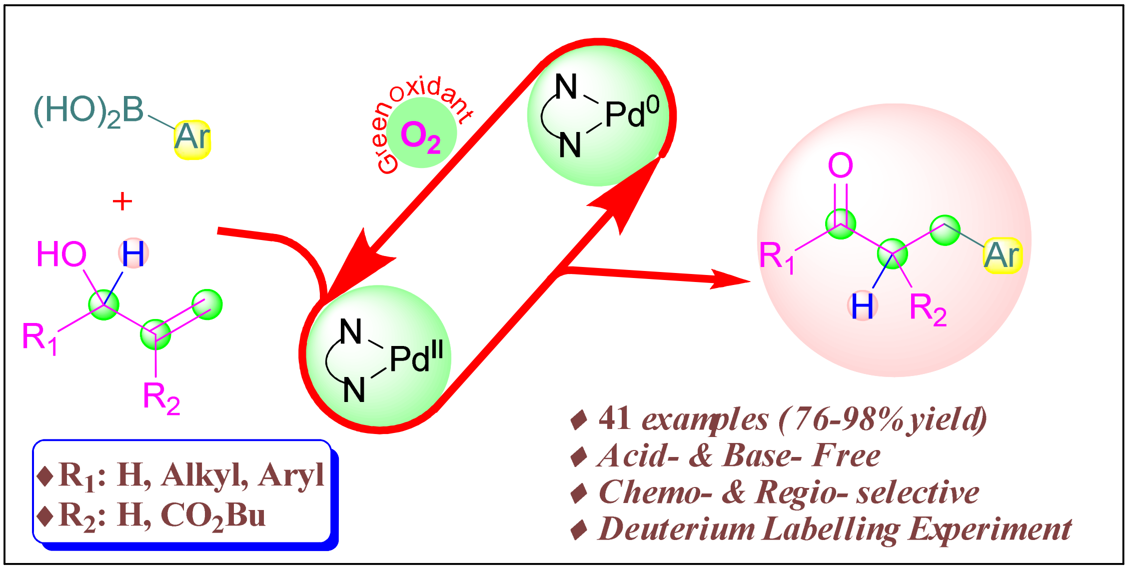
Graphical Abstract



Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Replacing Stoichiometric Silver Oxidant with Air: Ligated Pd(II)-Catalysis to β-Aryl Carbonyl Derivatives with Improved Chemoselectivity

Mári Vellakkaran,[a] Murugaiah M S Andappan[b] and Nagaiah Kommu[*a]

Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

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 the 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 ester and trifluoroborate salt. 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 commodities chemical industry and the academic labs. Dioxygen is an inexpensive and abundantly-available oxidant, which doesn't leave behind any solid waste. By the contrast, the transition metal oxidants (being required in stoichiometric quantities) are toxic, leave behind hazardous solid waste, and are known for promotion of undesirable side reactions.[1] Hence, replacement of metal oxidants in the 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 material chemistry.[3] The "β-aryl carbonyl" motif is known for widespread prevalence in the natural products of medicinal importance and also decorates the marketed drugs (Fig. 1).[4]

Because of the above significance, several synthetic routes have been pursued to construct these privileged motifs in the 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 β-aryl propanals or propanones, taking advantage of commercial availability / ready-accessibility of the allyl alcohols.[5] This versatile process is however encountered with limitations like decrease in chemoselectivity (aryl carbonyl *vs*. aryl allyl alcohol), decrease in regioselectivity (β-arylation *vs*. α-arylation) and necessity for high temperature and base.

Oxidative Pd(II)-mediated coupling of the allyl alcohols with transmetallation substrates presents a promising alternative approach to β-aryl aldehydes and ketones, considering key advantages. For example, the reaction can be performed at low temperature. Surprisingly, only few methods on the oxidative coupling of the allyl alcohols with organometallic reagents as aryl source have been reported in the literature.[6] However, these reactions suffer from limitations like toxic nature of 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 yield (<20%).[7] We recently reported the first ligand-modulated and regioselective Pd(II)-catalysis to β-aryl aldehydes and ketones, thereby enhancing the

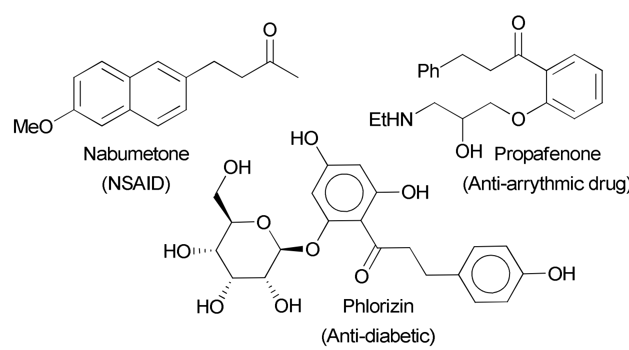
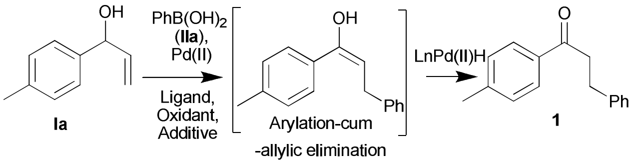


Fig.1 Compounds of pharmaceutical importance, encoded with β-aryl carbonyl skeleton.

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	$CuSO_4.5H_2O$	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** (1.5mmol), 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.

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.

