

Palladium-Catalyzed Oxidative Heck Coupling of Cyclic Enones with Simple Arenes by C—H Activation

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A simple catalyst system consisting of Pd(OAc)₂ and 3-nitropyridine for the aerobic oxidative Heck coupling of cyclic enones, in particular challenging unsubstituted cyclic enones, with simple arenes by C–H activation was investigated. This novel method was applied to various functionalized arenes and cyclic enones and allowed the synthesis of β -aryl cyclic enones in modest to high yields.

C3-Arylated cyclic enones are important intermediates^[1] in the synthesis of pharmaceuticals, fine chemicals, and materials, in particular as building blocks for chiral β -aryl ketones/amines,^[2] substituted phenols, and anilines.^[3] They are commonly synthesized by cross-coupling reactions of β -functionalized cyclic enones with organometallic reagents.^[4] The Heck arylation of cyclic enones with aryl halides to form arylated enones (Scheme 1a) is generally known to be challenging owing to chemoselectivity issues resulting from a typical side reaction, the conjugate addition reaction.^[5] Alternatively, modified Heck-type decarboxylative coupling by using aryl carboxylic acids^[6]



Scheme 1. Heck-type β -arylation of cyclic enones. Ts = *p*-toluenesulfonyl.

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 Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201500079. (Scheme 1 b) and oxidative Heck-type coupling by using aryl boronic acids^[7] (Scheme 1 c) have been reported for the chemoselective formation of aryl enones from the corresponding enones. However, these methods still use functionalized coupling partners and require the use of superstoichiometric amounts of bases and complex ligands. Oxidative Heck coupling^[8] of cyclic enones with simple arenes by C–H activation eliminates the need for prefixing and subsequent removal of the reactive functionalities and is intriguing in this context.

As part of our continued studies on the C–H arylation of arenes and heteroarenes,^[9] we were interested in the coupling of simple cyclic enones with arenes as an alternative strategy towards functionalized biaryls. We developed and report herein an operationally simple and efficient catalyst system consisting of Pd(OAc)₂ and 3-nitropyridine as the ligand for the oxidative Heck coupling of cyclic enones with arenes (Scheme 1d) by using molecular oxygen as the oxidant. In this perspective, Hong et al.^[10] recently reported an interesting sequential dehydrogenation–oxidative Heck coupling of chromanones with arenes to form β -aryl chromenones by using a catalyst system consisting of Pd(tfa)₂ (tfa=trifluoroacetate) and Cu(tfa)₂ in the presence of AgOAc as the oxidant (Scheme 2a). While we were preparing this manuscript, Gigant and Bäck-



Scheme 2. Dehydrogenative coupling of substituted cyclic ketones. BQ = benzo-1,4-quinone.

vall^[11] reported a sequential dehydrogenation–oxidative coupling of cyclic saturated ketones with arenes in the presence of molecular oxygen as the oxidant by using a catalyst system consisting of Pd(OAc)₂ together with electron-transfer mediators such as iron phthalocyanine and benzoquinone (Scheme 2b). Unfortunately, this catalyst system was particular to substituted cyclic ketones, and simple unsubstituted cyclic ketones were found to decompose under the reaction conditions. Our approach complements these methodologies and allows the oxidative coupling of challenging unsubstituted cyclic enones with simple arenes to form the corresponding β -aryl cyclic enones.

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In our preliminary experiments on the oxidative Heck coupling of cyclohex-2-en-1-one (**1a**) with *p*-xylene (**2a**) as the model substrates by using the reported procedure for the dehydrogenative coupling of chromanones,^[10] we found that only a trace amount of the coupled product 2',5'-dimethyl-5,6-dihydro-(1,1'-biphenyl)-3(4*H*)-one (**3a**; Table 1, entry 1) was formed. However, the yield of the product as determined by

NMR spectroscopy increased to 17% if Pd(OAc)₂/Cu(tfa)₂/acetic acid (AcOH) was used instead of Pd(tfa)₂/Cu(tfa)₂/pivalic acid (PivOH) in the presence of AgOAc as the oxidant. A preliminary examination of the solvents indicated that the reaction could also be performed under neat conditions or in diglyme (up to 25% yield) in the presence of a small amount of acetic acid, whereas other polar aprotic solvents such as DMF and DMSO

