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ARTICLE TYPE

Oxygen as Single Oxidant for Two Steps: Base-Free One-Pot Pd(II)-Catalyzed Alcohol Oxidation & Arylation to Halogen-Intact β-Aryl α,β-Enones

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Using oxygen as sole oxidant for two steps, we developed a new method for β-aryl α,β-enones by fine-tuning Pd(II)-catalyzed oxidation of allyl alcohol to subsequent arylation with arylboronic acids, arylboronic ester and aryltrifluoroborate salt. This one-pot green method doesn't require copper salt, base, and intermediate isolation. Halogen-bearing chalcones, dibenzylideneacetones and arylalkyl enones were synthesized in good yields.

Chalcones represent one of the most-prevalent classes of natural products, which are widely abundant in the plants and food items [*e.g.*, fruits, vegetables, spices, tea, soy, hop and beer]. The chalcones are of great interest to both academic and industrial community because of their wide range of pharmacological properties (Figure 1).[1] The chalcones are known for their anti-oxidant, cytotoxic, anti-cancer, anti-microbial, anti-protozoal, anti-ulcer, anti-histaminic, anti-inflammatory and immune suppressive properties.[2] Nevertheless, "α,β-unsaturated enone" motif is known for synthetic versatility (a) of delivering a diverse range of compounds through Michael addition, cycloaddition, Heck coupling, etc., and (b) as building blocks to assemble a range of heterocyclic compounds, functional materials and chemotypes for lead optimization.[3] The development of new methodologies for the chalcones and the synthetically-important arylalkyl enones will expand the accessibility of these compounds for drug discovery.

Conversion of allyl alcohols to the corresponding β-aryl enones through alcohol oxidation and Heck coupling with aryl halides was scarcely reported in the literature (only 2 hits as per SciFinder and Reaxys; Figure 2).[4] This versatile method suffers from limitations like (i) requirement of stoichiometric amount of toxic copper salt as the oxidant, (ii) requirement of organic / inorganic base, (iii) lack of chemoselectivity between chalcones and dihydrochalcones and (iv) limited substrate scope. Importantly, scope of such reaction is limited in the ability to produce the α,β-unsaturated enones with intact halogens. Halogens are strategically deployed on aryl rings by the medicinal chemists as handles,[5] to be exploited for diversification during lead optimization. Herein, we report a promising approach to β-arylated enones with -I and –Br functionalities through Pd(II)-mediated sequential oxidation of allyl alcohol followed by chelation-controlled oxidative arylation in one pot using arylboronic acids as the trans-metallation substrates. Especially, this approach deploys molecular oxygen as the sole oxidant for both the steps and doesn't require either a copper salt or a base (Figure 2).

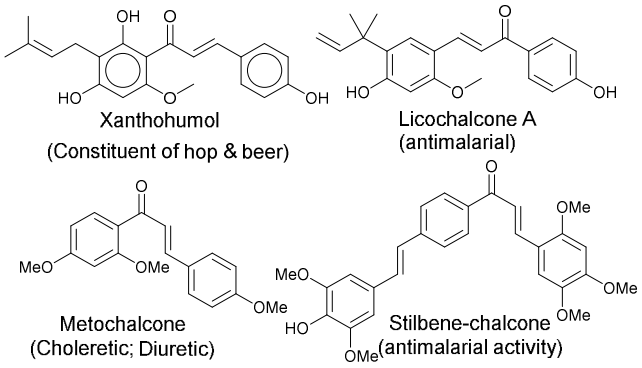


Fig. 1 Pharmaceutically-important β-aryl α,β-enones

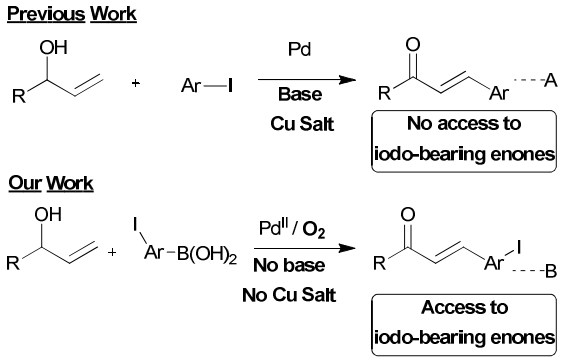
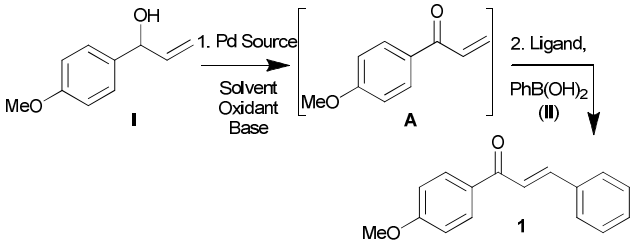


Fig. 2 Palladium-catalyzed synthesis of β-aryl enones from allylic alcohols.