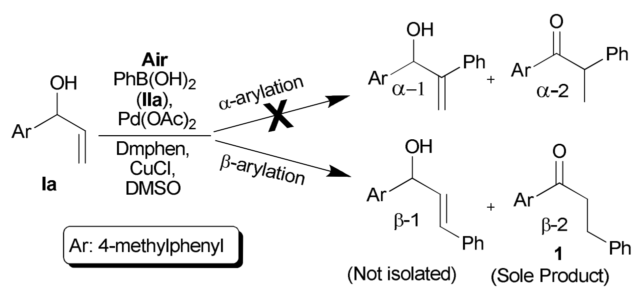
Results and discussion

We began our investigation by replacing Ag_2CO_3 oxidant in our earlier protocol[8] with air. We examined the coupling of 1-(4-methyl)phenyl prop-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 addition of catalytic CuCl additive (0.05 equiv.) led to the product formation, albeit, in low yield (entry 2).[9] Subsequently, identification of productive condition for regioselective vinylative enolization was undertaken in a combinatorial fashion through multifarious conditions in terms of 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 Pd(II) metal source with either catalytic or stoichiometric CuCl additive (entries 24&25). Pyridine, which is an example of monodentate ligand, gave moderate yield (entry 17). Dmphen, which is a bidentate nitrogenous ligand and routinely used in the 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 higher stability of the former under oxidative Pd(II)-mediated transformations than the oxidation-vulnerable phosphines. Importance of ligand control was realized through the reduced productivity in the absence of 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 moderate yield (entry 27). As there was no advantage in 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 was dramatically reduced on replacing air atmosphere with nitrogen 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 condition (Scheme 1). This indicates the β-regioselectivity of the insertion that the addition of the aryl moiety exclusively occurs at the terminal carbon of the double



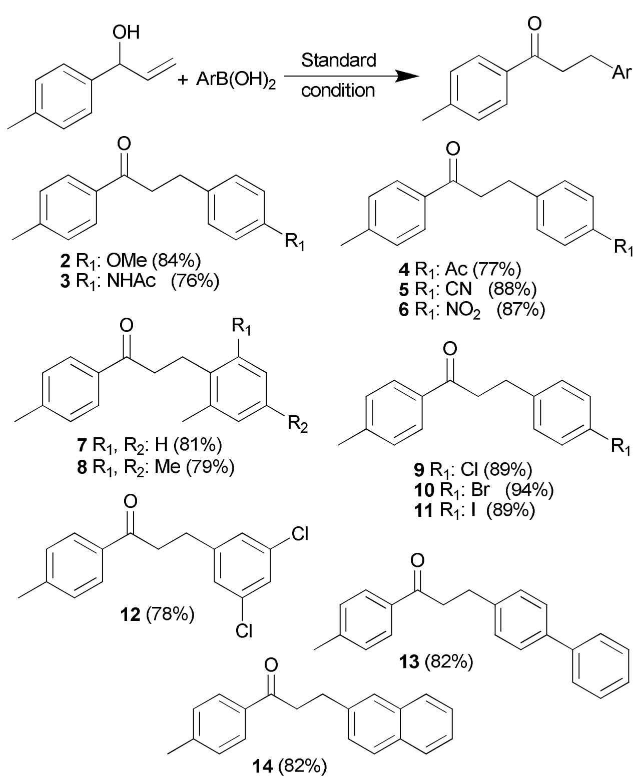
Scheme 1 Scope of regioselectivity and chemoselectivity in the aryl insertion and dehydropalladation steps

bond. 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 out of β-hydride elimination] was not detected under the present condition.[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 protocol.

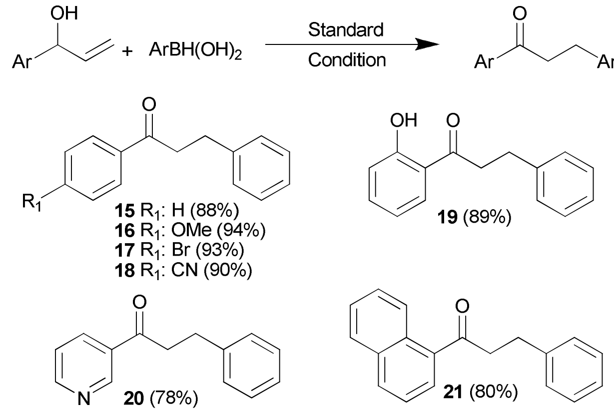
The optimized condition from Table 1 (entry 20) was deployed as a standard protocol to investigate the impact of electronic and steric modulation of both the allyl alcohols and the arylboronic acids on the preparative outcome. Though the electron-poor arylboronic acids were known to be less-productive 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 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**).

Scope and limitation of several different allyl alcohol derivatives was investigated (Scheme 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 generality of the method.

The propenols, bearing linear and branched alkyl substitutions at allylic position, furnished excellent yields (scheme 4, **22**-**24**). The olefins, derived from carbohydrate-based chiral synthons like



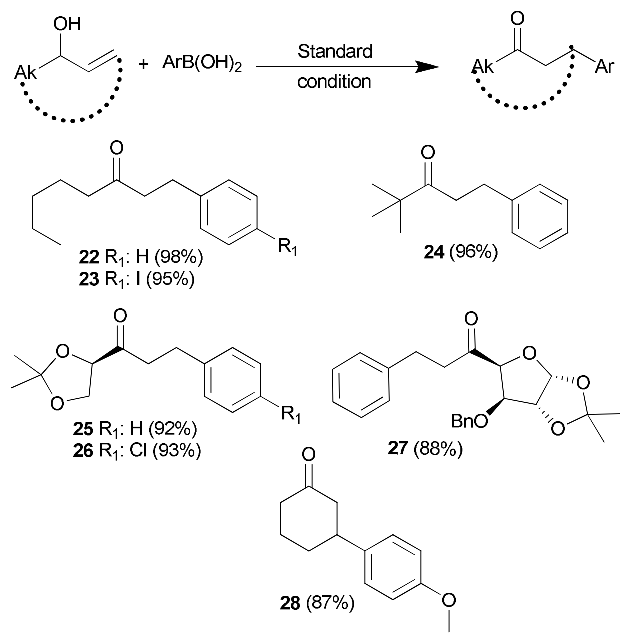
Scheme 2 Scope of the arylboronic acids: Synthesis of dihydrochalcones



