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Access to Cinnamyl Derivatives from Arenes and Allyl Esters by a Biomimetic Aerobic Oxidative Dehydrogenative Coupling

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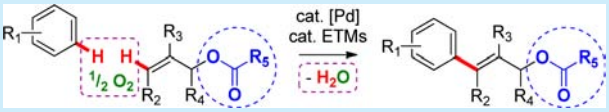
Supporting Information

ABSTRACT: An efficient biomimetic aerobic oxidative dehydrogenative alkenylation of arenes with allyl esters is presented. The reaction proceeds under an ambient pressure of oxygen with relatively low catalyst loading of palladium acetate, employing catalytic amounts of electron-transfer mediators (ETMs). This study represents a new environmentally friendly method for the synthesis of cinnamyl derivatives.

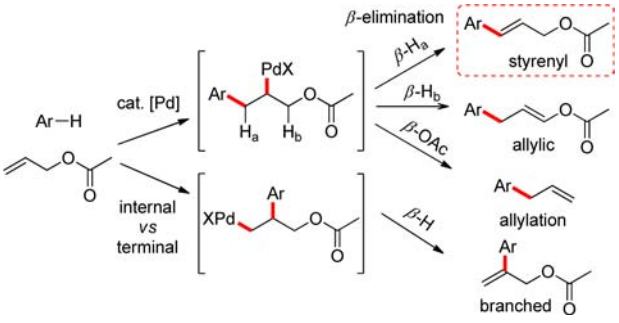


Owing to the versatility of the cinnamyl moiety as an indispensable component of many synthetic building blocks, natural products, and drug candidates, its fast and easy construction remains a continuous challenge.[1] For instance, transition-metal-catalyzed direct C−H activation offers a powerful and economical method to create C−C bonds without the conventional prefunctionalization.[2] In particular, direct cross-dehydrogenative coupling reactions are among the best strategies to link two C−H bonds together, producing only water as the molecular byproduct. Among these transformations, the intermolecular coupling of arenes and alkenes, also called "dehydrogenative Heck reaction", first explored by Fujiwara and Moritani,[3] has attracted considerable attention during the past decade.[4] Indeed, this reaction has been used to develop new methodologies for application in total synthesis.[5]

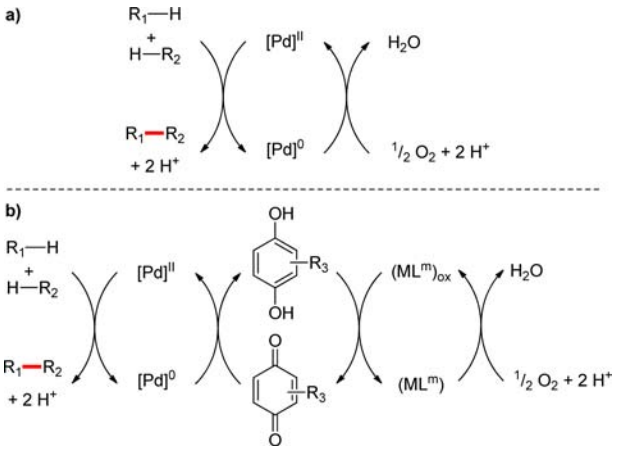
Despite recent major advancements, the "green" aspect of these transformations is often widely affected by the use of relatively high catalyst loading, stoichiometric, or often overstoichiometric amounts of nonenvironmentally friendly additives (Cu(II), Ag(I), etc.) and sometimes expensive sacrificial oxidants other than ideal molecular oxygen. The activation of the stable C−H bond and the catalyst regeneration to its active form are unfortunately not favored processes. In addition, the scope of alkenes is generally restricted to "activated" partners, like electron-deficient olefins and styrene derivatives. Even if allyl esters have been extensively studied as allylic alkylation reagents to create new C−C bonds,[6] their reactivity in the Heck reaction has only recently attracted attention due to the competing selectivities (Scheme 1).[7] The outcome of the reaction depends on: (i) Pd insertion (internal vs terminal), (ii) selectivity in β elimination (β-H vs β-OAc), and (iii) elimination regioselectivity (allylic vs styrenyl).