We investigated oxidation-cum-arylation using I and $PhB(OH)_2$ as the model substrates, using the conditions, conducive to alcohol oxidation[6] and/or arylation[7] (Table 1). Disappointingly, neither the keto intermediate nor the final product (β-aryl enone) was observed (entries 1-4). However, we were delighted to note the alcohol oxidation in excellent yield, when $PhB(OH)_2$ and the ligand were excluded from the reaction

(entries 5-7). This prompted us to first oxidize the alcohol and subsequently introduce $PhB(OH)_2$ and ligand in the same pot. Gratifyingly, we observed the formation of the desired β-aryl α,β-enone using THF as solvent, albeit in low yield (entry 8). Encouraged by this result, we undertook comprehensive screening of metal, ligand, solvent and base. Improvement in the yield was noted on exclusion of the base (entry 13). Dmphen, the oft-used bidentate ligand for Pd(II)-catalyzed oxidative Heck couplings, was identified as the superior ligand.[8] Other nitrogen ligands like pyridine, Phen and Bphen gave inferior yields (entries 16-18). The oxo-palladium source, $Pd(OAc)_2$, was turned out to be the best Pd(II) pre-catalyst. Disappointing results were obtained with other Pd(II) precursors like $Pd_2(dba)_3$ and $PdCl_2$ (entries 14-15). Considering the requirement of the catalyst for two steps, amount of the catalyst was raised further, which

Table 1 Optimization protocol for sequential allylic alcohol oxidation and oxidative Heck arylation [a]