Table 1. Optimization studies on the oxidative Heck coupling of cyclohex-2-en-1-one with <i>p</i> -xylene.						
Entry	Catalyst	Ligand	Co-catalyst	Oxidant	Solvent	Yield [%]
1	Pd(tfa) ₂	_	Cu(tfa) ₂	AgOAc	PivOH	trace
2	Pd(OAc) ₂	-	Cu(tfa) ₂	AgOAc	AcOH	17
3	Pd(OAc) ₂	-	Cu(tfa) ₂	AgOAc	diglyme	23
4	Pd(OAc) ₂	-	Cu(tfa) ₂	AgOAc	-	19
5	Pd(OAc) ₂		Cu(tfa) ₂	AgOAc	diglyme	25
6	Pd(OAc) ₂	N	Cu(tfa) ₂	AgOAc	diglyme	13
7	Pd(OAc) ₂	F F F F N F	Cu(tfa) ₂	AgOAc	diglyme	13
8	Pd(OAc) ₂	FN	Cu(tfa) ₂	AgOAc	diglyme	54
9	Pd(OAc) ₂	O ₂ N	Cu(tfa) ₂	AgOAc	diglyme	68
10	Pd(OAc)₂		Cu(tfa) ₂	AgOAc	diglyme	34
11	Pd(OAc) ₂		$Cu(tfa)_2$	AgOAc	diglyme	48
12	Pd(OAc) ₂		Cu(tfa) ₂	AgOAc	diglyme	39
13	Pd(OAc) ₂		Cu(tfa) ₂	Ag₂CO₃	diglyme	69
14	Pd(OAc) ₂		Cu(tfa) ₂	O ₂	diglyme	68
15	Pd(OPiv) ₂	O ₂ N	Cu(tfa) ₂	O ₂	diglyme	52
16	Pd(tfa) ₂	Į j	Cu(tfa) ₂	O ₂	diglyme	45
17	Pd(OAc) ₂	`N [™]	Cu(OAc) ₂	O ₂	diglyme	25
18	Pd(OAc) ₂		Cu(OTf) ₂	O ₂	diglyme	15
19	Pd(OAc) ₂	MeO -	-	O ₂	diglyme	75
20	Pd(OAc) ₂	N	-	0 ₂	diglyme	trace
21	Pd(OAc)		_	0,	DCE	80
22	Pd(OAc)	O ₂ N	-	0,	isopropyl acetate	66
23	Pd(OAc)	Ĩ Ì	-	0,	MeTHF	trace ^[c]
24	Pd(OAc),	[\] N [™]	-	0,	DMC	trace ^[c]
25	Pd(OAc)		-	0 ₂	DCE	37 ^[d]
[a] Deast	ion conditions.	Cualabay 2 an 1 ana	(1 - 0	-	al) establist (15, 20 mail	0/) linend

[a] Reaction conditions: Cyclohex-2-en-1-one (**1 a**, 0.5 mmol), *p*-xylene (15 mmol), catalyst (15–20 mol%), ligand (30–40 mol%), co-catalyst (15–20 mol%), silver oxidant (1.5 equiv.), O_2 (balloon), solvent (2 mL), AcOH (2 mmol), 100 °C, 14 h. [b] Yield was determined by ¹H NMR spectroscopy by using dibromomethane as an internal standard. [c] Formation of phenol was observed. [d] Reaction was performed at 80 °C.

were unsuitable. Further variation of the oxidant showed no significant improvement in the product yield. Prolonging the reaction time was also not beneficial, which indicated possible deactivation of the catalyst after the initial cycle. Formation of a significant amount of Pd black was also observed upon completion of the reaction. Consequently, we examined various nitrogen ligands that are stable under oxidative conditions to stabilize the active palladium species. In the presence of bidentate ligands such as 1,10phenanthroline and 2,2'-bipyridine, there was no reaction, possibly as a result of the formation of inactive PdL₂ complexes. Subsequently, after examining various monodentate pyridine ligands (Table 1, entries 5-12), we were delighted to find a remarkable increase in the yield upon using pyridine ligands containing electron-withdrawing substituents, including 2-fluoropyridine (54%), 3-nitropyridine (68%), 2,4-dichloropyridine (38%), isonicotinonitrile (48%), and 3-acetylpyridine (39%). Interestingly, weakly coordinating pentafluoropyridine was not useful. Unsubstituted pyridine or pyridine with electron-donating substituents such as 2,6-lutidine and 3-methoxypyridine were also not effective, which indicated the need for an electronically and sterically balanced ligand for good catalytic activity and stability. Thus, further studies were performed by using 3-nitropyridine as the ligand. The reaction was found to work equally well with Aq₂CO₃ and more remarkably by using molecular oxygen (balloon) as the oxidant. Other



palladium precursors such as Pd(OPiv)₂ and Pd(tfa)₂ as well as co-catalysts such as Cu(OAc)₂ and Cu(OTf)₂ (OTf=trifluoromethanesulfonate) were inferior. To our surprise, if the reaction was performed without any copper co-catalyst, a better outcome was obtained in that the coupled product was formed in 75% yield. Re-examination of the solvent under these conditions revealed that the yield of the product was improved in dichloroethane (DCE, 80%). Isopropyl acetate, $^{\left[12\right] }$ an environmentally more friendly alternative, performed to some extent, but the yield (66%) was not comparable to that obtained with diglyme or DCE. Other solvents such as dimethyl carbonate (DMC) and 2-methyltetrahydrofuran (MeTHF) were not suitable, as reactions in these solvents mainly led to the dehydrogenation of cyclohex-2-en-1-one to phenol. The optimum amount of AcOH was found to be 4 equivalents with respect to the enone. A ligand/palladium ratio of 2 was found to be optimal for good catalytic activity (Figure S1, Supporting Information). The concentration of the Pd catalyst also had a strong effect on the reaction and 15-20 mol% Pd was found to be necessary to attain high yields (80–87%, Figure S2).

