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SHORT COMMUNICATION

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Ligated Regioselective Pd^{II} Catalysis to Access β-Aryl-Bearing Aldehydes, Ketones, and β-Keto Esters

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Dedicated to Dr. Jhillu Singh Yadav

Keywords: β-Aryl carbonyl compounds / Palladium / Homogeneous catalysis / Allylic compounds / Arylboronic acids / Dihydrochalcones

By employing ligands in the Pd^{II}-mediated arylative isomerization of allyl alcohols, a milder and regioselective access to the versatile building blocks β-aryl aldehydes and ketones was developed. This new and chelation-controlled protocol enabled the compatibility of wide range of functionalities to generate dihydrochalcones, α-benzyl-α′-alkyl acetones, dihydrocinnamaldehydes, and α-benzyl β-keto esters (from Baylis–Hillman adducts). A practical multigram synthesis of an intermediate for Propafenone was also demonstrated.

Introduction

The "β-aryl carbonyl" motif has attracted considerable attention, because of the widespread prevalence in the medicinally important natural products and frequent use of β-aryl aldehydes and ketones as synthetic building blocks for drug candidates, agrochemicals, and materials. Naturally occurring flavanones and dihydrochalcones have been known to exhibit a variety of beneficial effects on human health and to protect plants. Flavanones are known to exhibit antioxidant, anti-inflammatory, antiviral, anticancer, and cardiovascular activity. Neohesperidine is widely used as flavor enhancer in foods and artificial sweeteners (Figure 1).[1] Recent examples utilizing 3-aryl propanals or propanones to construct diverse scaffolds or drug-like compounds include H-DAC enzyme inhibitors, c-met inhibitors, S1P1 inhibitors, IKK-β kinase inhibitors, anti-HIV agents, CCR10-antagonists, $5HT_4$ agonists, CXCR4 antagonists, glucan synthase inhibitors, orexin antagonists, HCV inhibitors, and leukotriene receptor agonists.[2]

The Pd^0-catalyzed coupling of allyl alcohols with aryl halides is one of the direct strategies to generate β-arylethyl carbonyl compounds. However, it suffers from reduced regioselectivity (β-aryl carbonyl vs. α-aryl carbonyl), reduced chemoselectivity (aryl carbonyl vs. aryl allyl alcohol), and

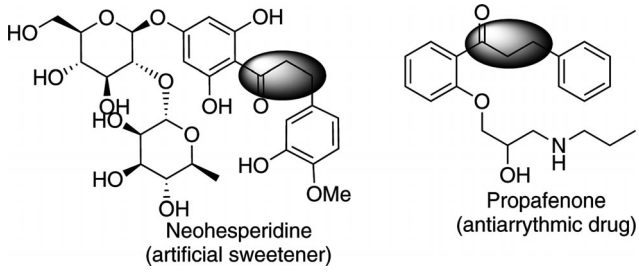

Figure 1. Examples for widely prevailing β-aryl carbonyl compounds.

the requirement of high temperature and base. Importantly, it offers less hope to generate halogen-appended aryl aldehydes or ketones (Figure 2).[3] Halogen substitution on aryl ring is often employed as the versatile handle for diversification during lead optimization.[4] In addition, 3-aryl aldehydes are prone to aldol condensation at high temperature in the presence of base. In continuation of our interest to synthesize diverse flavanone derivatives, we sought a selective protocol with broad scope through an alternative oxidative Pd^{II} coupling because of the mild conditions required and the selectivity of this method.[5]

Very few reports exist on oxidative coupling with aryl halide equivalents.[6] While these methods offer the advantage of "low reaction temperature", they suffer from limited scope [(a) toxicity of aryl precursors (arylmercuric salts and phenylantimony chlorides), (b) AcOH as cosolvent, precluding acid-sensitive functionalities, and (c) poor yield]. The total absence of ligand-modulated catalysis has further limited the scope of these reactions from the development of selective applications in organic synthesis.[7] Herein, we

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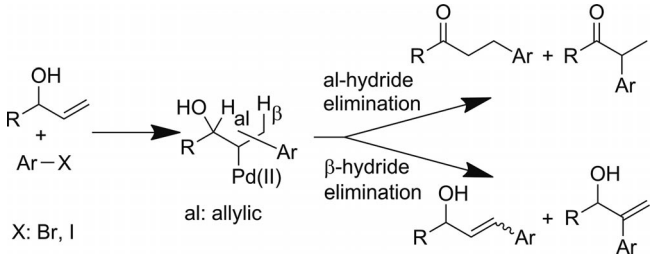


Figure 2. Heck arylation of allyl alcohol: multiple pathways.

report the first ligand-promoted regioselective coupling of allyl alcohols with arylboronic acids as arylpalladium(II) precursors.

