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Palladium-catalyzed tandem Heck and aldol reactions between 2-bromobenzaldehydes and functionalized alkenes leading to naphthalenes

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Abstract—2-Bromobenzaldehydes react with an array of suitably functionalized alkenes in the presence of a catalytic amount of a palladium catalyst together with a base to afford the corresponding naphthalenes in moderate to good yields.

It is well known that many carbo- and heterocycles play an important role as a basic skeleton for the design of many pharmacologically active compounds. Along with conventional routes, palladium-catalyzed reactions for such cyclic compounds have also been attempted as alternative methods because of the facility and efficiency of reaction and the wide availability of substrate.[1] During the course of our ongoing studies on palladium-catalyzed cyclization reactions for N- and O-heterocycles,[2,3] we have introduced 2-bromobenzaldehydes as a useful annulation counterpart for isobenzofuranones[3] and 1-aryl-1*H*-indazoles.[4] It was also reported by other groups that 2-halobenzaldehydes are cyclized with alkynes,[5,6] allyl or homoallyl alcohols[7] and carbonyl compounds[8] in the presence of a palladium catalyst to produce indenones (or indenols), indenes (or dihydronaphthalenes) and naphthols (or naphthalenes), respectively. Under these circumstances, herein we report on palladium-catalyzed synthesis of naphthalenes from 2-bromobenzaldehydes and suitably functionalized alkenes via consecutive Heck and aldol reactions.

The results of several attempted coupling and cyclizations between 2-bromobenzaldehyde (**1a**) and dimethyl itaconate (**2a**, **2**: $E^1 = E^2 = CO_2Me$) are listed in Table 1 (Scheme 1). When **1a** was generally treated with **2a** at 100 °C for 24 h in the presence of a catalytic amount of a palladium catalyst (5 mol %) and a base (3 equiv), the coupling and cyclized product dimethyl 2,3-naphthalenedicarboxylate (**3a**, **3**: $R^1 = R^2 = H$; $E^1 = E^2 = CO_2Me$) was produced without other identifiable products. From the activity of several palladium precursors examined under employment of NaOAc as base and THF as solvent $Pd(OAc)_2/2PPh_3$ is revealed to be the catalyst of choice (entries 1–5). Inorganic bases such as K_2CO_3 and NaOH were not effective, but Et_3N was moderately effective for the formation of **3a** under $Pd(OAc)_2/2PPh_3$/THF (entries 6–8). The kind of solvent was also critical for the effective formation of **3a** (entries 9–11). From solvents examined acetonitrile could be alternatively used, but the yield of **3a** was slightly lower than that when THF was used (entry 11). As a result, the best result in terms of both yield and complete conversion of **1a** is accomplished by the standard set of reaction conditions shown in entry 1 of Table 1.

Having established reaction conditions, various functionalized alkenes **2** were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. The reaction of **1b** and **1c** with **2a** gave the corresponding **3b** and **3c** in 50% and 61% yields, respectively. With dialkyl

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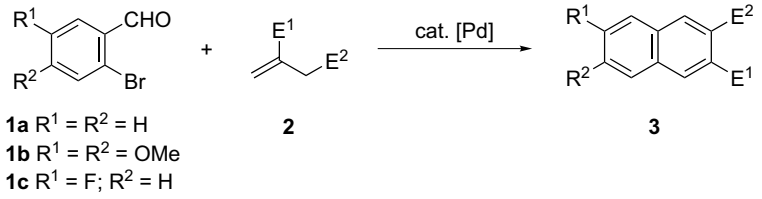
Table 1. Palladium-catalyzed coupling and cyclization between **1a** and **2a** under various conditions[a]

Entry	Palladium catalysts	Bases	Solvents	GLC yield (%)
1	$Pd(OAc)_2/2PPh_3$	NaOAc	THF	83
2	$PdCl_2/2PPh_3$	NaOAc	THF	37
3	$Pd(dba)_2/2PPh_3$	NaOAc	THF	38
4	$Pd(PPh_3)_4$	NaOAc	THF	30
5	$PdCl_2(PPh_3)_2$	NaOAc	THF	75
6	$Pd(OAc)_2/2PPh_3$	K_2CO_3	THF	16
7	$Pd(OAc)_2/2PPh_3$	NaOH	THF	Trace
8	$Pd(OAc)_2/2PPh_3$	Et_3N	THF	52
9	$Pd(OAc)_2/2PPh_3$	NaOAc	Toluene	5
10	$Pd(OAc)_2/2PPh_3$	NaOAc	Dioxane	46
11	$Pd(OAc)_2/2PPh_3$	NaOAc	MeCN	74

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), palladium catalyst (0.05 mmol), base (3 mmol), solvent (5 mL), 100 °C, for 24 h, under argon.



Scheme 1.

itaconate (**2a**–**c**[9]), alkyl 3-butenoates, which have carboalkoxy substituents at position 3, the coupling and cyclized products (**3a**, **3d** and **3e**) were formed in the range of 71–74% yields with complete disappearance of **1a** on TLC. In the case of propyl 3-butenoate (**2d**), the corresponding naphthalene **3f** was formed in only 7% yield, whereas isomerized Heck product **4** was rather produced as a major identifiable product (48%). Interestingly, when the reaction was performed under Et_3N in place of NaOAc, **3f** was formed as major product (53%) along with a small amount of **4** (5%). From the reaction between **1a** and 3-butenoic acid (**2e**), the cyclized product **3g** was also produced in an allowable yield (35%).[10] The reaction proceeds likewise with ethyl 3-butenoates (**2f**[11] and **2g**[11]) having acyl group at position 3 to give the corresponding naphthalenes (**3h** and **3i**) in high yields. Lower reaction rate and yield were observed with ethyl 3-butenoate **2h**,[12] which has aryl group at position 3. In the case of allyl phenyl sulfone (**2i**[13]), the reaction did not effectively proceed toward cyclization under the usual reaction conditions, **3k** being produced in only 11% yield along with a considerable amount of isomerized Heck product **5** (40%). Here again, as is the case for the reaction with **2d**, performing the reaction under Et_3N in place of NaOAc resulted in an increased yield of naphthalene **3k**. On the other hand, the coupling and cyclization did not take place at all between **1a** and ethyl 3-butenoate **2j**,[14] which has acetylenic group at position 3.

