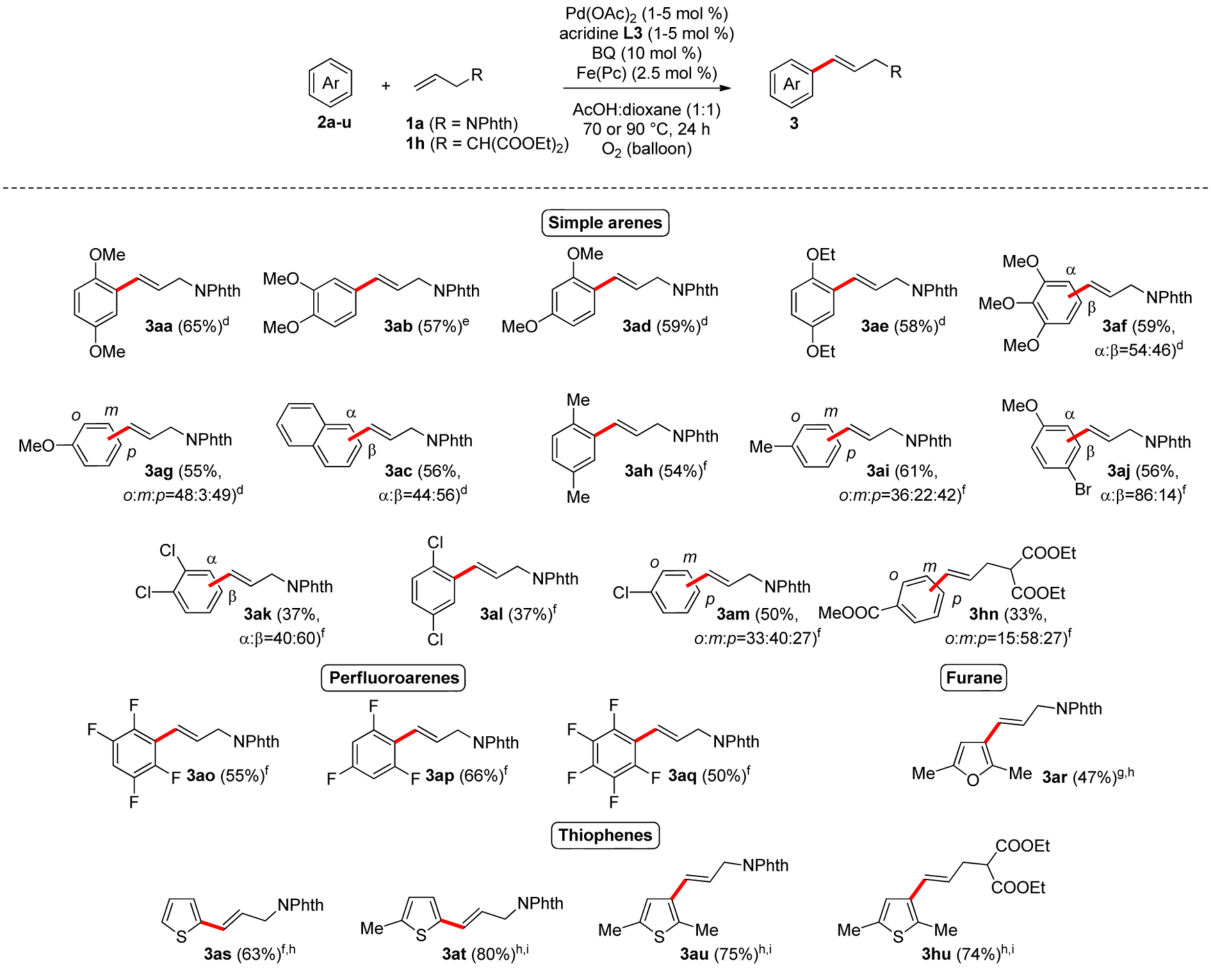
Scheme 4. Substrate Scope of Arenes[a,b,c]



[a]For reaction conditions, see Scheme 1. [b]Isolated yield. [c]Ratio of isomers (*o*:*m*:*p* or α:β) determined by NMR spectroscopy of isolated product. [d]$Pd(OAc)_2$ (2.5 mol %), **L3** (2.5 mol %). [e]$Pd(OAc)_2$ (1 mol %), **L3** (1 mol %). [f]Arene **2** (10 equiv), $Pd(OAc)_2$ (5 mol %), **L3** (5 mol %). [g]$Pd(OAc)_2$ (5 mol %), **L3** (5 mol %). [h]Reaction performed at 70 °C. [i]$Pd(OAc)_2$ (3.5 mol %), **L3** (3.5 mol %).

