Cross-Coupling

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Palladium-Catalyzed Dehydrative Heck Olefination of Secondary Aryl Alcohols in Ionic Liquids: Towards a Waste-Free Strategy for Tandem Synthesis of Stilbenoids**

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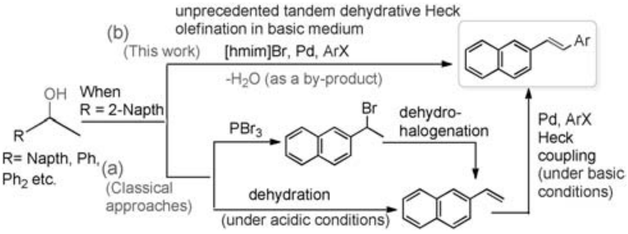
The development of new environmentally benign, tandem, cross-coupling strategies constitute one of the most cherished goals of contemporary organic synthesis because of several inherently unique benefits in terms of efficacy, economy, and environmental impact.[1,2] The above objective becomes additionally fruitful if expensive and unstable coupling partners can be replaced with readily available and inexpensive precursors.[1d]

The palladium-catalyzed cross-coupling of styrenes with aryl halides, known as the Heck reaction[3] is a powerful method for the synthesis of bioactive stilbenoids, including the anticancer agent resveratrol, DMU-212, et cetera. However, substituted styrenes are not frequently available and involve multistep synthesis in addition to the problem of storage because of their propensity towards polymerization.[1c] Thus, realization of a tandem Heck reaction by in situ formation of styrene and subsequent coupling with an aryl halide would be practically useful.

Currently, alcohols that are readily accessible have received great attention as precursors in various tandem oxidative[1a,4]/dehydrative[1d] cross-coupling strategies. However, direct use of secondary aryl alcohols as an in situ source of styrene (by dehydration) in Heck coupling has remained unexplored. The main reason is the cross-contamination of reagents/catalysts resulting from different media requirements in the Heck (basic) and dehydration (acidic) steps. Thus designing the above two steps to occur in one pot is a major problem. Moreover, secondary aryl alcohols under Heck-type conditions are generally converted into the respective carbonyls[5] through isomerization[5a] or oxidation[5b] processes.

In contrast, secondary aryl-substituted alkyl bromides (instead of secondary aryl alcohols) have been utilized for the synthesis of stilbenoids through a dehydrohalogenation/Heck methodology.[6] However, such substituted bromides are sometimes commercially unavailable or synthesized by the bromination of aryl alcohols with PBr_3 (Scheme 1), thus not ideal substrates from an atom-economical point of view.



Scheme 1. Prevalent approaches (a) and present work (b) for the conversion of secondary aryl alcohols into stilbenoids.

Our ongoing interest on the use of ionic liquids[7] (ILs) as well as the development of various tandem cross-coupling strategies[8] encouraged us to explore a hitherto unknown approach towards waste-free dehydrative Heck olefination through the concurrent coupling of in situ formed styrenes with aryl halides in ILs where water is the only by-product (Scheme 1).

After an initial survey of reaction conditions, 4-iodoanisole (0.2 g, 0.85 mmol, 1 equiv) was reacted with 1-(naphthalen-2-yl)ethanol (**1a**, 1.5 equiv) in [hmim]Br using $Pd(OAc)_2$ (4 mol %), PPh_3 (5 mol %), and Et_3N (1.5 equiv) as a base under microwave (MW) irradiation (120W, 150 °C) for 40 minutes (Table 1, entry 1). Thereafter, the crude reaction mixture was analyzed preferably by HPTLC (over HPLC/GC),[9] and **1b** was obtained in only 8 % yield (Figure 1 and Table 1, entry 1). To further increase the yield of **1b**, various other organic and inorganic bases were rapidly screened through HPTLC analysis (Figure 1 and Table 1, entries 2–9), and HCOONa surprisingly provided **1b** in 69 % yield (56 % upon isolation; entry 9). Furthermore, the synergism of two bases,[10] that is HCOONa (1.5 equiv) and piperidine (1 equiv), not only increased the reaction performance (entry 16), but also reduced the reaction time to 15 minutes from 40 minutes.