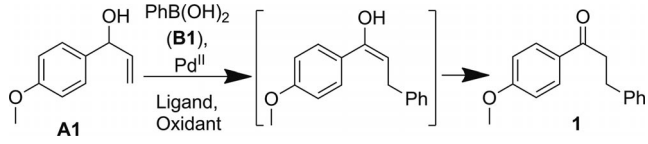
Results and Discussion

Regioselective vinylative isomerization was investigated with **A1** and $PhB(OH)_2$ (**B1**) as the model substrates (Table 1). Secondary alcohol **A1** was chosen instead of a primary alcohol, considering the stability of the product (ketone vs. aldehyde). In the absence of ligands, the reactions gave inferior yields (entries 1–5). The phosphane ligands were completely unsuitable (entries 6–9). The chelating nitrogen ligands gave improved yields over monodentate pyridine (entries 10–13). Dmphen was identified as the best ligand (entry 13).[8] The selection of oxidant was also critical. Ag_2CO_3 was found to be a superior oxidant. Other oxidants like dioxygen, $Cu(OAc)_2$, AgOAc, and Ag_2SO_4 gave disappointing results (entries 14–18). Replacement of MeCN with other coordinating solvents like DMF and dioxane proved less productive (entries 19 and 20).

The highest yield was observed by enhancing the amount of catalyst (entry 21). Although the reaction rate could be accelerated with $Pd_2(dba)_3$ as the Pd^{II} precursor, there was no advantage in terms of yield (entry 22). Neither the α-arylation product (α-aryl allyl alcohol or α-aryl carbonyl) nor the β-elimination product (Scheme 1) was observed, which indicates total regioselectivity in the respective migratory aryl insertion and hydride elimination steps in the catalytic cycle. The formation of byproducts from the isomerization of **A1** [1-(4-methoxyphenyl)propan-1-one] and allylation,[9] isolated in varying amounts in the less productive reactions, was significantly suppressed under the optimized protocol.

Armed with an efficient set of conditions (entry 21, Table 1), we next investigated the influence of electronic and steric factors by coupling diverse allyl alcohols and arylboronic acids (Schemes 1–5). The electron-poor arylboronic acids gave good yields, even though they have been reported to be poor substrates in chelation-controlled oxidative Heck Pd^{II} catalysis (**2**–**4**, **18**, and **27**).[7a] The electron-rich arylboronic acids gave comparable yields (**5**, **6**, **18**, **32**, and **36**). The sterically encumbered arylboronic acids underwent efficient coupling (**7**, **8**, and **26**). The halogen-bearing arylboronic acids and allyl alcohols gave the desired products (**9**, **13**, **22**, **28**, and **35**, **36**) chemoselectively without concomitant formation of competitive Pd^0-catalyzed Heck, Suzuki, and dehalogenation byproducts. However, 4-$IPhB(OH)_2$ gave the product in only moderate yield (compound **29**).[10]

Table 1. Identification of productive arylative isomerization.[a]