As to the reaction pathway, arylpalladium, initially formed by oxidative addition of a carbon–bromide bond

Table 2. Palladium-catalyzed synthesis of naphthalenes[a]

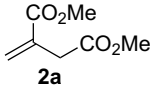
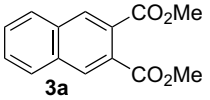
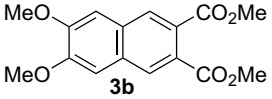
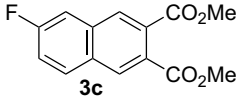
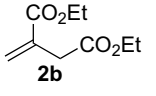
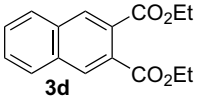
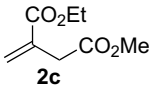
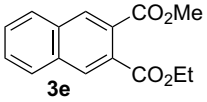
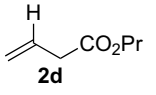
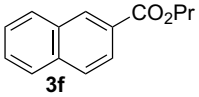
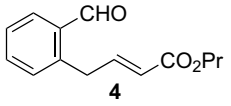
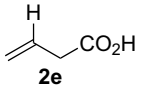
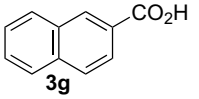
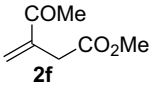
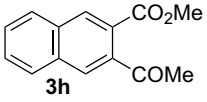
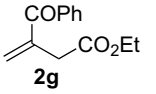
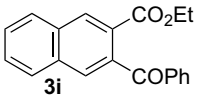
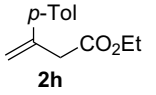
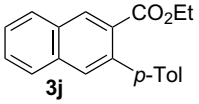
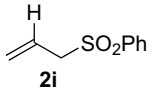
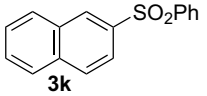
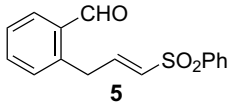
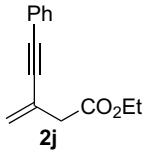
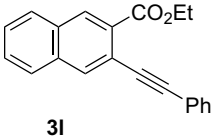
1	Alkenes 2	Bases	Products and isolated yield (%)	
1a	 **2a**	NaOAc	 **3a**	74
1b	**2a**	NaOAc	 **3b**	50
1c	**2a**	NaOAc	 **3c**	61
1a	 **2b**	NaOAc	 **3d**	70

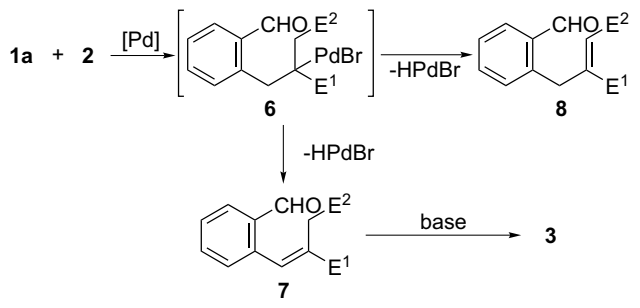
Table 2 (*continued*)

1	Alkenes 2	Bases	Products and isolated yield (%)			
1a	 **2c**	NaOAc	 **3e**	71		
1a	 **2d**	NaOAc Et_3N	 **3f**	7 53	 **4**	48 5
1a	 **2e**	NaOAc	 **3g**	25(35[b])		
1a	 **2f**	NaOAc	 **3h**	84		
1a	 **2g**	NaOAc	 **3i**	84		
1a	 **2h**	NaOAc	 **3j**	17		
1a	 **2i**	NaOAc Et_3N	 **3k**	11 28	 **5**	40 13
1a	 **2j**	NaOAc	 **3l**	0		

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), base (3 mmol), THF (5 mL), 100 °C, for 24 h, under argon.
[b] For 48 h.

of **1a** to palladium(0), adds to **2** to produce alkylpalladium **6**, which in turn triggers β-hydrogen elimination to form an Heck product **7** or isomerized Heck product **8** as shown in **4** and **5** (Scheme 2). The direction of β-hydrogen elimination toward **7** rather than **8** on **6** seems to be due to resonance stabilization from aromatic ring to substituent E^1. Intermediate **7** is followed by base-catalyzed intramolecular aldol reaction to afford naphthalene **3**.

General experimental procedure: a mixture of 2-bromobenzaldehyde (1 mmol), alkene (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol) and NaOAc (3 mmol) in dry THF (5 mL) was placed in a 50 mL pressure vessel. After the system was flushed with argon, the mixture was stirred at 100 °C for 24 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–chloroform) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give naphthalenes **3**.



Scheme 2.

In summary, we have demonstrated that 2-bromobenzaldehydes are coupled and cyclized with an array of functionalized alkenes in the presence of a catalytic amount of a palladium catalyst to give naphthalenes in moderate to good yields. The present reaction is a straightforward synthetic approach for naphthalenes via tandem Heck and aldol reactions between 2-bromobenzaldehydes and functionalized alkenes.

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