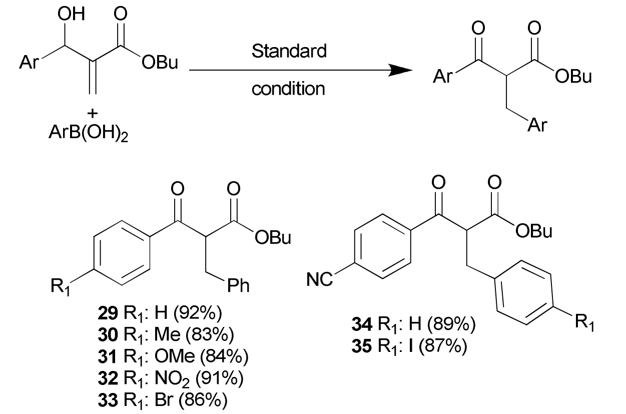
Scheme 3 Scope of the substituted aryl vinyl carbinols: Synthesis of dihydrochalcones

the protected (*S*)-glyceraldehyde (**25&26**) and protected xylose-5-carboxaldehyde (**27**), underwent efficient arylation. This is an indication of compatibility of this methodology with the acid-labile functionalities. Cyclohex-2-en-1-ol (**28**), which is an example for 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]

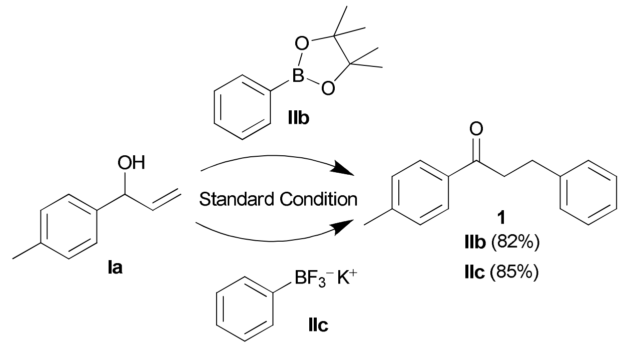
The α-Benzyl-β-keto ester derivatives are the important building blocks with extensive utility to construct the pharmaceutically-relevant heterocyclic compounds.[13] Though synthesis of the α-benzyl-β-keto esters from the Morita-Baylis-Hillman adducts through classical Heck-type coupling with aryl bromides is known, this coupling requires high temperature condition and is known for the formation of mixture of products.[14] 1,3-Dicarbonyl compounds are known to be susceptible to decarboxylation under elevated temperature. Keeping this in mind, we investigated coupling of arylboronic acids with highly-functionalized acrylic esters to further expand



Scheme 4 Scope of the alkyl vinyl carbinols: Synthesis of α,α′-dialkylketone derivatives



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



Scheme 7 Preparative scope of the phenylboronic reagents with pinacol ester and potassium trifluoroborate head groups

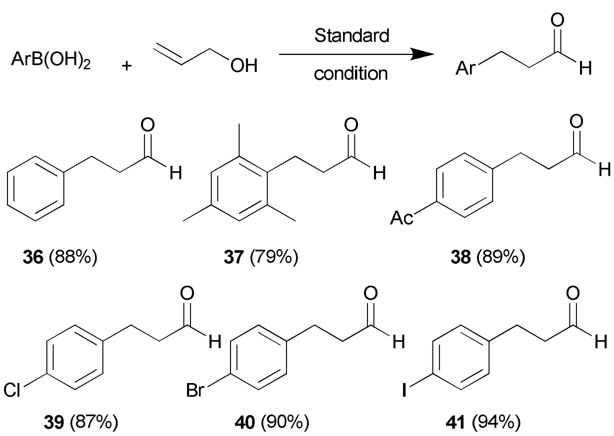
the scope, taking advantage of (a) requirement of lower temperature of the present protocol than that of classical Heck-type coupling (b) high regioselectivity of arylation and (c) chemoselectivity with the product formation. These adducts, differing in aryl substitution (electron-donating, electron-withdrawing and halogen groups [iodo and bromo]) underwent efficient coupling regioselectively (scheme 5, **29-35**). The side products arising out of decarboxylation, β-elimination and Pd(0)-directed oxidative addition were not observed.

The simple allyl alcohol with 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 protocol, in which the C–iodo bond was found to be less-compatible with the formation of 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 allylic hydride elimination pathway.3-Aryl propionaldehydes are known to be susceptible to aldol condensation at high temperature and /or in the presence of a base. This methodology, which obviates the need for high temperature and a base, provides facile and chemoselective access to generate the 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 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 nucleophilic character compared to free boronicacids.