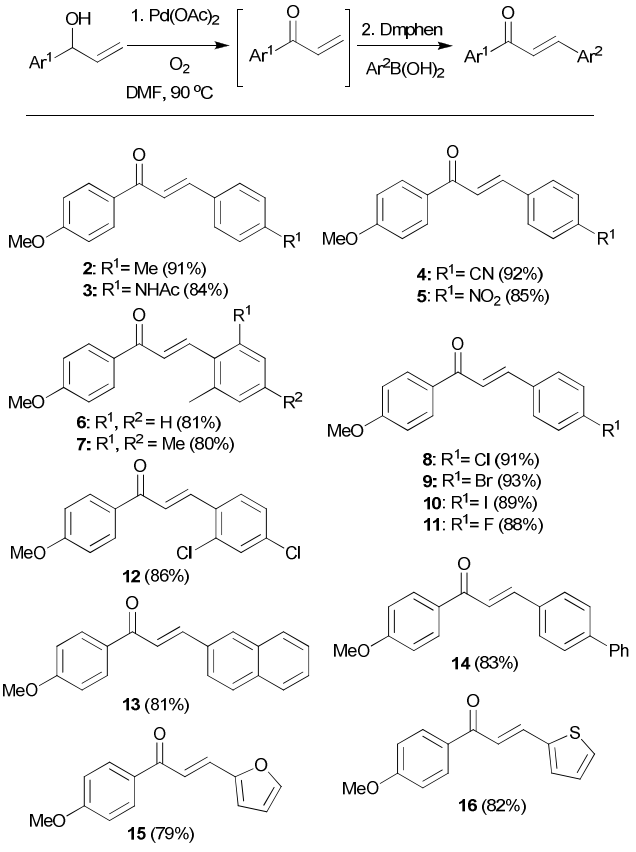


Entry	Pd	Additive	Solvent	Ligand	Yield of **1** (%)[b]
1[d]	$Pd(OAc)_2$	Et_3N	Toluene	-	0
2[d]	$Pd(OAc)_2$	Et_3N	Toluene	Dmphen[g]	0
3[d]	$Pd(OAc)_2$	-	DMF	-	0
4[d]	$Pd(OAc)_2$	-	DMF	Dmphen	0
5[c,e]	$Pd(OAc)_2$	Et_3N	Toluene	-	0
6[c,e]	$Pd(OAc)_2$	Et_3N	Toluene	Dmphen	0
7[c,e]	$Pd(OAc)_2$		Toluene	Dmphen	0
8[c,e]	$Pd(OAc)_2$	Et_3N	THF	Dmphen	15
9[e]	$Pd(OAc)_2$	Et_3N	DMSO	Dmphen	10
10[e]	$Pd(OAc)_2$	Et_3N	DMA	Dmphen	20
11[e]	$Pd(OAc)_2$	Et_3N	DMF	Dmphen	25
12[e]	$Pd(OAc)_2$	Na_2CO_3	DMF	Dmphen	31
13	$Pd(OAc)_2$	-	DMF	Dmphen	60
14[e]	$Pd_2(dba)_3$	-	DMF	Dmphen	36
15	$PdCl_2$	-	DMF	Dmphen	0
16[e]	$Pd(OAc)_2$	-	DMF	Pyridine	28
17[e]	$Pd(OAc)_2$	-	DMF	Phen[g]	44
18[e]	$Pd(OAc)_2$	-	DMF	Bphen[g]	33
19[c,f]	**$Pd(OAc)_2$**	**-**	**DMF**	**Dmphen**	**97**
20[c,f]	$Pd(OAc)_2$	-	DMAc	Dmphen	94
21[e]	$Pd(OAc)_2$	-	DMF	-	40
22[e]	$Pd(OAc)_2$	-	DMAc	-	35
23[e]	$Pd(OAc)_2$	-	DCE	-	0
24[e]	$Pd(OAc)_2$	-	1,4-Dioxane	-	0

[a] Unless specified, the reaction was carried out with allyl alcohol (I; 1.0 mmol),Pd source (0.05 equiv.), and additive (0.1 equiv.) under oxygen balloon (1 atm.) at 90 °C in a solvent (3.0 mL) for 4.0 h. After adding ligand (0.1 equiv.) and $PhB(OH)_2$ (II; 1.2 mmol), the reaction was continued for 18.0 h. [b] Isolated yield (average of two runs).[c] Isolated yield of Intermediate **A** (entries 5-8 & 19-20: 99%). [d] The reaction was carried out with **I** (1.0 mmol), **II** (1.2 mmol), Pd (0.05 equiv.), ligand (0.1 equiv.) and additive (0.1 equiv.) under oxygen balloon (1 atm.) at 90 °C in a solvent (3.0 mL) for 18.0 h. [e] Intermediate **A** was not consumed fully. [f] $Pd(OAc)_2$ (0.1 equiv.), Dmphen (0.2 equiv.). [g] Dmphen = 2,9-dimethyl-1,10-phenanthroline, Bphen = 4,7-diphenyl-1,10-phenanthroline & Phen = 1,10-phenanthroline.

resulted in the best yield (entries 19-20). Interestingly, the reaction could be promoted in moderate yield even in the absence of both base and ligand (entries 21-22). However, our attempts to further optimize the yield proved futile, indicating importance of the ligand in the stabilization of catalyst for high catalytic turnover (entries 23-24).

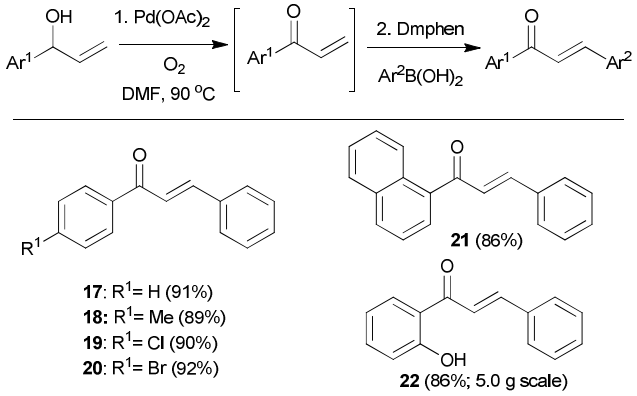
Armed with an efficient condition (entry 19, Table 1), we next investigated the influence of electronic and steric factors on preparative scope by coupling diverse arylboronic acids and allyl alcohols (scheme 1-4). The electron-rich arylboronic acids gave very good yields (scheme1, **2&3**) of the corresponding propenones. Interestingly, the electron-deficient arylboronic acids, which were known to bethe sluggish substrates in the Pd(II)-Dmphen catalysis, also gave excellent yields (**4&5**). The *ortho*-substituted arylboronic acids underwent efficient coupling (**6&7**), undeterred by steric overloading. Importantly, the halogen-bearing arylboronic acids (-Cl, -Br, -I and -F) gave the desired products (**8-12**) chemoselectively without concurrent formation of by-products, arising from Pd(0)-catalysed oxidative addition of Ar-X (X: I, Br& Cl) bond (Heck, Suzuki and dehalogenation reactions). This chemoselectivity provides an opportunity for organic and medicinal chemists to preserve the halogen handles, to be utilized for transition-metal catalyzed C-C, C-N, C-O bond-forming diversification like Heck, Suzuki, Sonogashira, Buckwald and Ullmann-type coupling to derive