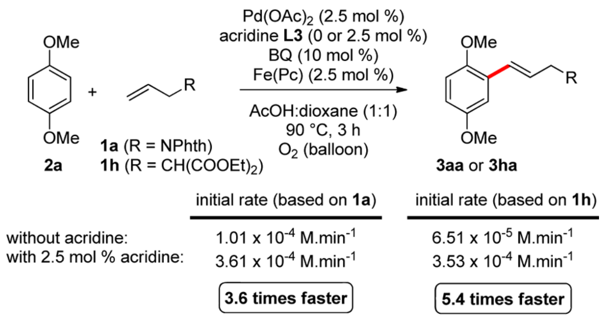
Alkenes **1a** and **1i** were selected as model substrates for the arene scope evaluation as presented in Scheme 4.[11]

Electron-rich arenes undergo smooth coupling with moderate to complete site selectivity in the presence of unsymmetrical substrates (**3aa**−**3ag**). Importantly, **3ab** could be a relevant synthetic intermediate for the short total synthesis of bioactive compounds abamine and abamine SG.[13] Starting from electron-neutral or -poor arenes, a slight increase of the catalyst/ligand loading as well as the amount of arene were necessary for obtaining synthetically useful yields (**3ah**−**3am** and **3hn**). Additionally, several alkenylated multifluoroarenes were also efficiently isolated (**3ao**−**3aq**), which are not commonly obtained from direct olefination of this category of arenes.[9c,14] Because of their high sensitivity to acidic conditions, heterocycles such as thiophenes and furans are usually poor substrates in the oxidative Heck reactions.[15] In the present method, these heterocycles efficiently react with unbiased alkenes (**3ar**−**3au** and **3hu**), leading the desired alkenylated scaffolds in good to high yields at 70 °C.

To obtain mechanistic information, two parallel reactions using **2i** and **2i**-d_8 with protected allylamine **1a** were performed.[16] The comparison of the initial rates gave a kinetic isotope effect of 4.4, indicating that the aromatic C−H bond cleavage by Pd is involved in the rate-determining step of the coupling.

To gauge the acridine effect, we measured the relative rate of the reaction starting from **1a** and **1h** with or without ligand (Scheme 5).[16] The initial rate of the coupling was roughly 3.6 and 5.4 times faster for **1a** and **1h**, respectively, in the presence of acridine when compared to the rate in the absence of acridine. In addition, two competitive reactions between **1a** and **1h** with 1,4-dimethoxybenzene **2a** without or with ligand were also performed, giving a mixture of products **3aa** and **3ha** in a

Scheme 5. Acridine-Accelerated Reaction



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1.9 and 1.4 ratio, respectively, after 2 h (at 3% and 9% conversion, respectively). The slight increase of relative rate of **1a**:**1h** (1.55:1.9 without **L3**) and (1.02:1.4 with **L3**) in the competitive experiment compared to the separate experiment in Scheme 5 suggests that there is a preference for coordination of **1a** over **1h** in the competitive experiment.

In summary, we have documented a new aerobic alkenylation of arenes through a biomimetic approach. The current work is a major advance over existing methods for coupling of unbiased olefins with simple arenes, perfluoroarenes, and heterocycles. Finally, it is noteworthy that the coupling described proceeds under relatively low catalyst loading at ambient oxygen pressure.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full characterization details including ^{1}H, ^{13}C NMR and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jeb@organ.su.se.

Notes

The authors declare no competing financial interest.

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(10) For complete optimization of the reaction and pyridine pK_a values, see the Supporting Information.

(11) All products were obtained in good to excellent *E*:*Z* and L:B ratios, but for clarity, these results are not directly reported in the paper. See the Supporting Information for complete assignment of the selectivity.

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(16) See the Supporting Information for more details.