Subsequently, a detailed optimization study was conducted to evaluate the effect of other ILs, palladium catalysts, and additives (Table 2). However, commonly used ILs such as $[bmim]BF_4$ and $[bmim]PF_6$ for the Heck reaction[11] provided **1b** in very low yield (entries 2 and 3) because of their inefficiency for the dehydration of **1a** in comparison to [hmim]Br. Interestingly, no reaction was observed with DMF (entry 5), thus emphasizing the crucial role of the IL. Use of

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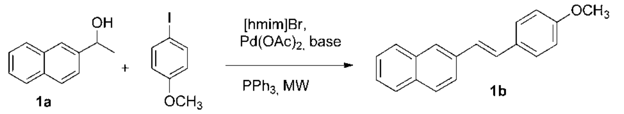
Table 1: Screening of different bases for the palladium-catalyzed tandem dehydrative Heck coupling in [hmim]Br.[a]



Entry	Base	Equiv.	*t* [min]	Yield [%][b]
1	Et_3N	1.5	40	8
2	Bu_3N	1.5	40	30
3	piperidine	1.5	40	32
4	DBU	1.5	40	5
5	Cs_2CO_3	1.5	40	6
6	K_2CO_3	1.5	40	7
7	NaOAc	1.5	40	n.d.
8	NH_4OAc	1.5	40	13
9	HCOONa	1.5	40	69 (56)[c]
10	$HCOONH_4$	1.5	40	(41)[c]
11	HCOOK	1.5	40	(52)[c]
12	HCOONa	1	40	(50)[c]
13	HCOONa	2.5	40	(52)[c]
14	HCOONa + K_2CO_3	1.5+1.5	15	(59)[c]
15	HCOONa + piperidine	1.5+1.5	15	(64)[c]
16	HCOONa + piperidine	1.5+1.0	15	(69)[c]
17	HCOONa + piperidine	1.5+0.5	15	(66)[c]

[a] CEM monomode microwave; General conditions: 4-iodoanisole (0.85 mmol), **1a** (1.28 mmol), $Pd(OAc)_2$ (4 mol%), PPh_3 (5 mol%), base, [hmim]Br (1.5 g), 120 W, 150 °C. [b] Yields determined by HPTLC using a reference standard. [c] Yield of isolated product **1b** (in parentheses). hmim = 1-*n*-hexyl-3-methylimidazolium, n.d. = not determined.

$[PdCl_2(PPh_3)_2]$ as a catalyst along with LiCl[8b,12] as an additive proved optimum (entry 10). The product **1b** was obtained with exclusively *E* selectivity (based upon NMR spectroscopy; see the Supporting Information). Earlier, this *E* isomer (**1b**), a naphthalene analogue of the anticancer agent combretastatin,[13] was isolated in 20% yield after a multistep Wittig protocol and tedious separation of the *E*/*Z* isomers.[13] In contrast, conventional heating (oil bath, 150 °C) of **1a** using [hmim]Br provided **1b** in low yield (20% after 14 h) along with polymeric side products (entry 13), thus emphasizing the crucial role of the MW conditions, wherein creation of microscopic hot spots[14] (having temperature well above 150 °C) are probably responsible for significant rate enhancement.

Mechanistically, it is presumed that the incipient styrene (formed in situ by IL/MW assisted dehydration[7] contemporary to bromination/dehydrobromination[15] sequence) simultaneously undergoes palladium-catalyzed cross-coupling[8b] with an aryl halide leading to formation of stilbenes in one pot (Scheme 2).

