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Replacing a stoichiometric silver oxidant with air: ligated Pd(II)-catalysis to β-aryl carbonyl derivatives with improved chemoselectivity†

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Air was employed as a green reoxidant of Pd(0), replacing stoichiometric and toxic silver salt, in the chelation-controlled Pd(II)-modulated arylative enolization of prop-2-en-1-ols to acquire synthetically-important β-aryl carbonyl derivatives. This green approach, which didn't require acid or base, allowed the compatibility of a range of functionalities (inclusive of –I, –Br & –Cl), resulting in the construction of structurally-diverse dihydrochalcones, α-benzyl-α′-alkyl acetones, α-benzyl β-keto esters and dihydrocinnamaldehydes. In addition to organoboronic acids, efficient coupling was also achieved with boronic esters and trifluoroborate salts. A deuterium labelling experiment revealed an interesting 1,2-hydrogen shift after β-arylation in the catalytic process.

Introduction

Due to highly-attractive green and sustainable advantages, molecular oxygen finds increasing use in both the commodity chemical industry and academic labs. Dioxygen is an inexpensive and abundantly-available oxidant, which doesn't leave behind any solid waste. In contrast, transition metal oxidants (being required in stoichiometric quantities) are toxic, leave behind hazardous solid waste, and are known for promoting undesirable side reactions.[1] Hence, replacement of metal oxidants in transition-metal catalyzed organic transformations would serve as an environmentally-conscious strategy. In recent years, Pd(II)-catalysis has found widespread utility in C–C bond formation[2] (*e.g.*, oxidative-Heck), C–H functionalization, oxidation (alcohol oxidation, Wacker oxidation & Saegusa oxidation), *etc.* Sustainability of the catalysis in these transformations is accomplished by the oxidation of Pd(0) (produced at the terminal phase of the catalytic cycle) to Pd(II) by an oxidant.

β-Aryl alkyl carbonyl intermediates have found extensive use as versatile synthetic building blocks in medicinal chemistry to construct diverse scaffolds or drug-like compounds for a plethora of therapeutic targets, and also in agricultural and materials chemistry.[3] The "β-aryl carbonyl" motif is known for its widespread prevalence in natural products of medicinal importance, and it is also present in marketed drugs (Fig. 1).[4]

Because of their above-mentioned significance, several synthetic routes have been pursued to construct these useful motifs in recent years. Of these, arylative transformation of allyl alcohols in a single step through cross-coupling with aryl halides in the presence of Pd(0) represents a shortcut strategy to synthesize β-aryl propanals or propanones, taking advantage of the commercial availability/ready-accessibility of the allyl alcohols.[5] However, when using this versatile process, limitations are encountered such as a decrease in chemoselectivity (aryl carbonyl *vs.* aryl allyl alcohol), decrease in regioselectivity (β-arylation *vs.* α-arylation) and a necessity for high temperatures and a base.

Oxidative Pd(II)-mediated coupling of allyl alcohols with transmetallation substrates presents a promising alternative

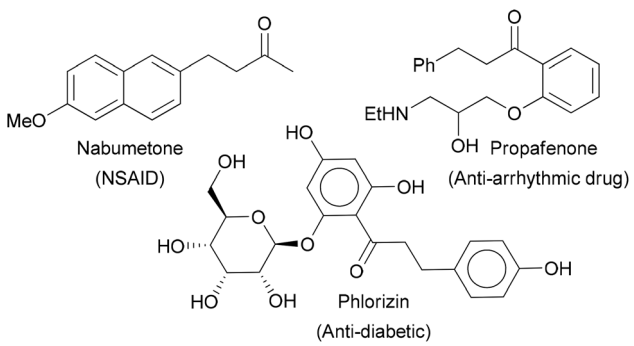

Fig. 1 Compounds of pharmaceutical importance, encoded with β-aryl carbonyl skeleton.

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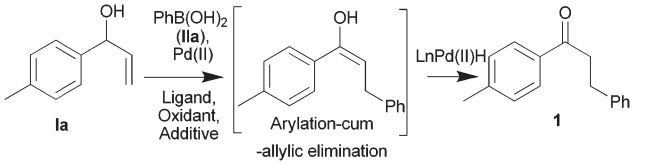
approach to synthesize β-aryl aldehydes and ketones, considering key advantages. For example, the reaction can be performed at low temperatures. Surprisingly, only a few methods for the oxidative coupling of allyl alcohols with organometallic reagents as an aryl source have been reported in the literature.[6] However, these reactions suffer from limitations like the toxic nature of the aryl metallic reagents (*e.g.*, aryl mercuric salts and aryl antimony halides), incompatibility of acid-sensitive functionalities due to the use of acetic acid as a co-solvent[6c] and poor yields (<20%).[7] We recently reported the first ligand-modulated and regioselective Pd(II)-catalysis method to synthesize β-aryl aldehydes and ketones, thereby enhancing the scope of these reactions from the development of selective applications in organic synthesis.[8] However, this method still suffers from the use of hazardous silver salt as a stoichiometric oxidant and limited compatibility of halogen functionalities. This article illustrates the utility of oxygen as an environmentally-friendly alternative to silver salt in the ligated regioselective coupling of allylic alcohols with arylboronic acids as arylpalladium(II) precursors and enhanced chemoselective coupling with iodo-containing arylboronic acids.

Results and discussion

We began our investigation by replacing the Ag_2CO_3 oxidant used in our earlier procedure[8] with air. We examined the coupling of 1-(4-methyl)phenylprop-2-en-1-ol (**Ia**) and $PhB(OH)_2$ (**IIa**) as the model substrates. The secondary alcohol (**Ia**) was selected as the model olefin instead of a primary alcohol, taking into account the stability of the corresponding products (ketone *vs.* aldehyde). Disappointingly, no product was obtained (Table 1, entry 1). However, we were encouraged to note that the addition of catalytic CuCl additive (0.05 equiv.) led to product formation, albeit, in a low yield (entry 2).[9] Subsequently, identification of the optimum conditions for regioselective vinylative enolization was undertaken in a combinatorial fashion by varying conditions such as the palladium source, ligand, additive and solvent with air/oxygen.