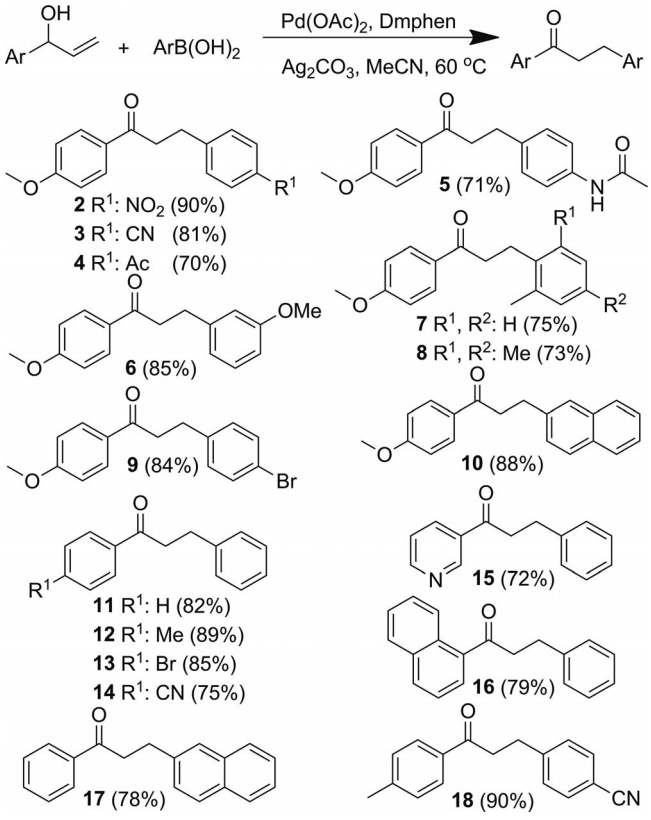


Entry	Pd	Ligand	Oxidant	Solvent	Yield [%][b]
1[c]	$Pd(OAc)_2$		O_2	MeCN	0
2	$Pd(OAc)_2$		BQ[d]	MeCN	0
3[c]	$Pd(OAc)_2$		$Cu(OAc)_2$	MeCN	29
4[c]	$Pd(OAc)_2$		AgOAc	DMF	10
5[c]	$Pd(OAc)_2$		Ag_2CO_3	MeCN	38
6	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	MeCN	0
7	$Pd(OAc)_2$	X-Phos[d]	Ag_2CO_3	MeCN	0
8	$Pd(OAc)_2$	DPPP[d]	Ag_2CO_3	MeCN	0
9	$Pd(TFA)_2$	DPPP	O_2	Dioxane	0
10	$Pd(OAc)_2$	Pyridine	Ag_2CO_3	MeCN	28
11[c]	$Pd(OAc)_2$	Phen[d]	Ag_2CO_3	MeCN	48
12	$Pd(OAc)_2$	Bpy[d]	Ag_2CO_3	MeCN	46
13	$Pd(OAc)_2$	Dmphen	Ag_2CO_3	MeCN	70
14	$Pd(OAc)_2$	Dmphen[d]	O_2	MeCN	0
15	$Pd(OAc)_2$	Dmphen	O_2	DMF	10
16[c]	$Pd(OAc)_2$	Dmphen	$Cu(OAc)_2$	MeCN	40
17	$Pd(OAc)_2$	Dmphen	Ag_2SO_4	MeCN	0
18[c]	$Pd(OAc)_2$	Dmphen	AgOAc	MeCN	38
19	$Pd(OAc)_2$	Dmphen	Ag_2CO_3	DMF	10
20	$Pd(OAc)_2$	Dmphen	Ag_2CO_3	Dioxane	0
21[e]	$Pd(OAc)_2$	Dmphen	Ag_2CO_3	MeCN	92
22[e,f]	$Pd_2(dba)_3$	Dmphen	Ag_2CO_3	MeCN	70
23[c,e,g]	$Pd(OAc)_2$	Dmphen	Ag_2CO_3	MeCN	20
24[c,e]	$Pd(OAc)_2$	Dmphen		MeCN	10

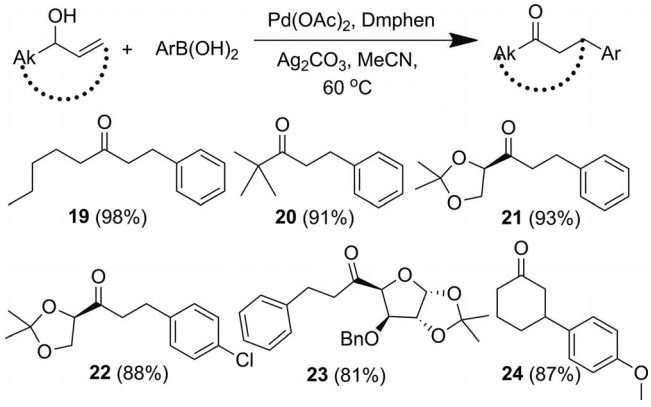
[a] Unless specified, the reaction was carried out with **A1** (1.0 mmol), **B1** (2.0 mmol), Pd (0.05 equiv.), ligand (0.1 equiv.), and solid oxidant (2.0 equiv.) or O_2 (in a balloon, 1 atm.), at 60 °C in a solvent (3.0 mL) for 24.0 h. [b] Isolated yield (average of two runs). [c] The starting material was not consumed fully. [d] BQ = benzoquinone, X-Phos = 2-(dicyclohexylphosphanyl)-2′,4′,6′-triisopropylbiphenyl, Dmphen = 2,9-dimethyl-1,10-phenanthroline, Phen = 1,10-phenanthroline, DPPP = 1,3-bis(diphenylphosphanyl)-propane, Bpy = 2,2′-bipyridyl. [e] Pd (0.1 equiv.), Dmphen (0.2 equiv.). [f] Time: 6.0 h. [g] LiCl as additive (5.0 equiv.).