With the optimized conditions, we studied the scope of this method for the coupling of different functionalized arenes and cyclic enones (Table 2). In general, electron-rich arenes were more reactive than their electron-poor counterparts, and the respective coupled products were delivered in moderate to high yields. Thus, the coupling of symmetric di- or trisubstituted arenes 2a-e with cyclohex-2-en-1-one (1a) gave coupled products 3a-e in yields of 46–83%. For instance, *p*-xylene, 1,4-dimethoxybenzene, and 1,3,5-trimethoxybenzene formed coupled products 3a (80%), 3b (83%), and 3c (81%) in high yields. Mesitylene formed 3d in 46% yield. Electron-poor 1,4-dichlorobenzene also reacted under these conditions to form 3e in 57% yield.

As expected for unsymmetrically substituted arenes, the corresponding regioisomers were formed. For instance, as shown in the Table 2, in the case of o-xylene the regioisomers of 3 f were formed in a ratio of 1:0.7 in a total yield of 73%. In the case of naphthalene, 3 g was formed in 51% yield with a regioisomeric ratio of 1:0.12. Similarly, 2,6-dimethylnaphthalene gave product 3h (46%) as a regioisomeric mixture (1:0.26). In the case of anisole, the corresponding ortho, meta, and para isomers of **3i** were formed in a total yield of 68% (o/m/p =1:0.8:0.2). tert-Butylbenzene yielded a 1:1 ratio of the corresponding meta/para isomers in a total yield of 60%. The ortho isomer was not detected in this case, possibly because of steric hindrance of the bulky tert-butyl group. Interestingly, the reaction of 1,2-dimethoxy-4-methylbenzene proceeded well and gave the corresponding isomers of 3k (1:0.5) in 57% yield. Similarly 1-chloro-2-methylbenzene offered the corresponding isomers of 31 (0.4:1). The method was also applicable to other cyclic enones. For instance, cyclopent-2-en-1-one reacted with p-xylene and 1,4-dimethoxybenzene to form coupled products 3n and 3o in yields of 66 and 71%, respectively. 4-Methylcyclohex-2-en-1-one reacted with p-xylene to give 2',5',6-trimethyl-5,6-dihydro-(1,1'-biphenyl)-3(4H)-one (3m) in 40% yield. Unfortunately, these aerobic oxidative coupling conditions were not suitable for fluorinated arenes, for which only trace



amounts of the coupled products were detected. Nevertheless, Ag_2CO_3 was proven to be a good oxidant in these cases, and fluorinated β -arylenones **3 q**-**s** were obtained in moderate to high yields.

To understand the C–H activation of the arenes, we studied the kinetic isotope effect (KIE)^[13] with respect to the arene. Interestingly, a very prominent primary KIE ($k_{\rm H}/k_{\rm D}$ =7.7) was observed in a competition reaction between *p*-xylene/[D₁₀]*p*xylene (see the Supporting Information) and cyclohex-2-en-1-





Scheme 3. Proposed catalytic cycle.

one, which indicates that cleavage of the C–H bond occurs during activation of the arene by the palladium catalyst; this may be the rate-determining step of this oxidative coupling. The catalytic cycle shown in Scheme 3 is proposed. The arene C–H bond is activated by palladium(II) complex i, which results in the formation of arylpalladium species ii. Coordination and migratory insertion of the enone^[11] to the Pd–C bond in a *syn* fashion then leads to species iii. Then, iii is converted into v via palladium enolate intermediate iv to give product 3 and palladium hydride vi by *syn* β -hydride elimination. Pd⁰ species vii formed by reductive elimination of AcOH from vi is then oxidized back by the oxidant to active Pd^{II} catalyst i.

In conclusion, we developed a simple catalyst system for the oxidative coupling of cyclic enones, in particular challenging unsubstituted cyclic enones, with simple arenes by C–H activation. The coupling reaction works efficiently in the presence of molecular oxygen as the oxidant except for fluoroarenes, in which case Ag₂CO₃ was found to be more suitable. This new procedure is applicable to a range of arenes and cyclic enones and allows the synthesis of β -aryl cyclic enones in reasonably good yields.

Experimental Section

In a glove box, a Radleys reaction tube was charged with $Pd(OAc)_2$ (0.075 mmol), 3-nitropyridine (0.15 mmol), the arene (15 mmol), AcOH (2 mmol), the cyclic enone (0.5 mmol), and the solvent (2 mL). The tube was closed, removed from the glove box, and heated at 100 °C under an atmosphere of O₂ (balloon) for 14 h. The mixture was then cooled to room temperature and filtered

through Celite. The crude mixture was analyzed by GC–MS and ¹H NMR spectroscopy and was then purified by flash column chromatography (silica gel).

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