The oxo-palladium source, $Pd(OAc)_2$, proved to be more efficient than other Pd(II) precursors (entries 3–5 & 20).[9] No product was obtained in the absence of a Pd(II) metal source with either catalytic or stoichiometric CuCl additives (entries 24 & 25). Pyridine, which is an example of a monodentate ligand, gave a moderate yield (entry 17). Dmphen, which is a bidentate nitrogenous ligand and is routinely used in palladium(II)-mediated oxidative Heck transformations, turned out to be an efficient ligand (entry 20).[10] Other nitrogen-chelating ligands like Bphen, Phen, and Bpy gave moderate yields (entries 14–16). The phosphine ligands, TPP (monodentate) and DPPP (the oft-used bis-phosphine ligand to generate the cationic Pd(II) complex) were found to be unsuitable (entries 18–19). Superiority of the nitrogen ligands over the phosphines is presumably due to the higher stability of the former under oxidative Pd(II)-mediated transformations than the oxidation-vulnerable phosphines. The importance of ligand control was realized through the reduced productivity in the absence of the Dmphen ligand (entry 26). A catalytic amount of copper salt was deemed necessary for promoting the coupling (entries 20 & 23).[6c] Cuprous salt performed better than cupric salt, as evident from CuCl *vs.* $CuCl_2$ and CuBr *vs.* $CuBr_2$ (entries 6–13). Replacement of DMSO with other polar aprotic solvents like DMF and DMAc was found to be counterproductive (entries 28–29). The less-polar solvent, 1,2-dichloroethane, gave a moderate yield (entry 27). As there was no advantageous effect on the reaction output on replacing air with oxygen (entries 20 & 21), inexpensive and safer air was subsequently chosen as the oxidant of choice for preparative reactions. The yield dramatically reduced on replacing an air atmosphere with a nitrogen

Table 1 Optimization protocol for arylative enolization[a]



Entry	Pd (0.1 equiv.)	Ligand (0.2 equiv.)	Additive (0.05 equiv.)	Solvent	Yield[b] (%)
1[c]	$Pd(OAc)_2$	Dmphen[d]	—	CH_3CN	0
2[c]	$Pd(OAc)_2$	Dmphen	CuCl	CH_3CN	31
3	$PdCl_2$	Dmphen	CuCl	DMSO	10
4	$Pd_2(dba)_2$	Dmphen	CuCl	DMSO	50
5[c]	$Pd(MeCN)_2Cl_2$	Dmphen	CuCl	DMSO	28
6[c]	$Pd(OAc)_2$	Dmphen	$CuCl_2$	DMSO	15
7	$Pd(OAc)_2$	Dmphen	CuBr	DMSO	33
8[c]	$Pd(OAc)_2$	Dmphen	$CuBr_2$	DMSO	15
9[c]	$Pd(OAc)_2$	Dmphen	CuI	DMSO	20
10[c]	$Pd(OAc)_2$	Dmphen	$CuSO_4{\cdot}5H_2O$	DMSO	5
11[c]	$Pd(OAc)_2$	Dmphen	$Cu(OAc)_2$	DMSO	5
12[c]	$Pd(OAc)_2$	Dmphen	$Cu(OTf)_2$	DMSO	10
13[c]	$Pd(OAc)_2$	Dmphen	$Cu(acac)_2$	DMSO	10
14	$Pd_2(dba)_3$	Bphen[d]	CuCl	DMSO	48
15	$Pd(OAc)_2$	Phen[d]	CuCl	DMSO	65
16[c]	$Pd(OAc)_2$	Bpy[d]	CuCl	DMSO	43
17[c]	$Pd(OAc)_2$	Pyridine	CuCl	DMSO	45
18[c]	$Pd(OAc)_2$	PPh_3	CuCl	DMSO	21
19[c]	$Pd(OAc)_2$	DPPP[d]	CuCl	DMSO	10
20	**$Pd(OAc)_2$**	**Dmphen**	**CuCl**	**DMSO**	**93**
21[e]	$Pd(OAc)_2$	Dmphen	CuCl	DMSO	93
22[c,f]	$Pd(OAc)_2$	Dmphen	CuCl	DMSO	9
23[c]	$Pd(OAc)_2$	Dmphen	—	DMSO	0
24[c]	—	Dmphen	CuCl	DMSO	0
25[c,g]	—	Dmphen	CuCl	DMSO	0
26	$Pd(OAc)_2$	—	CuCl	DMSO	50
27	$Pd(OAc)_2$	Dmphen	CuCl	DCE	62
28[c]	$Pd(OAc)_2$	Dmphen	CuCl	DMF	10
29[c]	$Pd(OAc)_2$	Dmphen	CuCl	DMAc	10
30[h]	$Pd(OAc)_2$	Dmphen	CuCl	DMSO	57
31[i]	$Pd(OAc)_2$	Dmphen	CuCl	DMSO	85

[a] Unless specified, the reaction was carried out with **Ia** (1.0 mmol), **IIa** (1.5 mmol), Pd (0.1 equiv.), ligand (0.2 equiv.), additive (0.05 equiv.) under an air balloon (1 atm) at 50 °C in a solvent (3.0 mL) for 12.0 h. [b] Isolated yield (average of two runs). [c] The starting material was not consumed fully. [d] Dmphen = 2,9-dimethyl-1,10-phenanthroline, Bphen = 4,7-diphenyl-1,10-phenanthroline, Phen = 1,10-phenanthroline, Bpy = 2,2′-bipyridyl, DPPP = 1,3-bis(diphenylphosphino)propane. [e] Oxygen was used instead of air. [f] Nitrogen was used instead of air. [g] Stoichiometric CuCl was used. [h] CuCl (1.0 equiv.) with N_2 atmosphere. [i] CuCl (2.0 equiv.) with N_2 atmosphere.

atmosphere, which clearly underscored the necessity of dioxygen for promoting the reaction (entries 20 & 22).