An ongoing area of research in our laboratory is the development of green and sustainable methodologies for the formation of new C−C bonds.[8] Toward this end, we envisaged exploration of a selective oxidative coupling between simple arenes and allyl esters via a biomimetic approach. With this strategy, catalytic electron-transfer mediators (ETMs), e.g., a benzoquinone derivative and an oxygen-activating metal-containing macrocycle, interact to decrease the barrier between the reduced catalyst and O_2 (Scheme 2).[9] In this way, a low energy pathway is created between Pd and O_2, circumventing the high energy pathway often associated with reoxidation of

Scheme 1. Competitive Pathways in the Heck Coupling between Arenes and Allyl Esters



Scheme 2. Aerobic Dehydrogenative Coupling (a) vs Biomimetic Aerobic Dehydrogenative Coupling (b)



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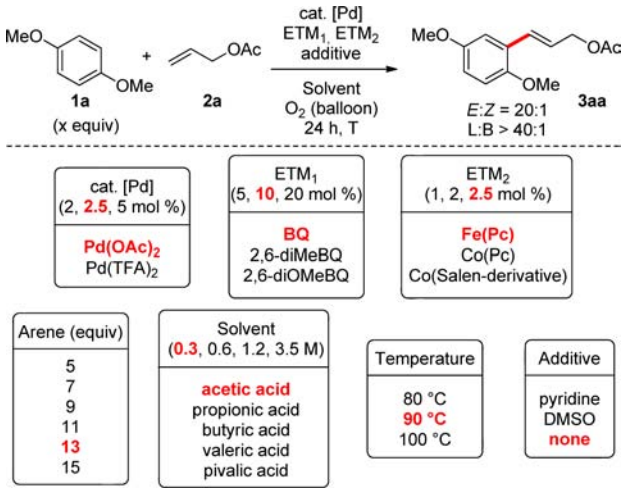
Pd by O_2. In this paper, we report our results regarding the aerobic oxidative coupling of arenes and allyl esters through a biomimetic approach, and this new environmentally friendly method overcomes several of the limitations mentioned above.

To investigate the Pd-catalyzed aerobic biomimetic coupling, 1,4-dimethoxybenzene (**1a**) and allyl acetate (**2a**) were chosen as model substrates for the initial optimization of the reaction conditions (Scheme 3).[10] The seven tested parameters are

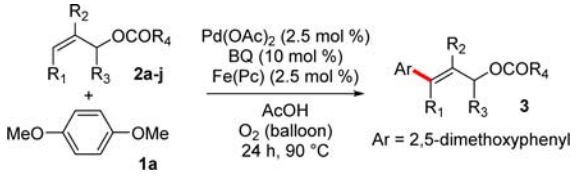
Scheme 3. Optimization of Reaction Conditions[10]

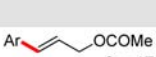
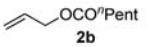
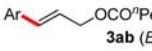
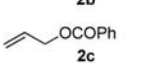
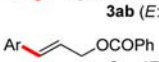
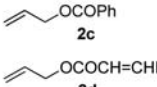
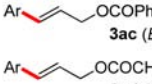
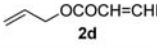
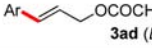
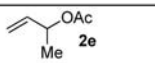
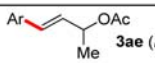
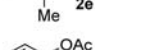
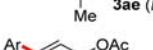
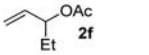
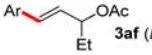
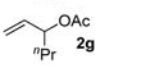
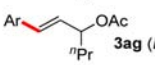