The utility of the optimized protocol was additionally ascertained through tandem synthesis of a diverse array of stilbenes possessing electron-donating as well as electron-withdrawing groups either on the secondary aryl alcohol or on the aryl halide moiety (Table 3). Notably, polyaromatic alcohols (entries 1–5 and 7–9) provided good yields whereas electron-deficient (entry 10) or methoxylated benzyl alcohols (entries 11 and 12) provided moderate yields as a result of the polymerization tendency of the intermediate styrene[16] and formation of the dehalogenated aryl halide as a side product. Also, coupling of aryl alcohol with π-electron-deficient heteroaryl halides[17] (entry 6) afforded **6b** in 47% yield. In addition, the developed methodology successfully provided the hydroxylated stilbenoids (entries 2, 7, and 9), including a naphthyl analogue of the anticancer agent combretastatin (**2b**),[13] in very good yields without any protection/deprotection manipulations. However, a primary alcohol (entry 13) was found to be reluctant to undergo dehydration and subsequent Heck coupling.

Under similar reaction conditions, the acetylated derivative of alcohols underwent a novel one-pot tandem deacetoxylative Heck coupling to afford the corresponding stilbenes in good yields (Scheme 3).

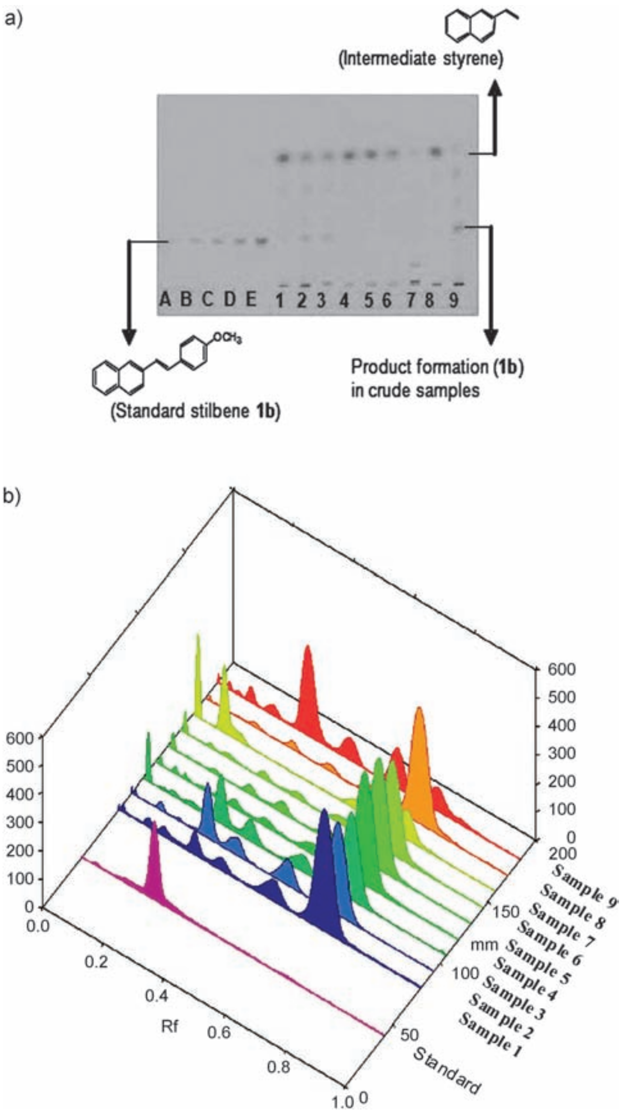
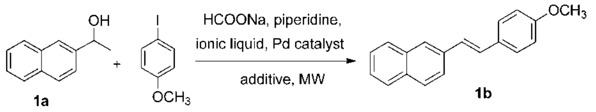


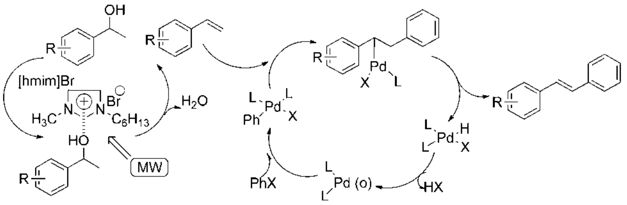
Figure 1. a) HPTLC CCD image at 254 nm: standard samples (A–E) of **1b** at different concentrations; samples (1–9 correspond to Table 1, entries 1–9) indicating formation of **1b**. b) Three-dimensional HPTLC densitogram of samples 1–9 (all tracks at 254 nm). Yields expressed in terms of percent peak area, wherein yield varies from 0 to 69% (Table 1, entries 1–9, and see the Supporting Information). Rf = retention factor.