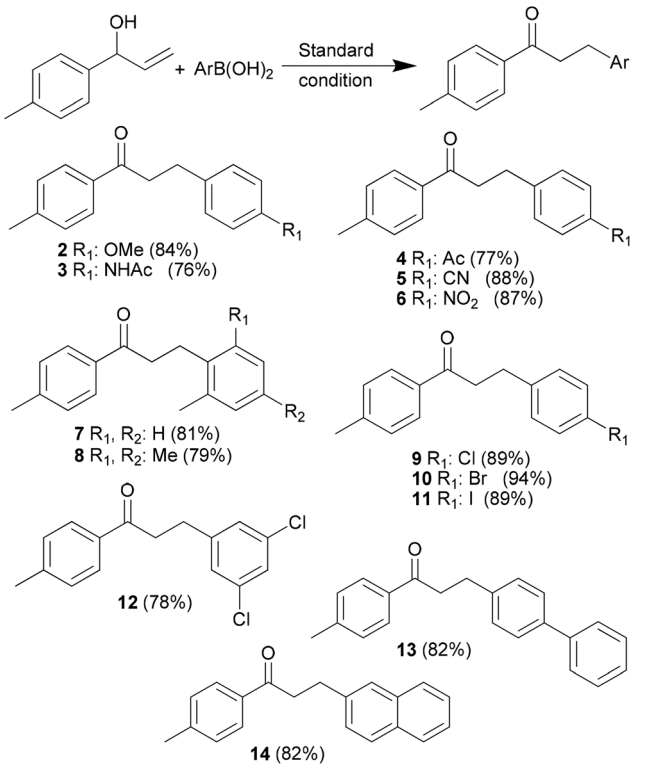
α-Arylation products (**α-1** & **α-2**) were not isolated from the reaction under the optimized conditions (Scheme 1). The fact that the addition of the aryl moiety exclusively occurs at the terminal carbon of the double bond indicates the β-regioselectivity of the insertion. Nevertheless, β-arylation delivered the β-aryl keto compound (**β-2**) as the exclusive product. The oxidative Heck product, β-aryl allyl alcohol (**β-1**) (arising from β-hydride elimination) was not detected under the present conditions.[5e] The side reactions like isomerization of the alkenol starting material and allylation of the arylboronic acid,[11] which were evident in the Pd(II)–Ag_2CO_3 system,[8] were not noticed in the present procedure.

The optimized conditions from Table 1 (entry 20) were employed as standard protocol to investigate the impact of electronic and steric modulation of both the allyl alcohols and the arylboronic acids on the reaction outcomes. Though the electron-poor arylboronic acids were known to be less productive in chelation-controlled Pd(II)-catalysis (because of the presumed sluggish transmetallation), they underwent efficient coupling (Scheme 2). Nevertheless, the electronic disparity between electron-rich and electron-poor arylboronic acids had no impact on the reaction outcome (**2–6**). Satisfactory yields were observed, even with sterically-demanding arylboronic acids (**7–8**). The β-aryl ketones, bearing halogen handles, were also obtained in excellent yields (**9–12**). Relatively-deactivated aryl ring systems, like naphthyl and biphenyl, also underwent smooth coupling (**13–14**).

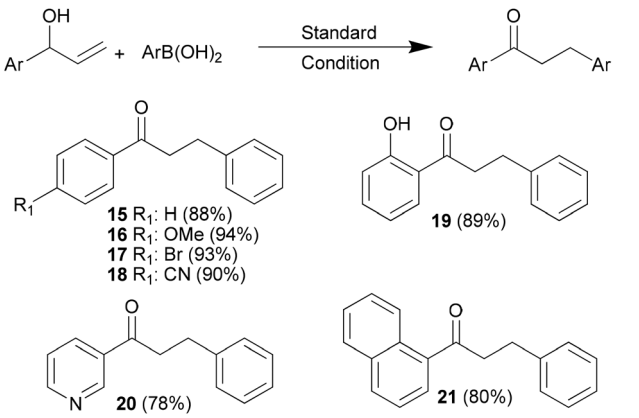
The scopes and limitations of several different allyl alcohol derivatives were investigated (Schemes 3–6). 1-Arylpropenols with differently-activated aryl ring systems of electron-withdrawing, electron-donating and halogen groups reacted efficiently (**15–18**). An aryl propenol, bearing an unprotected phenolic OH group, a heteroaryl propenol and a fused ring propenol also furnished the corresponding coupling products in good yields (**19–21**) (Scheme 3), indicating the generality of the method.

The propenols, bearing linear and branched alkyl substituents at the allylic position, furnished excellent yields (Scheme 4, **22–24**). The olefins, derived from carbohydrate-based chiral synthons like the protected (*S*)-glyceraldehyde (**25** & **26**) and protected xylose-5-carboxaldehyde (**27**), underwent efficient arylation. This is an indication of the compatibility of this methodology with acid-labile functionalities. Cyclohex-2-en-1-ol (**28**), which is an example of an internal olefin and a challenging substrate for oxidative coupling, was also arylated successfully. This example opens up an opportunity to develop an asymmetric arylative enolization by replacing achiral ligands with chiral ligands.[12]

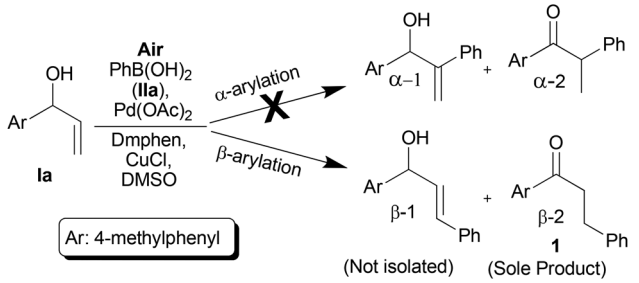
α-Benzyl-β-keto ester derivatives are important building blocks with extensive value in constructing pharmaceutically-relevant heterocyclic compounds.[13] Though synthesis of the α-benzyl-β-keto esters from Morita–Baylis–Hillman adducts