depicted in Scheme 3. $Pd(OAc)_2$ (2.5 mol %) was the most efficient catalyst. Screening of ETMs showed that 1,4-benzoquinone (BQ) (10 mol %) in combination with iron phthalocyanine Fe(*Pc*) (2.5 mol %) gave the best activity. More electron-rich BQ derivatives, other metal complexes, or different loadings did not give any improvement of the yield of the desired product **3aa**. In addition, pyridine or DMSO as ligands did not increase the yield of the reaction and it was found that 90 °C was the optimal temperature. A variety of solvents were then examined, but none of them was more efficient than acetic acid. Finally, our last efforts were focused on the number of equivalents of arene. Whereas 5, 7, or 9 equiv did not affect the yield, 11 or 13 equiv increased the yield to 61%. A further increase to 15 equiv decreased the yield. With the current protocol using 13 equiv of **1a**, **3aa** was isolated in 61% yield with complete retention of the leaving group and high levels of selectivity (*E*/*Z* = 20:1, L/B > 40:1).

The oxidative Heck coupling was then extended to other allyl ester derivatives, and the results are given in Table 1. First, different esters were tested under optimized conditions using arene **1a** (Table 1, entries 1−4). Allyl hexanoate, allyl benzoate, and allyl cinnamate furnished products **3ab**, **3ac**, and **3ad**, respectively, in moderate to good yields. The selectivity for the attack of the aryl group at the terminal position was high. The effect of the substitution on the allyl moiety was next examined. Allyl esters bearing aliphatic chains next to the oxygen atom were also good alkenylating partners, giving **3ae**−**ag** with high selectivities (Table 1, entries 5−7). Surprisingly, a phenyl substituent next to the oxygen reversed the *E*/*Z* ratio in favor of the *Z* isomer of **3ah** (Table 1, entry 8). For allyl acetate **2i**, the L/B ratio was affected (3:1) even if a significant preference for the desired cinnamyl product **3ai** was preserved (Table 1, entry 9). Furthermore, when cinnamyl acetate was subjected to our experimental conditions, a mixture of linear and branched products **3aj** was isolated in high yield (Table 1, entry 10).

Table 1. Biomimetic Aerobic Oxidative Dehydrogenative Coupling between Various Allyl Esters 2 and 1,4-Dimethoxybenzene 1a[a]



entry	allyl acetat	product[c]	Yield (%)[b] (L:B)[c]
1	 **2a**	 **3aa** (*E*:*Z* = 20:1)	61 (>40:1)
2	**2b**	**3ab** (*E*:*Z* = 18:1)	35 (19:1)
3	 **2c**	 **3ac** (*E*:*Z* = 9:1)	43 (13:1)
4	 **2d**	 **3ad** (*E*:*Z* = 12:1)	52[d] (15:1)
5	 **2e**	 **3ae** (*E*:*Z* = 12:1)	43 (19:1)
6	 **2f**	 **3af** (*E*:*Z* = 21:1)	59[d] (25:1)
7	 **2g**	 **3ag** (*E*:*Z* = 19:1)	34[d] (22:1)
8	 **2h**	 **3ah** (*E*:*Z* = 1:1.4)	58 (18:1)
9	 **2i**	 **3ai** (*E*:*Z* = 3.5:1)	49 (3:1)
10	 **2j**	 **3aj-α** (*E*:*Z* = 1.1:1) **3aj-β** (*E*:*Z* = 6:1)	76 (47:53)

[a]Unless otherwise noted, the reactions were carried out at 90 °C using **2** (0.30 mmol), **1a** (13 equiv), $Pd(OAc)_2$ (2.5 mol %), BQ (10 mol %), and Fe(*Pc*) (2.5 mol %) in AcOH (1 mL) for 24 h under O_2 (balloon). [b]Isolated yield. [c]*E*/*Z* and L/B ratios determined using ^{1}H NMR analysis of isolated mixtures. [d]Reaction performed in a mixture of AcOH/dioxane (0.5 mL/0.5 mL).

Steric effects certainly play an important role in this coupling and it seems reasonable to expect that the phenyl moiety favors the external Pd insertion (Scheme 1).