In terms of olefinic substitution, seven different classes of allyl alcohols underwent arylation with notable yields. The 1-heteroaryl and 1-bicyclic allyl alcohols gave the corresponding products with reasonable yields (compounds **15** and **16**). Both 1-aryl- and 1-alkyl-substituted substrates gave the coupling products with excellent yields. The carbohydrate-derived chiral synthons, bearing the sensitive acetonide functionality, also underwent efficient cross-coupling (**21**–**23**). Even the β-substituted cyclic allyl alcohol was arylated successfully (compound **24**) (Scheme 2).

The simple allyl alcohol (prop-2-en-1-ol), known to be a poor substrate[6d] in the oxidative Heck catalysis of the β-hydride elimination pathway, reacted efficiently to deliver a range of dihydrocinnamaldehydes (compounds **25**–**28**) in a highly regioselective fashion, undeterred by varying steric and electronic factors (Scheme 3). Even the cumbersome β-



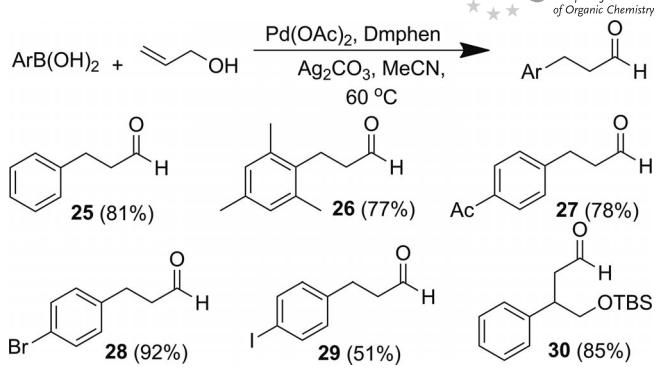
Scheme 1. Preparative scope of dihydrochalcones.



Scheme 2. Synthesis of α,α′-dialkyl ketones from 1-alkyl (secondary) allyl alcohols.

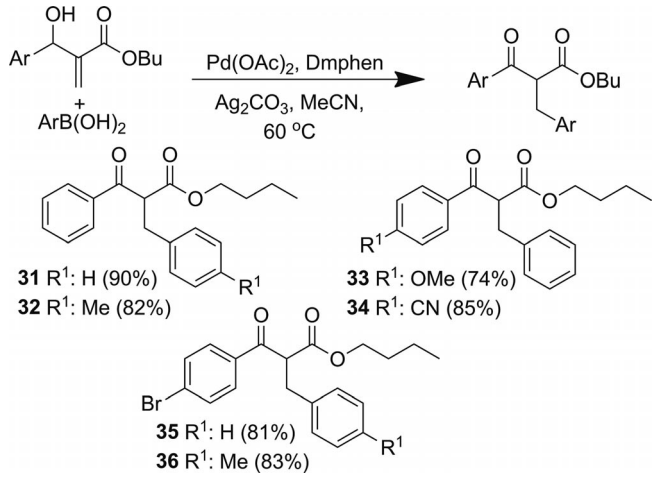
substituted allyl alcohol furnished the expected products with the highly acid-labile group (OTBS) intact (compound **30**).

To further expand the scope, we investigated the manipulation of Baylis–Hillman adducts to derive α-benzyl-β-keto esters, which are valuable building blocks with extensive utility to construct heterocyclic compounds.[11] These adducts, differing in aryl substitution (electron-donating, electron-withdrawing, and halogen groups) underwent efficient coupling regioselectively (Scheme 4). 1,3-Dicarbonyl compounds are prone to decarboxylation under elevated temperature. No decarboxylation and β-elimination products



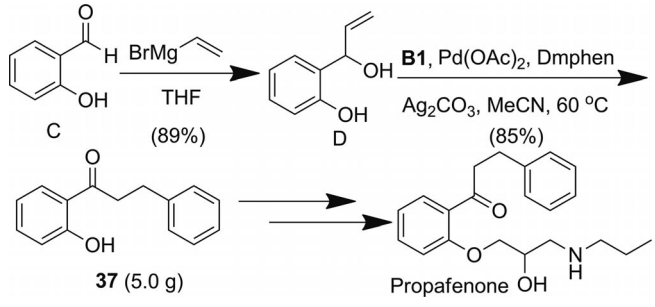
Scheme 3. Synthesis of dihydrocinnamaldehydes from primary allyl alcohols.

were observed. Thus this method offers an advantage over high-temperature and decarboxylation-susceptible classical Heck coupling.