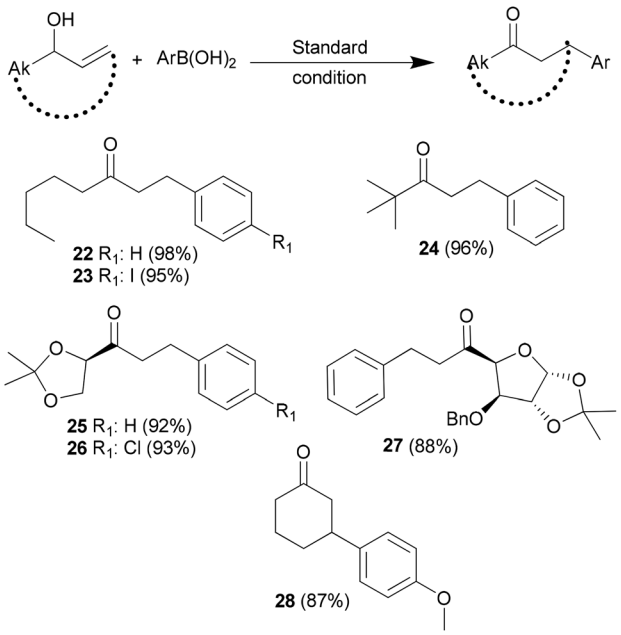
Scheme 2 Scope of the arylboronic acids: synthesis of dihydrochalcones.



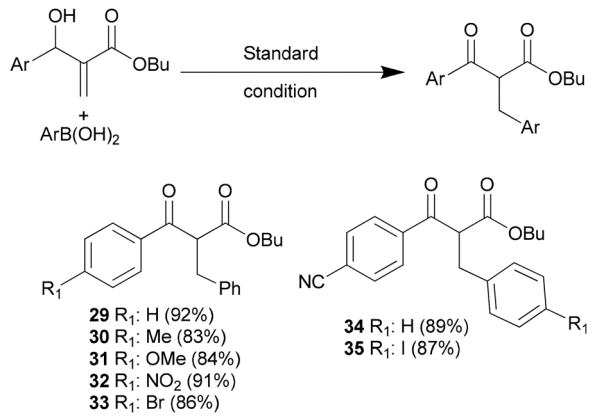
Scheme 3 Scope of the substituted aryl vinyl carbinols: synthesis of dihydrochalcones.



Scheme 1 Scope of regioselectivity and chemoselectivity in the aryl insertion and dehydropalladation steps.

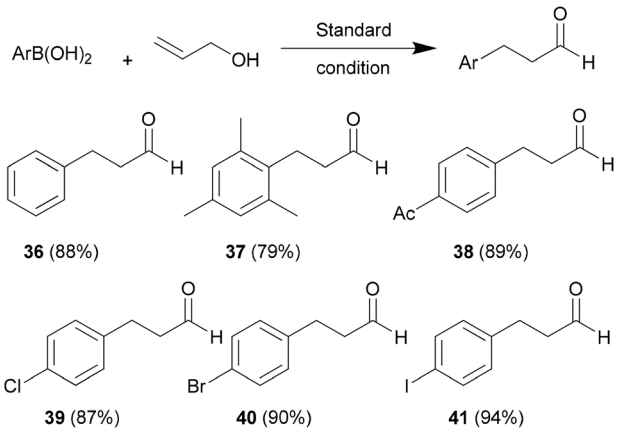


Scheme 4 Scope of the alkyl vinyl carbinols: synthesis of α,α′-dialkyl-ketone derivatives.



Scheme 5 Scope of the Morita–Baylis–Hillman adducts: synthesis of α-benzyl-β-keto esters.

through classical Heck-type coupling with aryl bromides is known, this coupling requires high temperatures and is known for the formation of a mixture of products.[14] 1,3-Dicarbonyl compounds are known to be susceptible to decarboxylation under elevated temperatures. Keeping this in mind, we investigated the coupling of arylboronic acids with highly-functionalized acrylic esters to further expand the scope, taking advantage of (a) the requirement of a lower temperature for the present procedure than that of a classical Heck-type coupling; (b) the high regioselectivity of arylation and (c) the chemoselectivity of the product formation. These adducts, differing in aryl substitution (electron-donating, electron-withdrawing and halogen groups (iodo and bromo)) underwent efficient coupling regioselectively (Scheme 5, **29–35**). Side products arising from decarboxylation, β-elimination and Pd(0)-directed oxidative addition were not observed.

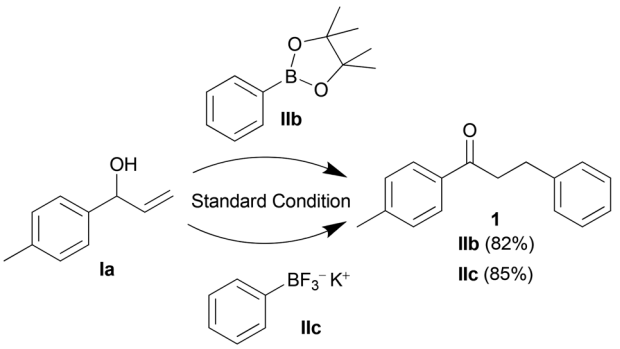


Scheme 6 Scope of the primary allyl alcohols: synthesis of substituted dihydrocinnamaldehydes.