Scheme 1 Synthetic scope of chalcones from organoboronic acids

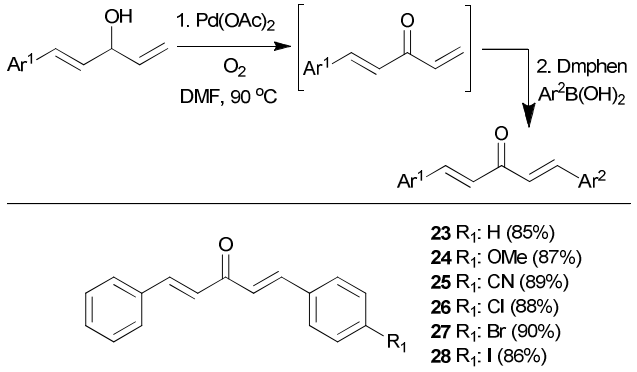
pharmaceutically important compounds. Reasonably-deactivated aryl ring systems, naphthyl and biphenyl, also underwent effient coupling (**13&14**). The heteroaryl-bearing boronic acids (2-furyl & 2-thienyl) underwent smooth coupling to give the corresponding products in good yields (**15&16**), indicating the compatibility of the catalytic method with furan and thiophene ring systems.

We next investigated the scope and limitation of different types of allyl alcohols (Scheme 2-4). 1-Arylpropenols with differently-activated aryl ring systems of electron-donating, electron-withdrawing and halogen substitutions reacted efficiently (Scheme 2; **17-20**). A fused 1-(1-naphthyl)propenol also furnished the coupling product in good yield (**21**), indicating the generality of the procedure. This methodology is also amenable to multi-gram scale (5.0 g), as demonstrated in the synthesis of 2'-hydroxy chalcone derivative (**22**) [required by us for the construction of flavanone and flavones derivatives][9] from the corresponding propenol in excellent yield.[10] The successful reaction outcome in the presence of unprotected phenolic group indicated the generality of the method.



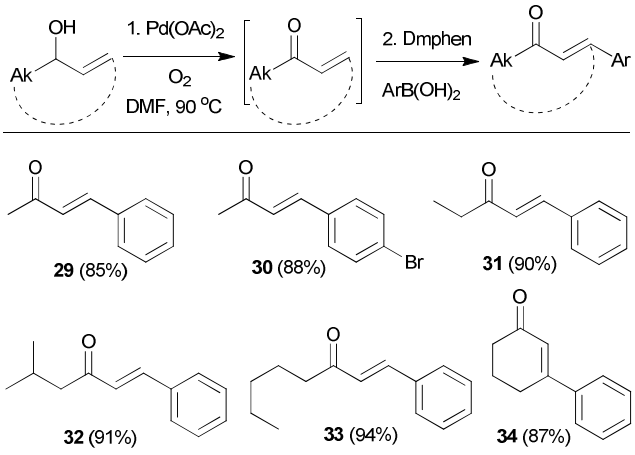
Scheme 2 Synthetic scope of chalcones from allylic alcohols

Dibenzylideneacetone derivatives serve as the important building blocks in organic synthesis[11] (e.g., construction of piperidones, spiro compounds, etc.). Dibenzylideneacetone (DBA) is widely used as a ligand in organometallic chemistry[12] [*e.g.*, tris(dibenzylideneacetone)dipalladium(0)] and also as a sunscreen component to prevent skin cancer. The 1-styrenylpropen-1-ol reacted efficiently with electronically-different arylboronic acids to give the desired dibenzylideneacetone derivatives (scheme 3, **23-28**). DBA analogues with -I, -Br and -Cl substitutions were also realized with excellent yields.