Table 2: Screening of palladium catalysts, ILs, and additives for the tandem dehydrative Heck coupling under microwave irradiation.[a]

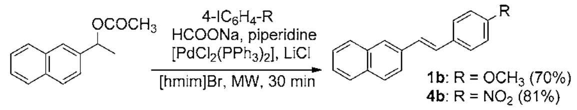


Entry	Ionic liquid	Pd catalyst	Ligand	Additive	t [min]	Yield[b]
1	[hmim]Br	$Pd(OAc)_2$	PPh_3	–	15	69
2	[bmim]BF_4	$Pd(OAc)_2$	PPh_3	–	25	22
3	[bmim]PF_6	$Pd(OAc)_2$	PPh_3	–	25	21
4	[bmim]OH	$Pd(OAc)_2$	PPh_3	–	25	19
5	DMF[c]	$Pd(OAc)_2$	PPh_3	–	50	n.d.[d]
6	[hmim]Br	$PdCl_2$	PPh_3	–	15	71
7	[hmim]Br	$[Pd(PPh_3)_4]$	–	–	15	68
8	[hmim]Br	$Pd(CF_3COO)_2$	PPh_3	–	15	72
9	[hmim]Br	$[PdCl_2(PPh_3)_2]$	–	–	15	74
10	[hmim]Br	$[PdCl_2(PPh_3)_2]$	–	LiCl	15	78
11	[hmim]Br	$[PdCl_2(PPh_3)_2]$	–	Ag_2O	15	67
12	[hmim]Br	$[PdCl_2(PPh_3)_2]$	–	Ag_2CO_3	15	62
13	[hmim]Br[e]	$[PdCl_2(PPh_3)_2]$	–	LiCl	840	20

[a] CEM monomode microwave; General conditions: 4-iodoanisole (0.85 mmol), **1a** (1.28 mmol), Pd catalyst (4 mol%), ligand (5 mol%), additive (8 mol%), HCOONa (1.28 mmol), piperidine (0.85 mmol), ionic liquid (1.5 g), 120 W, 150 °C. [b] Yield of isolated product. [c] Ionic liquid was replaced with 4 mL of DMF. [d] Not detected on the basis of NMR spectroscopy. [e] Conventional heating (oil bath 150 °C) instead of microwave. DMF = *N,N'*-dimethylformamide, bmim = 1-butyl-3-methylimidazolium.

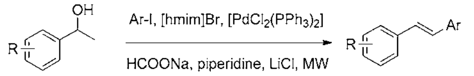


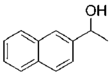
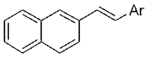
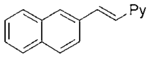
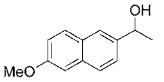
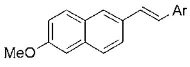
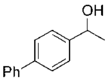
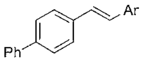
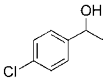
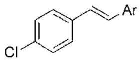
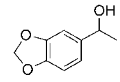
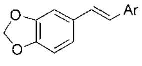
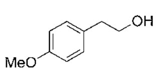
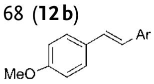
Scheme 2. Proposed mechanism for tandem dehydrative Heck coupling in an IL under microwave irradiation.



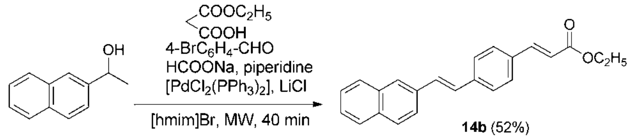
Scheme 3. Deacetoxylative Heck sequence.