The simple allyl alcohol with a primary hydroxy group (prop-2-en-1-ol) underwent C–C bond formation effectively with a range of arylboronic acids of varying electronic and steric character (Scheme 6, **36–41**). As seen before with the secondary alcohol, iodo, bromo, and chloro functionalities were intact. Thus, this method was superior over the previous procedure, in which the C–iodo bond was found to be less-compatible with the formation of a Heck-type product as the side product. Prop-2-en-1-ol is known to undergo Pd(II)-mediated oxidative Heck coupling to afford the corresponding cinnamyl alcohol through the competitive β-hydride elimination pathway.[7] However, we observed dihydrocinnamaldehyde as the exclusive product, indicating the high regioselective outcome of this methodology through the allylic hydride elimination pathway. 3-Aryl propionaldehydes are known to be susceptible to aldol condensation at high temperatures and/or in the presence of a base. This methodology, which obviates the need for high temperatures and a base, provides facile and chemoselective access to generate dihydrocinnamaldehydes.

To expand the scope of this catalysis further, two different derivatives of phenylboronic acid were considered for coupling (Scheme 7). The pinacolboronic ester of phenylboronic acid (**IIb**) and the potassium salt of phenyl trifluoroborate (**IIc**) underwent smooth coupling to afford the corresponding arylative enolization product (**1**). While boronic esters demonstrate higher solubility in organic solvents, trifluoroborate salts are endowed with higher degrees of nucleophilic character compared to free boronic acids.

The mild and neutral nature of the reaction conditions allowed robust functional group tolerance (–NO_2, –CN, –CO–, –NHAc, ketal, –I, –Br, & –Cl). Compatibility of the halogens under the present conditions has facilitated access to diverse halogen-intact β-aryl carbonyl derivatives with complete chemoselectivity. Even though the aryl–halogen bonds (Ar–I, Ar–Br, and Ar–Cl) were expected to be susceptible to the oxidative addition with Pd(0) species (generated in the penulti-



Scheme 7 Scope of the phenylboronic reagents with pinacol ester and potassium trifluoroborate head groups.

mate step through dehydropalladation) in the catalytic cycle, no competitive Heck, Suzuki and dehalogenation products were observed. Halogens are strategically employed in the aryl ring by medicinal chemists as handles for diversification during lead-optimization. Thus, this method offers chemoselective access to halogen-appended β-aryl carbonyl compounds, which are of limited scope in Pd(0)-mediated coupling of allyl alcohols with aryl halides. Importantly, this methodology can be considered to be an alternative to Rh-catalyzed Michael addition of arylboronic acids to α,β-unsaturated enones.[15] Allyl alcohols provide the advantages of higher stability, and easy availability over the enal and the enone counterparts.

To investigate the influence of the oxidant on the chemoselective compatibility of the iodo group, reactions were performed with four structurally-different propenols and iodo-bearing arylboronic acids following the previously reported Pd(II)–Ag_2CO_3 procedure for comparison. The results (Table 2) indicated clearly that oxygen was superior as the oxidant in terms of productivity. Diminished productivity, achieved in the case of the Ag_2CO_3 oxidant, was due to the promotion of side reactions involving iodo functionality.[8]

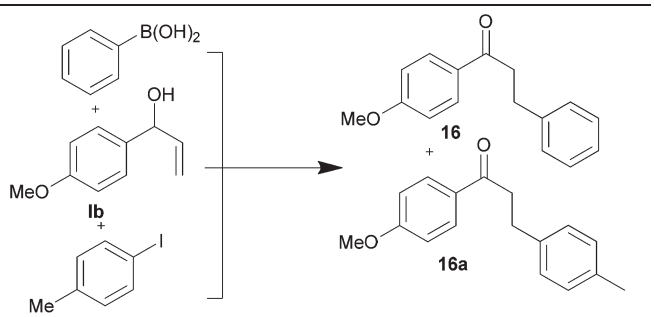
An intermolecular competition experiment was performed to understand the kinetic and mechanistic aspects using 4-methyliodobenzene (1.5 equiv.), phenylboronic acid (1.5 equiv.) and the alkenol **Ib** (1.0 equiv.) (Table 3) under the standard conditions. The arylboronic acid-derived product (**16**) was exclusively obtained with no concomitant formation of Heck and Suzuki products (entry 1). The absence of a base, low

Table 2 Enhanced chemoselectivity with the (*N*,*N*)Pd(II)–O_2 system over the previous (*N*,*N*)Pd(II)–Ag^+ system[a]

Entry	Compound	(*N*,*N*)Pd(II)–oxygen[b]	(*N*,*N*)Pd(II)–Ag_2CO_3[c]
1	**11**	89%	41%
2	**23**	95%	38%
3	**35**	87%	43%
4	**41**	94%	51%

[a] Isolated yield (average of two runs). [b] Standard conditions. [c] Olefin (1.0 mmol), $PhB(OH)_2$ (2.0 mmol), $Pd(OAc)_2$ (0.1 equiv.), Dmphen (0.2 equiv.), Ag_2CO_3 (2.0 equiv.) at 60 °C in CH_3CN (3.0 mL) for 24.0 h.

Table 3 Competitive coupling: formation of a Heck-type product, indicating the generation of Pd(0) in the catalytic cycle[a]