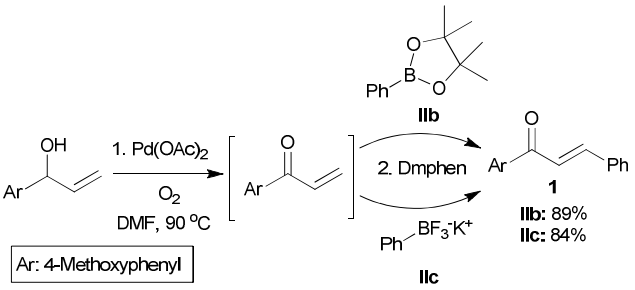
Scheme 3 Synthetic scope of dibenzylideneacetone derivatives

Replacement of 1-aryl substitution with 1-alkyl substitution (e.g., 1-methyl, 1-ethyl, 1-isopropyl and 1-pentyl) didn't affect the reaction outcome (scheme 4, **29-33**).[13] Even the β-substituted cyclohex-2-en-1-ol underwent productive oxidation-cum-arylation to afford β-phenylcyclohex-2-en-1-one (**34**).



Scheme 4 Synthesis of β-aryl α,β-enones from allylic alcohols

To further expand the scope of this green catalysis, two different alternatives of phenylboronic acid were considered for oxidative coupling with propenol (Scheme 5).[14] The pinacolboronic ester (**IIb**) and potassium phenyl trifluoroborate (**IIc**) underwent efficient oxidative coupling to afford the desired α,β-unsaturated β-aryl carbonyl compound (**1**) with good yield.



Scheme 5 Synthetic scope of boronic ester and borate salt

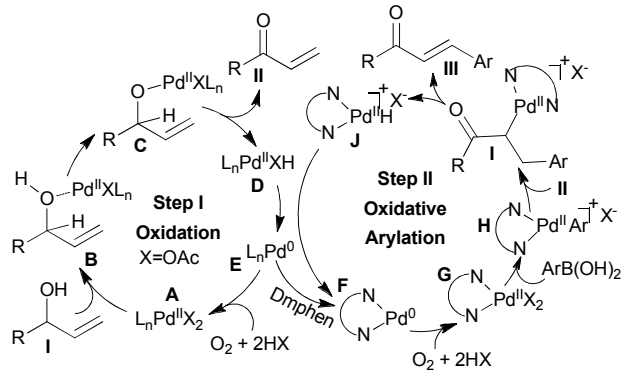


Fig. 3 Plausible mechanism of Pd-catalyzed alcohol oxidation and subsequent oxidative arylation.

A plausible mechanism is illustrated in Figure 3. The first step, which involves the oxidation of allylic alcohol to enone, begins with the coordination of alcohol to $L_nPd^{II}X_2$ (X=OAc) to form the complex **B**, which subsequently undergoes deprotonation to afford the Pd-alkoxide complex **C**. Subsequent β-hydride elimination leads to enone **C** and Pd^{II}-H **D**. Then **D** decomposes to Pd(0) species **E**, which is oxidized by O_2 and HX, regenerating the active Pd^{II} catalyst. The second step, which involves the chelation-controlled oxidative arylation of the enone, begins with the generation of (neocuproine)$Pd^{II}X_2$ complex **G** [through the chelation of neocuproine to **E** followed by oxidation or the chelation of neocuproine to **A** directly] by the addition of neocuproine into the reaction mixture. **G** undergoes trans-metalation with the arylboronic acid to afford the cationic aryl(neocuproine)Pd(II) species **H**. This is followed by migratory insertion of enone **II** to form Pd^{II}-alkyl complex **I**. Consequent β-hydride elimination liberates the β-aryl α,β-enone **III** and (neocuproine)Pd^{II}-H **J**. Then **J** undergoes reductive elimination to give Pd(0) species **F**, which is oxidized by O_2 and HX, regenerating the (neocuproine)Pd(II) catalyst.

Conclusions

In Conclusion, a sustainable methodology was developed to synthetically- and pharmaceutically-important β-aryl α,β-enones by employing oxygen as the non-toxic oxidant for two steps of Pd(II)-modulated oxidation of allyl alcohol and oxidative arylation. The method eliminated the requirement of copper salt and base by using organoboronic acids as the surrogates of aryl halides. The reaction was highly chemoselective, thereby allowing access to halogen-installed β-aryl enones, not accessible previously.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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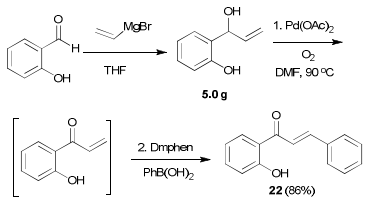
10 Multi-gram scale synthesis of 2-hydroxy chalcone from 2-hydroxybenzaldehyde is given below.



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