Table 3: Substrate scope of tandem dehydrative Heck coupling.[a]



Entry	Aryl alcohol	Ar (Aryl iodide)	t [min]	Yield [%][b]
				
1		$4-MeOC_6H_4$	15	78 (**1b**)
2		$4-HOC_6H_4$	30	77 (**2b**)
3		$4-ClC_6H_4$	15	84 (**3b**)
4		$4-NO_2C_6H_4$	15	89 (**4b**)
5		$4-CF_3C_6H_4$	15	83 (**5b**)
				
6		$3-C_5H_4N$	25	47 (**6b**)
				
7		$4-HOC_6H_4$	30	75 (**7b**)
8		$4-COCH_3C_6H_4$	15	76 (**8b**)
				
9		$4-HOC_6H_4$	30	74 (**9b**)
				
10		$4-COCH_3C_6H_4$	15	59 (**10b**)
				
11		$4-COCH_3C_6H_4$	15	63 (**11b**)
12		$4-CNC_6H_4$	15	68 (**12b**)
				
13		$4-MeOC_6H_4$	30	n.d.[c] (**13b**)

[a] CEM monomode microwave; General conditions: aryl halide (0.85 mmol), aryl alcohol (1.28 mmol), $[PdCl_2(PPh_3)_2]$ (4 mol%), LiCl (8 mol%), HCOONa (1.28 mmol), piperidine (0.85 mmol), [hmim]Br (1.5 g), 120 W, 150 °C. [b] Yield of isolated product. [c] Not detected.



Scheme 4. Tandem dehydration/Heck/Knoevenagel–Doebner condensation sequence.

Subsequently, another novel tandem strategy involving hitherto unknown sequential dehydration/Heck/Knoevenagel–Doebner condensation into the stilbene cinnamoyl hybrid **14b**, a naphthalene[13] analogue of a PTPIB inhibitor,[18] was successfully accomplished in one pot with 52% yield (Scheme 4) instead of the reported tedious seven-step protocol.[18]

In conclusion, a new one-pot approach towards a waste-free strategy for the preparation of stilbenoids involving a dehydrative Heck sequence assisted by the ionic liquid [hmim]Br has been developed. The method utilizes readily accessible and inexpensive secondary aryl alcohols as an in situ source of styrenes and do not require an inert atmosphere. The developed method is an efficient, atom-economic, and ecofriendly alternative to the exisiting multistep approaches as it eliminates the isolation of the polymerization prone styrenes, as well as protection/deprotection manipulations in the case of hydroxy-substituted stilbenoids.

Experimental Section

Representative procedure for the synthesis of 2-[(*E*)-2-(4-methoxyphenyl)ethenyl]naphthalene (**1b**): A mixture of 1-(naphthalen-2-yl)ethanol **1a** (0.22 g, 1.28 mmol), 4-iodoanisole (0.2 g, 0.85 mmol),

[$PdCl_2(PPh_3)_2$] (4 mol %), HCOONa (1.28 mmol), piperidine (0.85 mmol), and LiCl (8 mol %) in [hmim]Br (1.5 g) was irradiated under focused MW (120W, 150 °C) for 15 min. Thereafter water (20 mL) was added to the reaction mixture and the organic phase was extracted with EtOAc (2 × 25 mL). The EtOAc fraction was washed with water (2 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4, and evaporated under vacuum. The obtained residue was subsequently purified by column chromatography on silica gel (60–120 mesh size) using 2 % ethyl acetate in hexanes to give a white solid, which was then recrystallized in methanol to provide pure **1b** in 78 % yield.

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[9] The crude reaction mixture (Table 1, entry 1) could not be analyzed through the commonly used C18 reverse-phase HPLC analysis because of its precipitation in the mobile phase (e.g. in a mixture of MeOH or ACN and H_2O etc.). Similarly, GC/MS analysis of the same was unsuccessful, probably because of low volatility; hence HPTLC analysis of **1b** (Table 1, entries 1–9) was preferred over HPLC or GC/MS.

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[12] The use of LiCl as an additive was found to the reduce amount of the regioisomeric α-arylated product[3c,8b] formed along with the desired stilbene.

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[15] Transformation of the secondary aryl alcohols into styrene with [hmim]Br (Br as counter anion) preferably proceeds through dehydration and not through a bromination/dehydrobromination route (see the Supporting Information).

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