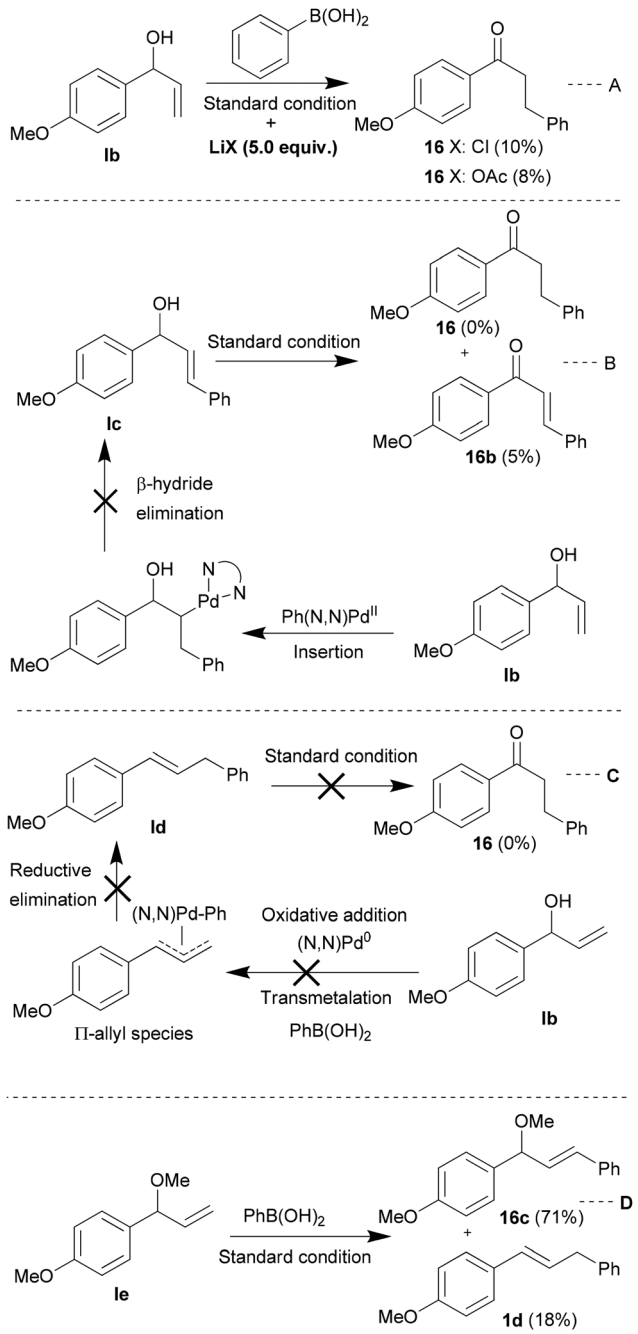
Entry[b]	Oxidative (Pd^{II}) product **16**	Heck (Pd^0) product **16a**
1	85%	0%
2[c]	71%	15%
3[d,e]	0%	51%

[a] Isolated yield (average of two runs). [b] Standard condition. [c] 100 °C. [d] Triethylamine (2.0 equiv.), 100 °C, nitrogen atmosphere. [e] The starting material was not consumed fully.

temperature, and presence of an efficient oxidant might have suppressed the oxidative addition of 4-methyliodobenzene with the transient Pd(0), and hence the formation of a Heck-type product. Considering the requirement of a higher activation energy for the oxidative addition of aryl halides to Pd(0) compared to the transmetallation of arylboronic acids, the reaction was performed at an elevated temperature (100 °C). This resulted in the formation of a Heck-type Pd(0) product (**16a**) in a 15% yield, in addition to the formation of an oxidative Pd(II)-arylation product (**16**) in a 71% yield (entry 2). The yield of the Heck-type product was further enhanced by the addition of a soluble (tertiary amine) base and by replacing the O_2 atmosphere with a N_2 atmosphere (thereby reducing the rate of oxidation of Pd(0)), which resulted in the requirement of a base in the reductive elimination step to convert the palladium(II) hydride complex to Pd(0) in the Heck catalytic pathway. The formation of the Heck-type product supports the mechanism, which involves the generation of Pd(0) in the catalytic cycle.

A reduction in the reaction rate is expected, if the arylpalladium(II) complex (obtained after the transmetallation with $ArB(OH)_2$) is stabilized. A detrimental effect on the reaction rate was observed on the addition of LiCl to the reaction mixture (reaction A, Scheme 8).[2q,r,16] This indicated the involvement of a cationic complex in the catalytic cycle. The halide coordination might neutralize the cationic (*N*,*N*)Pd(II)-complex, thereby blocking the vacant site, which is required for the olefin to form the metal–olefin π-complex. This prohibits the forward catalytic step, thereby halting the reaction.

To investigate the elimination pathway after migratory insertion of the allyl alcohol into the arylpalladium(II) precursor, the substituted cinnamyl alcohol, **Ic** (the presumptive β-dehydropalladation product), was synthesized, as this intermediate was not detected under the present protocol. When **Ic**



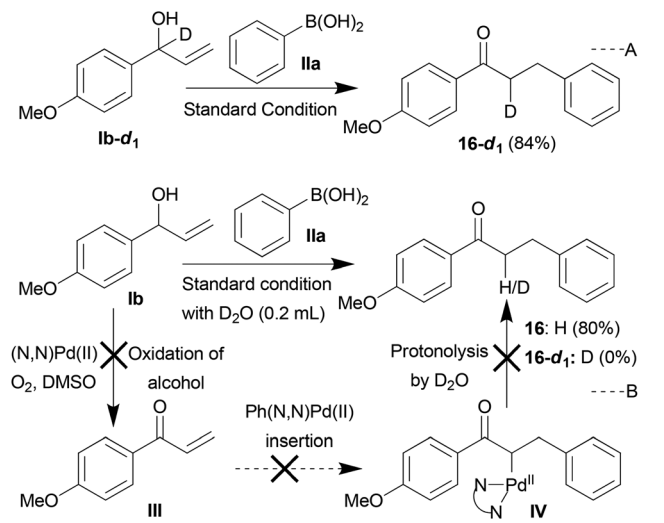
Scheme 8 Control experiments: diminished productivity with lithium salts as additives, implying a cationic pathway (reaction A); ruling out cascaded β-arylation, β-elimination & isomerisation as the mechanism (reaction B); ruling out sequential formation of π-allylic species & Wacker type oxidation as the mechanism (reaction C) and absence of the allylic hydrogen elimination pathway with protected OH group (reaction D).

was subjected to the standard conditions (reaction B, Scheme 8),[5e,7] the expected allylic isomerisation of 2-en-1-ol (**Ic**) to deliver the corresponding product (**16**) did not take place and only a small amount of the product of alcohol oxidation was isolated (**16b**). This ruled out the possibility of the generation of a cinnamyl-type β-aryl allyl alcohol (**Ic**) as a transient species in the catalytic cycle and subsequent isomerisation of **1c** to the β-ketoaryl product (**16**).