Mild and neutral nature of the reaction condition allowed robust functional group tolerance (-NO_2, -CN, -CO-, -NHAc, ketal, -I, -Br, & -Cl). Compatibility of the halogens under present conditions has facilitated the 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] are expected to be susceptible to the oxidative addition with Pd(0) species [generated in the penultimate step through dehydropalladation] in the catalytic cycle, no competitive Heck, Suzuki and dehalogenation products were observed. Halogens are strategically deployed 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 the Pd(0)-mediated coupling of allyl alcohols with aryl halides. Importantly, this methodology can be considered as an alternative to Rh-catalyzed Michael addition of arylboronic acids to α,β-unsaturated enones.[15] The allyl alcohols provide the advantage 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 iodo group, reactions were performed with four structurally-different propenols and iodo-bearing arylboronic acids under previously-reported Pd(II)-



Scheme 6 Scope of the primary allyl alcohol: Synthesis of substituted dihydrocinnamaldehydes

Table 2 Enhanced chemoselectivity with (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%

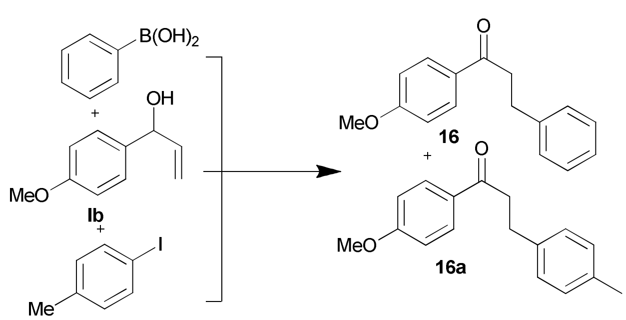
[a] Isolated yield (average of two runs); [b] Standard condition; [c] Olefin (1.0 mmol), $PhB(OH)_2$ (2.0 mmol), $Pd(OAc)_2$ (0.1 equiv.), Dmphen (0.2 equiv.), Ag_2CO_3 (2.0 equiv.) at 60 °C in CH_3CN (3.0 mL) for 24.0 h.

Ag_2CO_3 protocol for comparison. The results (Table 2) indicated clearly that oxygen was superior as the oxidant in terms of productivity. Diminished productivity, obtained in the case of 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 condition. The arylboronic acid-derived product (**16**) was exclusively obtained with no concomitant formation of Heck and Suzuki products (entry 1). Absence of base, low temperature, and presence of the efficient oxidant might have suppressed the oxidative addition of 4-methyliodobenzene with the transient Pd(0), and hence the formation of Heck-type product. Considering the requirement of higher activation energy for the oxidative addition of aryl halides to Pd(0) in comparison to the transmetallation of arylboronic acids, the reaction was performed at the elevated temperature (100 °C). This resulted in the formation of Heck-type Pd(0) product (**16a**) in 15% yield in addition to the formation of oxidative Pd(II)-arylation product (**16**) in 71% yield (entry 2). The yield of Heck-type product was further enhanced by the addition of a soluble (tertiary amine) base and replacing O_2 atmosphere with N_2 atmosphere [thereby reducing the rate of oxidation of Pd(0)], which resonated with the requirement of a base in the reductive elimination step to convert palladium(II) hydride complex to Pd(0) in the Heck catalytic pathway. The formation of Heck-type product supports the mechanism, which involves the generation of Pd(0) in the catalytic cycle.

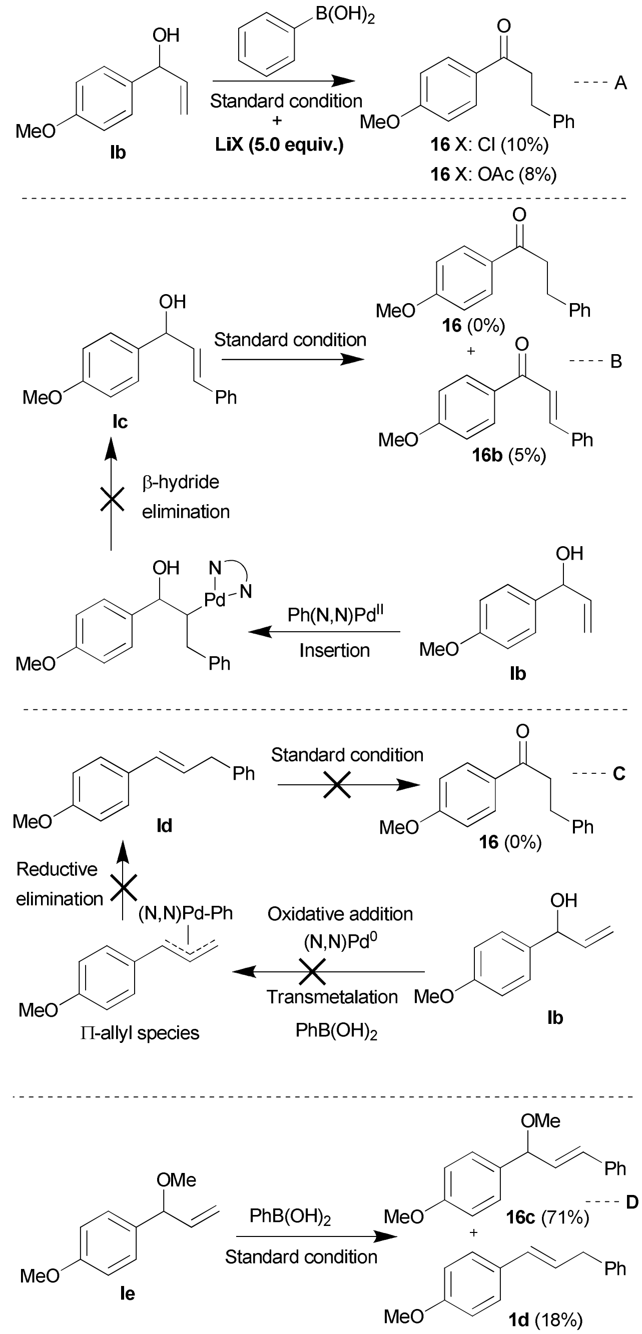
Impediment to the reaction rate is expected, if the arylpalladium(II) complex [obtained after the transmetallation with $ArB(OH)_2$] is stabilized. A detrimental effect on the reaction rate was observed on addition of LiCl to the reaction mixture (Reaction A, Scheme 8).[2q, r, 16] This indicated the involvement of