Scheme 4. Direct synthesis of α-benzyl β-keto esters from Baylis–Hillman adducts.

This method is amenable to multigram synthesis, as demonstrated in Scheme 5.[12] Dihydrochalcone derivative **37**, an intermediate of Propafenone, was synthesized in two high-yielding steps from inexpensive salicylaldehyde by treatment with a vinyl Grignard reagent and subsequent arylation. No protection of the phenol group was necessary, which indicates the usefulness of the method.



Scheme 5. Multigram synthesis of the Propafenone intermediate.

The formation of products **21** and **30** was investigated under previously reported conditions (DMSO-AcOH as solvent).[6c] While **21** was obtained only in 20% yield, it was not possible to obtain **30** at all. This indicated the compatibility of the present method in the case of substrates bearing acid-sensitive groups.

Preliminary mechanistic investigation suggested a chelation-controlled cationic Pd^{II} catalytic cycle. Addition of LiCl suppressed product formation, indicating the neutralization of the cationic complex by halide coordination, thereby blocking the vacant site necessary for olefin coordination (entry 23, Table 1). Incomplete reaction on exclusion of oxidant supported the generation of Pd^0 and the necessity of oxidant to regenerate Pd^{II} (entry 24). A detailed experimental and theoretical investigation of the mechanism is in progress.

Conclusions

A ligand-mediated Pd^{II}-catalyzed regioselective arylation was demonstrated to yield highly functionalized β-aryl carbonyl derivatives in high yields. The mild conditions (acid free, base-free, and relatively low temperature) allowed the tolerance of a wider range of functionalities than previously possible. This methodology prospers as an alternative to "Rh-catalyzed arylboronic addition to enones" with the advantage of using inexpensive and stable allyl alcohols as enone equivalents. Incorporation of ligands has now made the method feasible for asymmetric arylation, which is to be reported in due course.

Experimental Section

General Procedure for the Synthesis of β-Aryl Carbonyl Compounds from Allyl Alcohols: A mixture of arylboronic acid (2.00 mmol), $Pd(OAc)_2$ (0.022 g, 0.10 mmol), and 2,9-dimethyl-1,10-phenanthroline (0.042 g, 0.20 mmol), allyl alcohol (1.00 mmol), and Ag_2CO_3 (2.00 mmol) was dissolved in acetonitrile (3.0 mL) in a 10 mL round-bottomed flask. The mixture was vigorously stirred at 60 °C for 24.0 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (25.0 mL) and water (25.0 mL) and filtered through a Celite pad. The filtrate was transferred to a separatory funnel. The organic layer was washed with water and brine, dried with anhydrous Na_2SO_4 (s), and concentrated in vacuo. The residue was purified by column chromatography by using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

Supporting Information (see footnote on the first page of this article): General experimental details, experimental procedures, and analytical data of all the compounds.

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[10] The competitive Heck product was also observed. Further optimization of the oxidant led to the exclusive formation of the desired product **29** (> 85% yield), to be reported in a separate communication.

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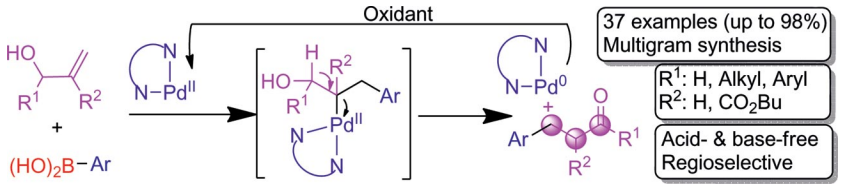

Ligand deployment was critical in developing an acid-free mild method to access β-aryl aldehydes and ketones from allyl alcohols with more tolerance of functionalities than previously possible. This regioselective and chelated Pd^{II} catalysis also allowed the transformation of Baylis–Hillman adducts to β-aryl β-keto esters and the multigram synthesis of an intermediate for Propafenone.

Access to β-Aryl Carbonyl Compounds

Keywords: β-Aryl carbonyl compounds / Palladium / Homogeneous catalysis / Allylic compounds / Arylboronic acids / Dihydrochalcones