The complete absence of the α-aryl keto product (or exclusive formation of the β-aryl ketone) can be explained by a mechanism involving a π-allylpalladium complex (Scheme 8, reaction C). The product **Id** can be envisaged to arise from the activation of the hydroxyl group by $PhB(OH)_2$, subsequent formation of the π-allylpalladium complex by the oxidative addition of (*N*,*N*)Pd(0), transmetallation of the π-allylpalladium complex with $PhB(OH)_2$ and the final reductive elimination.[11] The resultant compound **Id** can undergo Wacker-type oxidation [Pd(II)/CuCl/O_2][17] to afford the β-arylketone (**16**). However, we didn't observe the intermediate **Id** under the present conditions. To eliminate the possibility of the transient formation of **Id** and subsequent oxidation, we prepared the aryl–allyl product **Id** and subjected it to the standard conditions, but could not observe the Wacker oxidation of **Id**. This unambiguously ruled out the feasibility of the allylation mechanism that would involve the π-allylpalladium complex.

The methyl ether derivative, **1e**, did not afford the β-aryl ketone under the standard conditions but gave the oxidative Heck product (**16c**) and allylation product (**1d**) in a 4 : 1 ratio. This suggests that on masking the hydroxyl group, the catalytic route deviates from the normal pathway through (a) β-hydride elimination after aryl insertion and subsequent termination and (b) the formation of the π-allylpalladium(II) complex, arylation and elimination. This strongly suggested the necessity of a free hydroxyl group for the operation of the allylic hydride elimination pathway.

To further probe the hydride elimination, the deuterium-labelled propenol (**Ib-*d*$_1$**), was synthesized and reacted with $PhB(OH)_2$ under the standard conditions. The deuterium-installed 1-(4-methoxyphenyl)-3-phenyl-2($^2H_1$)-propan-1-one (**16-*d*$_1$**) was obtained exclusively (reaction A, Scheme 9). This critical observation indicates that the propenol (**Ib-*d*$_1$**), after



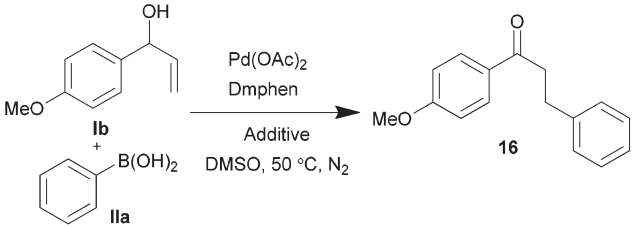
Scheme 9 Migration of allylic deuterium to the adjacent position during the arylation.

carbopalladation with (*N*,*N*)ArPd(II), undergoes a 1,2-hydrogen shift.[5,6] The isotopically-unmodified product (**16**), was not detected (reaction B, Scheme 9). Nevertheless, the insertion of any deuterium atom by the addition of deuterated water to the reaction of **Ib** with $PhB(OH)_2$ under the standard protocol was not evident. This probably rules out the pathway involving the formation of an α,β-unsaturated ketone (**III**) through the oxidation of the alcohol (**Ib**) and the subsequent insertion of a phenyl palladium(II) precursor into the α,β-unsaturated ketone (**III**), followed by protonolysis of the σ-alkyl complex (**IV**).[18] This is further corroborated by the fact that the intermediate, **III**, was not observed in the experiment.

Experimental observations from Table 1 indicated the necessity of Cu(I) for the successful outcome of the reaction, and the higher performance of the Cu(I) oxidation state over that of Cu(II). To investigate further, control experiments were performed with 0.05, 1.0 and 2.0 equiv. of CuCl in an oxygen-free nitrogen atmosphere (Table 1, entries 22, 30 and 31). The formation of the desired arylation product (9%, 57%, and 85%) is evidence that the role of the copper(I) salt is as an electron-transfer mediator for the reoxidation of Pd(0). In the present procedure, Cu(I) can potentially play dual roles as both a co-oxidant for the reoxidation of Pd(0) with the oxygen as the terminal oxidant, and as a Lewis acid, coordinating to the allyl hydroxyl group to facilitate selective allylic hydride elimination after carbopalladation. Molecular oxygen was used as the sole oxidant with no necessity for copper salt as the co-catalyst in a number of recent Pd(II)-catalyzed oxidative transformations (*e.g.*, direct O_2-coupled Wacker oxidation), when nitrogenous ligands were employed.[2i] Dioxygen reacts readily with a (bathocuproine)Pd(0) complex to afford a Pd(II)peroxo complex, which can be protonated with AcOH (2.0 equiv.) to afford (bathocuproine)$Pd(OAc)_2$ and H_2O_2.[19] Hence, the other role of catalytic copper(I) salts, behaving like Lewis acids in the present procedure, which was modulated by the bidentate neocuproine ligand, could not be ruled out. Control experiments were undertaken with a range of Lewis acids (CuCl, $ZnCl_2$, $ZnBr_2$, and $InBr_3$) in the presence of stoichiometric $Pd(OAc)_2$ in an oxygen-free nitrogen atmosphere (Table 4, entries 2–5). Similar yields were obtained as with that of CuCl, which would substantiate the role of Cu(I) as a Lewis acid.

Based on the results from the above mechanistic investigations, a plausible catalytic cycle can be depicted (Fig. 2). The foremost step of the catalysis might involve the transmetallation of arylboronic acid with the Dmphen-chelated palladium(II) complex (**A**)[20] to form the cationic arylpalladium(II) complex (**B**).[2q,r] Subsequently, the olefin (**Ib-*d*$_1$**) coordinates to the metal centre of the Pd(II)-aryl species through the vacant site to form the π-complex (**C**). The latter complex then undergoes migratory insertion to form the σ-alkylpalladium complex (**D**). This is followed by β-hydride elimination involving allylic hydrogen to form the enol-bound palladium(II) deuteride complex (**E**). The coordination of the copper(I) salt to the hydroxyl group of the allyl alcohol could potentially increase the acidic character of allylic hydrogen, which could potentially contribute to the regioselective β-hydride elimination.