After evaluating the scope with allyl esters, we next applied this catalytic system to various arenes to demonstrate the efficiency and scope of the present method (Table 2). Gratifyingly, it should be noted that all products were obtained in high levels of selectivity (*E*/*Z* and L/B ratios). A series of 1,4-disubstituted arenes were coupled to produce the desired scaffolds in moderate to good yields. Symmetrical arenes gave a single isomer, and the coupling was efficient with only a catalyst loading of 2.5 mol % for electron-rich arenes **1a**,**b** (Table 2, entries 1 and 2). Electron-neutral or -poor arenes **1c**−**e** were less reactive and required an increase to 5 mol % of $Pd(OAc)_2$ (Table 2, entries 3−5). We presume that the lower reactivity is due to the decreased nucleophilicity of the arene. Interestingly, a wide range of *p*-functionalized anisole derivatives underwent the coupling smoothly: either methyl, chloro, bromo, or fluoro moieties were tolerated, giving **3fa**−**ia** as a mixture of isomers in satisfying yields (Table 2, entries 6−9). Additionally, the

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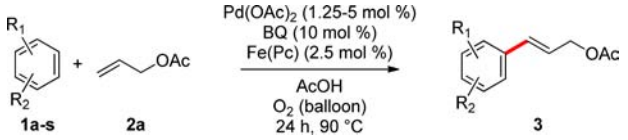
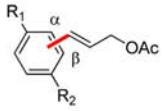
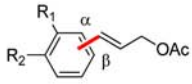
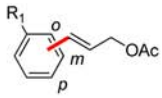
Table 2. Biomimetic Aerobic Oxidative Dehydrogenative Coupling between Allyl Acetate 2a and Various Arenes 1[a]



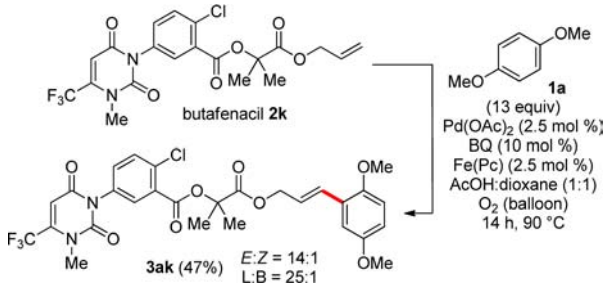
entry	product		R_1	R_2	Yield (%)[b]	α/β or *o*/*m*/*p*[c]	*E*:*Z*[c]	L:B[c]
1		**3aa**	OMe	OMe	61[d]	-	20:1	>40:1
2		**3ba**	OEt	OEt	55[d]	-	17:1	25:1
3		**3ca**	Me	Me	52[e]	-	18:1	>40:1
4		**3da**	H	H	44[e,f]	-	31:1	24:1
5		**3ea**	Cl	Cl	16[e]	-	24:1	>40:1
6		**3fa**	OMe	Me	56[d]	90:10	20:1	25:1
7		**3ga**	OMe	Cl	50[e]	84:16	23:1	33:1
8		**3ha**	OMe	Br	51[e]	92:08	27:1	25:1
9		**3ia**	OMe	F	43[e]	50:50	20:1	35:1
10		**3ja**	Me	Me	60[e]	25:75	30:1	35:1
11		**3ka**	Cl	Cl	19[e]	29:71	26:1	>40:1
12		**3la**	CH=CH=CH=CH		57[d]	43:57	22:1	16:1
13		**3ma**	$CH_2CH_2CH_2CH_2$		49[g]	28:72	25:1	17:1
14		**3na**	$CH_2CH_2CH_2$		55[d]	46:54	23:1	30:1
15		**3oa**	OCH_2O		62[h]	62:38	25:1	9:1
16		**3pa**	OMe	-	66[d]	37:5:58	18:1	19:1
17		**3qa**	OEt	-	58[d]	36:8:56	26:1	26:1
18		**3ra**	Cl	-	44[e]	35:37:28	23:1	25:1
19		**3sa**	Br	-	34[e]	33:37:30	21:1	24:1

[a]For reaction conditions, see Table 1. [b]Isolated overall yields of the *E*/*Z* and B isomers. [c]Product ratios determined by ^{1}H NMR analysis of isolated mixtures. [d]$Pd(OAc)_2$ (2.5 mol %). [e]$Pd(OAc)_2$ (5 mol %). [f]Reaction performed at 80 °C. [g]$Pd(OAc)_2$ (3.75 mol %). [h]$Pd(OAc)_2$ (1.25 mol %).