Table 3 Competitive Coupling: Formation of 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%

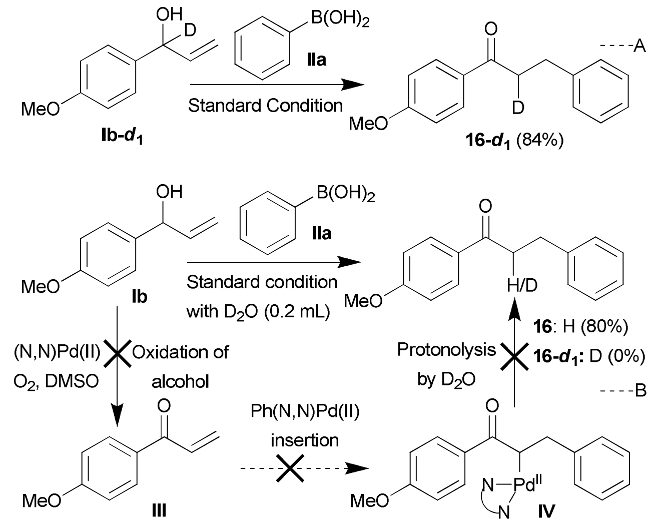
[a] Isolated yield (average of two runs). [b] Standard Condition. [c] 100 °C. [d] Triethylamine (2.0 equiv.), 100 °C, nitrogen atmosphere. [e] The starting material was not consumed fully.



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

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 arylpalladium(II) precursor, the substituted cinnamyl alcohol, **Ic** [the presumptive β-dehydropalladation product], was synthesized, as this



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

Intermediate was not detected under the present protocol. When **Ic** was subjected to the standard condition (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 product of alcohol oxidation was isolated (**16b**). This ruled out the possibility of generation of 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**).

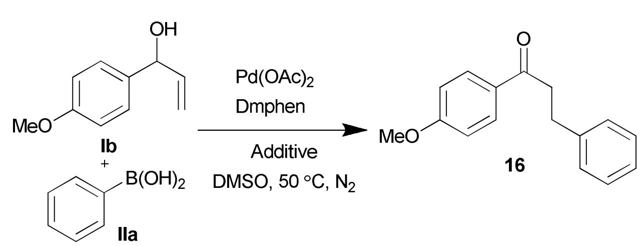
The complete absence of α-aryl keto product (or exclusive formation of β-aryl ketone) can be explained by a mechanism, involving π-allylpalladium complex (Scheme 8, Reaction C). The product **Id** can be envisaged to arise from the activation of hydroxyl group by $PhB(OH)_2$, subsequent formation of 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 **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 protocol. To eliminate the possibility of transient formation of **Id** and subsequent oxidation, we prepared the aryl-allyl product **Id** and subjected it to the standard condition, but could not observe the Wacker oxidation of **Id**. This unambiguously ruled out the feasibility of the allylation mechanism that would involve π-allylpalladium complex.

The methyl ether derivative, **1e**, did not afford the β-aryl ketone under the standard condition but gave the oxidative Heck product (**16c**) and allylation product (**1d**) in 4:1 ratio. This suggests that on masking of hydroxyl group, the catalytic route deviates from normal pathway through (a) β-hydride elimination after aryl insertion and subsequent termination and (b) formation of π-allylpalladium(II) complex, arylation and elimination. This strongly suggested the necessity of free hydroxyl group for the operation of 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 condition. 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 carbopalladation with (N,N)ArPd(II) undergoes 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 deuteriated water to the reaction of **Ib** with $PhB(OH)_2$ under the standard protocol was not evident. This probably ruled out the pathway of formation of α,β-unsaturated ketone (III) through oxidation of the alcohol (Ib) and subsequent insertion of 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 1indicated the necessity of Cu(I) for the successful outcome of the reaction and the higher performance of 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 under oxygen-excluded nitrogen atmosphere (Table 1, entries 22, 30 and 31). The formation of desired arylation product (9%, 57%, and 85%) renders the supporting evidence for the role of copper(I) salt as an electron-transfer mediator for reoxidation of Pd(0). In the present protocol, Cu(I) can potentially play a dual role of co-oxidant for reoxidation of Pd(0) with the oxygen as the terminal oxidant and of Lewis acid, coordinating to allyl hydroxyl group to facilitate selective allylic hydride elimination after carbopalladation. Molecular oxygen were used as the sole oxidant with no necessity for copper salt as the co-catalyst in a number of recent of Pd(II)-catalyzed oxidative transformations (e.g., direct O_2-coupled Wacker oxidation), when nitrogenous ligands were employed.[2i] Dioxygen reacts readily with (bathocuproine)Pd(0) complex to afford 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, other role of catalytic copper(I) salt like Lewis acid in the present protocol, 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 $Pd(OAc)_2$ under oxygen-free nitrogen atmosphere (Table 4, entries 2-5). Similar yields were obtained as that of CuCl, which would substantiate the role of Cu(I) as Lewis acid.

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).