Table 4 Different Lewis acids promoting efficient (*N*,*N*)Pd(II)-catalysis[a]



Entry	**Ib**/**IIa** (equiv.)	Additive	**16**[b] (%)
1	1.0/1.5	No additive	<5
2	1.0/1.5	CuCl	91
3	1.0/1.5	$ZnCl_2$	92
4	1.0/1.5	$ZnBr_2$	92
5	1.0/1.5	$InBr_3$	93

[a] $Pd(OAc)_2$ (1.0 equiv.), Dmphen (2.0 equiv.), additive (1.0 equiv.) in DMSO at 50 °C under N_2 atm for 12.0 h. [b] Isolated yield (average of two runs).

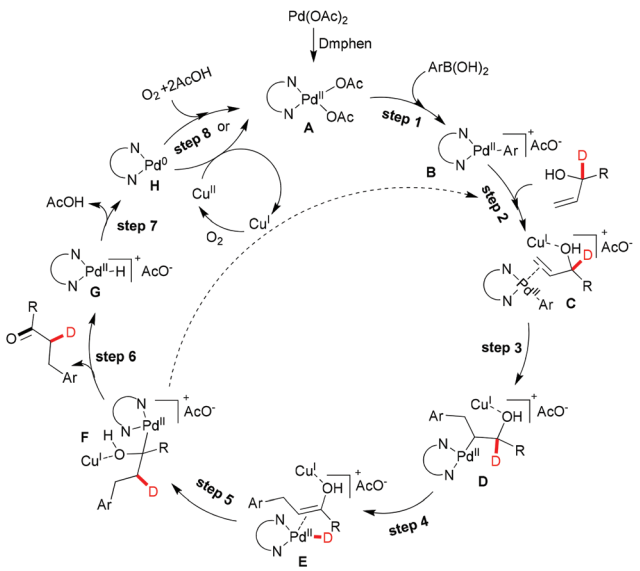


Fig. 2 Proposed catalytic cycle of aerobic cationic Pd(II) mediated arylation; Dmphen = 2,9-dimethyl-1,10-phenanthroline.

The complex (**E**) spontaneously undergoes insertion, resulting in the formation of the σ-alkylpalladium complex with the transfer of deuterium to the α-carbon (**F**). The resulting palladium(II) complex finally undergoes elimination to form the β-aryl keto compound (**16-*d*$_1$**) and the cationic (neocuproine)palladium hydride (**G**). The palladium hydride subsequently decomposes to (neocuproine)Pd(0) (**H**), which is then oxidised by molecular oxygen and/or Cu(I), thereby regenerating the active Pd(II) catalyst and initiating the new catalytic cycle. Cu(I) could potentially coordinate to the hydroxyl group through 2–5 steps to enable the elimination of allylic hydrogen and extrusion of β-aryl ketone, and could act as the co-oxidant in the final step, similar to Tsuji–Wacker oxidation [Pd(II)/CuCl/O_2].[17]

Conclusions

Air was shown to be an eco-friendly oxidant to enhance the sustainability of Pd(II)-directed arylation of prop-2-en-1-ols with arylboronic acids as the arylpalladium precursors, which eliminated the use of non-green silver salts and the generation of solid waste. This green approach proceeds with very high regioselectivity and chemoselectivity and does not require a base or an acid (as co-solvent) or high temperature, thereby offering mild conditions. This allowed the tolerance of a wide range of functionalities compared to what was previously possible. Hence, this method provided expeditious access to functionalized β-aryl aldehydes and ketones, and β-keto esters. The incorporation of ligands has now made asymmetric arylation feasible and this is under investigation. A mechanistic investigation has shed light on the involvement of the cationic palladium(II) species, generation of Pd(0) in the catalytic cycle, and migration of the allylic hydrogen in the catalytic cycle after arylative insertion.

Experimental section

General experimental details

All solvents and reagents were used as received from the suppliers. TLC was performed using Merck Kiesel gel 60, F_{254} plates with a layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100–200 mesh) using a gradient of ethyl acetate and hexane as the mobile phase. Melting points were determined using a Fisher Johns melting point apparatus and were uncorrected. IR spectra were recorded using a Perkin-Elmer RX-1 FT-IR system. ^{1}H NMR spectral data were collected at 300 (AVANCE & JCAMP), 400 (INOVA) and 500 (AVANCE & INOVA) MHz, while ^{13}C NMR were recorded at 75, 100 and 125 MHz. ^{1}H NMR spectral data are given as chemical shifts in ppm followed by the multiplicity (s – singlet; d – doublet; dd – doublet of doublet; t – triplet; q – quartet; m – multiplet), number of protons and coupling constants. ^{13}C NMR chemical shifts are expressed in ppm. HRMS (ESI) spectral data were collected using Q-star & ORBITRAP high resolution mass spectrometers.

General procedure for the synthesis of β-aryl carbonyl compounds from allyl alcohols

A mixture of arylboronic acid (1.5 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), 2,9-dimethyl-1,10-phenanthroline (0.042 g, 0.20 mmol), CuCl (0.005 g, 0.05 mmol) and allyl alcohol (1.0 mmol) was dissolved in DMSO (3 mL) in a 10.0 mL RB flask. The flask was then fitted to an air balloon (1 atm pressure). The mixture was vigorously stirred at 50 °C for 12 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (25.0 mL) and water (25.0 mL) and the contents were transferred to a separatory funnel. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 (s) and concentrated *in vacuo*. The residue was purified by column chromatography using silica gel and a gradient of hexane and ethyl acetate (eluent) to afford the pure product.

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