reactivity of 1,2-difunctionalized arenes was also investigated. When *o*-xylene was allowed to react with allyl acetate, the desired cinnamyl derivative **3ja** was isolated in good yield, whereas *o*-dichlorobenzene **1k** was less reactive (Table 2, entries 10 and 11). Under similar reaction conditions, other simple bicyclic substrates such as naphtalene, tetralin, or indane reacted efficiently with allyl acetate, forming the corresponding derivatives **3la**–**na** with moderate selectivities in good yields (Table 2, entries 12–14). Importantly, a very low palladium loading (1.25 mol %) was successfully employed with 1,3-benzodioxole **1o** as coupling partner, and surprisingly, the sterically more hindered position was favored (Table 2, entry 15). Monosubstituted arenes **1p** and **1q** bearing an electron-donating group gave the desired alkenylated anisole **3pa** and phenetole **3qa**, respectively, in good yields in a similar ratio of *o*/*m*/*p* regioisomers (Table 2, entries 16 and 17). Both chlorobenzene **1r** and bromobenzene **1s** were tolerated, providing valuable handles for further functionalization (Table 2, entries 18 and 19).

Late-stage diversification of biologically active molecules is a unique method to easily elaborate analogous compounds with improved pharmacologic activity or for the detection of structure–activity relationships (SAR).[2c] To this end, a late-stage arylation of butafenacil, which is a commercial herbicide mainly providing rapid knockdown of grass weeds, was performed. The corresponding functionalized analogue **3ak** was produced in reasonable yield (47%) (Scheme 4).

Scheme 4. Biomimetic Late-Stage Arylation of Butafenacil



As documented previously, an electrophilic palladation pathway can be envisaged in the oxidative coupling between **1** and **2**.[4,5b] In order to confirm this mechanistic scenario, isotope effect studies were carried out. A significant kinetic isotopic effect (KIE) of 4.2 was measured by comparing the initial rates for two parallel reactions between **1d** or **1d**-d_6 and allyl acetate **2a**, revealing that the C–H bond cleavage of the aromatic ring is involved in the rate-determining step of the biomimetic coupling (Scheme 5).[10] The high selectivity in favor of the cinnamyl derivative can be explained by a strong

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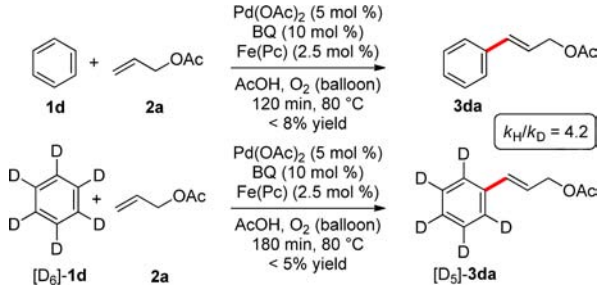
Scheme 5. Evaluation of Deuterium Isotope Effect



coordination between Pd and the carbonyl oxygen, locking the conformation after the olefin insertion and making possible only the β-H_a elimination (Scheme 1).[7h] In our biomimetic approach, the fundamental step is the reoxidation of Pd^0 to Pd^{II} (Scheme 2b). The catalyst is simply regenerated in its active form thanks to the involvement of catalytic amounts of BQ and Fe(*Pc*) as electron-transfer mediators in the presence of molecular oxygen at atmospheric pressure to finally complete the catalytic cycle.

In conclusion, a selective biomimetic aerobic oxidative dehydrogenative coupling between simple arenes and allyl esters yielding cinnamyl derivatives has been developed. The major advantage of this method is that molecular oxygen at ambient pressure can be used as the oxidant. The aerobic system employed leads to milder reaction conditions and allows a lower catalyst loading. This transformation tolerates a wide range of arenes, and it was applied to a late-stage arylation strategy.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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