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 later complex then undergoes migratory insertion to form the σ-alkylpalladium complex (**D**). This is followed by the 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. The complex (**E**) spontaneously undergoes insertion, resulting in the formation of 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 elimination of allylic hydrogen and extrusion of β-aryl ketone and as the co-oxidant in the final step, similar to Tsuji-Wacker oxidation [Pd(II)/CuCl/O_2].[17]

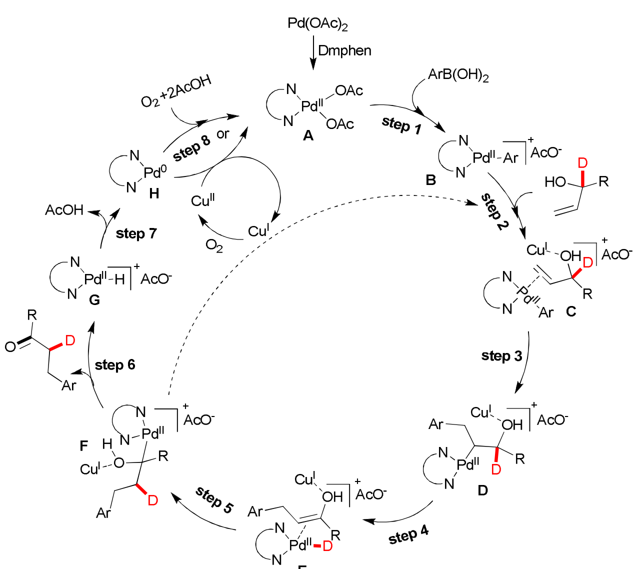


Fig. 2 Proposed catalytic cycle of aerobic cationic Pd(II) mediated arylation; Dmphen = 2,9-dimethyl-1,10-phenanthroline

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 salt 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 the wide range of functionalities than what was previously possible. Hence, this method provided an expeditious access to functionalized β-aryl -aldehydes, -ketones and β-keto esters. Incorporation of ligands has now made the feasibility for asymmetric arylation, which is under investigation. Mechanistic investigation has shed light on involvement of cationic palladium(II) species, generation of Pd(0) in the catalytic cycle, and migration of 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 on Merck Kiesel gel 60, F_{254} plates with the 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 mobile phase. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on 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 125MHz. ^{1}H NMR spectral data are given as chemical shifts in ppm followed by 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 were expressed in ppm. HRMS (ESI) spectral data were collected using Q-star & ORBITRAP high resolution mass spectrometer.

‡ 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 (1atm 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 content was 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.

Acknowledgements

We thank the Director of CSIR-Indian Institute of Chemical Technology for the generous support and CSIR, New Delhi for funding through the programme ORIGIN XII FVP (CSC0108). V. M thanks CSIR, New Delhi for the Senior Research Fellowship.

Notes and references

[a] *Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad, India-500007. E-mail:nagaiah@iict.res.in*
[b]*Syngene, Biocon Park, Bengaluru, India-560009; E-mail: murugaiah.andappan@gmail.com*
† Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data. See DOI: 10.1039/b000000x/

1 (a) X. Mi, M. Huang, H. Guo and Y. Wu, *Tetrahedron*, 2013, **69**, 5123; (b) E. Song, J. Park, K. Oh, H. M. Jung and S. Lee, *Bull. Korean Chem. Soc.,*2010, **31**, 1789; (c) Z. He, S. Kirchberg, R. Frchlich and A. Studer, *Angew. Chem. Int. Ed*., 2012**, 51**, 3699; (d) D. Kim, K. Ham and S. Hong, *Org. Biomol. Chem*., 2012, **10**, 7305; (e) P. Sun, Y. Zhu, H. Yang, H.Yan, L. Lu, X. Zhang and J. Mao, *Org. Biomol. Chem*., 2012, **10**, 4512.

2 (a) S. S. Stahl, *Science*, 2005, **309**, 1824; (b) S. S. Stahl, *Angew. Chem. Int. Ed.*, 2004, **43**, 3400; (c) B. M. Stoltz, *Chem. Lett.,* 2004, **33**, 362; (d) M. J. Schultz and M. S. Sigman, *Tetrahedron*, 2006, **62**, 8227; (e) J. Muzart, *Chem.–Asian J*., 2006, **1**, 508; (f) M. S. Sigman and D. R. Jensen, *Acc. Chem. Res*., 2006, **39**, 221; (g) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev*., 2007, **107**, 5318; (h) J. Piera and J. E. Backvall, *Angew. Chem., Int. Ed.,* 2008, **47**, 3506; (i) K. M. Gligorich and M. S. Sigman, *Chem. Commun.,* 2009, 3854; (j) R. M. Trend, Y. K. Ramtohul, E. M. Ferreira and B. M. Stoltz,*Angew. Chem. Int. Ed.,* 2003, **42**, 2892; (k) R. M. Trend, Y. K. Ramtohul and B. M. Stoltz, *J. Am. Chem. Soc*., 2005, **127**, 17778; (l) K. T. Yip, M. Yang, K. L. Law, N. Y. Zhu and D. J. Yang, *J. Am. Chem. Soc.,* 2006, **128**, 3130; (m) W. He, K. T. Yip, N. Y. Zhu and D. Yang, *Org. Lett.,* 2009, **11**, 5626; (n) C. C. Scarborough, A. Bergant, G. T. Sazama, I. A. Guzei, L. C. Spencer and S. S. Stahl, *Tetrahedron,* 2009, **65**, 5084; (o) F. Jiang, Z. Wu and W. Zhang, *Tetrahedron Lett.*, 2010, **51**, 5124; (p) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3381; (q) M. M. S. Andappan, P. Nilsson, H. Schenck and M. Larhed, *J. Org. Chem*., 2004, **69**, 5212; (r) P. Enquist, P. Nilsson, P. Sjoberg and M. Larhed, *J. Org. Chem.*, 2006, **71**, 8779.

3 (a) G. Rassias, N. G. Stevenson, N. R. Curtis, J. M. Northall, M. Gray, J. Prodger and A. J. Walker, *Org. Process Res. Dev.*, 2010, **14**, 92; (b) C. S. N. Krishnamurthy, T. Kashyap and J. Singh, *PCT Int. Appl*. 2010, WO 2010064109 A2 20100610; (c) J. Liu, S. He, T. Jian, P. H. Dobbelaar, I. K. Sebhat, L. S. Lin, A. Goodman, C. Guo, P. R. Guzzo and M. Hadden, *Bioorg. Med. Chem. Lett*., 2010, **20**, 2074; (d) P. D. A. Amaral, J. Petrignet, N. Gouault, T. Agustini, F. Lohezic-Ledevehat, A. Cariou, R. Gree, V. L. Eifler-Lima and M. David, *J. Braz. Chem. Soc*., 2009, **20**, 1687; (e) M. R. Gesinski, K. Tadpetch and S. D. Rychnovsky, *Org. Lett*., 2009, **11**, 5342; (f) D. C. K. Rathwell, Y. Sung-Hyun, K. T. Tsang and M. A. Brimble, *Angew. Chem, Int. Ed*., 2009, **48**, 7996; (g) Y. Hiraiwa, A. Morinaka, T. Fukushima and T. Kudo, *Bioorg. Med. Chem. Lett*., 2009, **19**, 5162; (h) E. E. Boros, C. E. Edwards, S. A. Foster, M. Fuji, T. Fujiwara, E. P. Garvey, P. L. Golden, R. J. Hazen, J. L. Jeffrey and B. A. Johns, *J. Med. Chem*., 2009, **52**, 2754; (i) A. Heim-Riether, *Synthesis*, 2008, **6**, 883; (j) O. Benavente-García and J. Castillo, *J. Agric. Food Chem.,* 2008, **56***,* 6185; (k) L. H. Cazarolli, L. Zanatta, E. H. Alberton, M. S. Figueiredo, P. Folador, R. G. Damazio, M. G. Pizzolatti and F. R. Silva, *Mini. Rev. Med. Chem.,* 2008, **8***,* 1429; (l) L. Marzocchella, M. Fantini, M. Benvenuto, L. Masuelli, I. Tresoldi, A. Modesti and R. Bei, *Recent Pat. Inflamm. Allergy Drug Discov.,* 2011, **5***,* 200; (m) M. Kobori, H. Shinmoto,T. Tsushida and K. Shinohara, *Cancer Lett.,*1997, **119**, 207; (n) L. Mathiesen, K. E. Malterud and R. B. Sund, *Free Radic. Biol.Med.,*1997, **22**, 307; (o) D. H. S. Silva, S. C. Davino, B. M. S. Barros and M. Yoshida, *J. Nat. Prod.,*1999, **62**, 1475; (p) B. M. Rezk, G. R. M. M. Haenen, W. J. F. Van der Vijah and A. Bast, *Biochem. Biophys. Res. Commun.,*2002, **295**, 9; (q) R. M. Horowitz and B. Gentili, *J. Agric. Food Chem.,*1969, **17**, 696; (r) G. E. DuBois, G. A. Crosby and P. Saffron, *Science*, 1977, **195**, 397; (s) G. E. DuBois, G. A. Crosby and R. A. Stephenson, *J. Med. Chem.,*1981, **24**, 408; (t) M. L.Whitelaw, H. J. Chung and J. R. Daniel, *J. Agric. Food Chem.,*1991, **39**, 663; (u) A. Bakal, *Alternative Sweeteners*, 2nd ed.; Dekker: New York, 1991; (v) B. O. Garcia, J. Castillo, M. J. Del Bano and J. Lorente, *J. Agric. Food Chem.,*2001, **49**, 189.

4 (a) S. D. Roughly and A. M. Jordan, *J. Med. Chem.,* 2011, **54***,* 3451;(b) S. W. Martin, P. Glunz, B. R. Beno, C. Bergstrom, J. L. Romine, E. S. Priestley, M. Newman, M. Gao, S. Roberts, K. Rigat, R. Fridell, D. Qiu, G. Knobloh and Y. K. Wang, *Bioorg. Med. Chem. Lett.,*2011, **21***,* 2869.

5 (a) G. Satyanarayana and M. Maier, *Tetrahedron,* 2008, **64**, 356; (b) I. Ambrogio, S. Cacchi, G. Fabrizi, A. Goggiamani and S. Galla, *Synlett.,* 2009, 620; (c) J. M. Kim, K. H. Kim, T. H. Kim and J. N. Kim, *Tetrahedron Lett.*, 2008, **49**, 3248; (d) P. Colbon, J. Ruan, M. Purdie, K. Mulholland and J. Xiao, *Org. Lett*., 2011, **13**, 5456; (e) E. Alacid and C. Najera, *Adv. Synth. Catal.,* 2007, **349***,* 2572; (f) J. Mo, L. Xu, J. Ruan, S. Liu and J. Xiao, *Chem. Commun.,* 2006, 3591; (g) V. Calo, A. Nacci, A. Monopoli and V. Ferola, *J. Org. Chem.,* 2007, **72***,* 2596; (h) A. Briot, C. Baehr, R. Brouillard, A. Wagner and C. Mioskowski, *J. Org. Chem.,*2004, **69***,* 1374; (i) X. Fang, X. Yang, X, Yang, M. Zhao, G. Chen and F. Wu, *Tetrahedron Lett.*, 2006, **47**, 8231; (j) G. Satyanarayana and M. Maier, *Tetrahedron,* 2012, **68**, 1745; (k) J. B. Melpolder and R. F. Heck, *J. Org. Chem.,*1976, 41*,* 265; (l) S. Bouquillon, B. Ganchegui, B. Estrine, F. Henin and J. Muzart, *J. Organomet. Chem.*, 2001, **634**, 153.

6 (a) R. F. Heck, *J. Am. Chem. Soc*., 1968, **90***,* 5518; (b) K. Matoba, S. I. Motofusa, C. S. Cho, K. Ohe and S. Uemura, *J. Organomet. Chem.*, 1999, **574***,* 3; (c) M. Chen, J. Wang, Z. Chai, C. You and A. Lei, *Adv. Synth. Catal.,* 2012**, 354***,* 341; (d) L. Huang, Q. Ji, H. Kefan and H. Jiang, *Org. Lett*., 2013, **15**, 2330.

7 L. Yuting, Y. Fan, W. Kun and W. Yangjie, *Tetrahedron*, 2010, **66**, 1244.

8 V. Mari, A. M. S. Murugaiah and K. Nagaiah, *Eur. J. Org. Chem*., 2012, 4694.

9 As suggested by the referee, two reactions were performed by replacing CuCl (5 mol%) with Ag_2CO_3 (5 mol%) in MeCN and DMSO (Table 1, entries 2 and 20). While 28% yield was obtained with MeCN as solvent, no product was obtained with DMSO.

10 (a) A. Nordqvist, C. Bjorkelid, M. Andaloussi, A. M. Jansson, S. L. Mowbray, A. Karlen and M. Larhed, *J. Org. Chem.,* 2011, **76**, 8986; (b) K. S. Yoo, C. H. Yoon and K. W. Jung, *J. Am. Chem. Soc.,* 2006, **128**, 16384.

11 H. Tsukamoto, T. Uchiyama, T. Suzuki and Y. Kondo, *Org. Biomol. Chem.,* 2008, **6**, 3005.

12 K. S. Yoo, C. P. Park, C. H. Yoon, S. Sakaguchi, J. O'Neill and K. W. Jung, *Org. Lett.*, 2007, **9**, 3933.

13 (a) A. N. Shestopalov, A. A. Shestopalov and L. A. Rodinovskaya, *Synlett*., 2008, 1; (b) C. Simon, T. Constantieux and J. Rodriguez, *Eur. J. Org. Chem*., 2004, **24**, 4957; (c) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc*., 2004, **126**, 9906; (d) J. Luo, L.-W. Xu, R. A. S. Hay and Y. Lu, *Org. Lett*., 2008, **11**, 437; (e) P. Maity and S. D. Lepore, *J. Org. Chem*., 2009, **74**, 158; (f) A. R. Katritzky, Z. Wang, M. Wang, C. R. Wilkerson, C. D. Hall and N. G. Akhmedov, *J. Org. Chem*.,2004, **69**, 6617; (g) N. Ismabery and R. Lavila, *Chem. Eur. J.*,2008, **14**, 8444.

14 (a) D. Basavaiah and K. Muthukumaran, *Tetrahedron*, 1998, **54**, 4943; (b) J. L. Bras and J. Muzart, *Synthesis*, 2011, **22**, 3581; (c) J. Muzart, *Tetrahedron*, 2005, **61**, 4179; (d) R. Kumareswaran and Y. D. Vankar, *Synthetic Commun.*, 1998, **28**, 2291; (e) F. Coelho, B. R. V. Ferreira, R. V. Pirovani and L. G. Souza-Filho, *Tetrahedron*, 2009, **65**, 7712; (f) O. A. C. Antunes, R. Perez, D. Veronese and F. Coelho, *Tetrahedron Lett.*, 2006, **47**, 1325; (g) N. Sunder and S. V. Bhat, *Synthetic Commun.*, 1998, **28**, 2311.

15 (a) A. Segura and G. C. Aurelio, *Org. Lett.*,2007, **9**, 3667; (b) M. Pucheault, S. Darses and J. P. Genet, *Tetrahedron Lett.*, 2002, **43**, 6155; (c) Y. Ma, C. Song, C. Ma, Z. Sun, Q. Chai and M. B. Andrus, *Angew. Chem. Int. Ed*., 2003, **42**, 5871.

16 As suggested by the referee, LiOAc (5.0 equiv.) was employed instead of LiCl. The referee reasoned that the detrimental effect of LiCl could be attributed to the fact that it generates *in situ* $PdCl_2$, a precursor ineffective for the reaction. LiOAc had similar detrimental effect on reaction outcome (8% yield). This further corroborates the involvement of cationic Pd(II) species in the catalytic cycle.

17 (a) J. Tsuji, Palladium Reagents and Catalysts, Wiley, Chichester, 2004; (b) P. M. Henry, *Handbook of Organopalladium Chemistry for*

Organic Synthesis, Vol. 2 (Ed.: E. Negishi), Wiley, New York, 2002, p. 2119; (c) J. Tsuji, *Synthesis,*1984, 369.

18 (a) H. Peng and G. Liu, *Org. Lett*., 2011, **13**, 772. (b) J. Chen, X. Lu, W. Lou, Y. Ye, H. Jiang and W. Zeng, *J. Org. Chem*., 2012, **77**, 8541; (c) L. Zhao and X. Lu, *Org. Lett*., 2002, **4**, 3903. (d) S. Lin and X. Lu, *Org. Lett*., 2010, **12**, 2536.

19 N. R. Conley, L. A. Labios, D. M. Pearson, C. C. L. McCroy and R. M. Waymouth, *Organometallics,* 2007, **26**, 5447

20 I. W. C. E. Arends, G. J. Ten Brink and R. A. Shledon. *J. Mol. Catal. A: Chem.* 2006, **251**, 246.