ORGANIC LETTERS

2011
Vol. 13, No. 20
5456–5459

Double Arylation of Allyl Alcohol via a One-Pot Heck Arylation–Isomerization–Acylation Cascade

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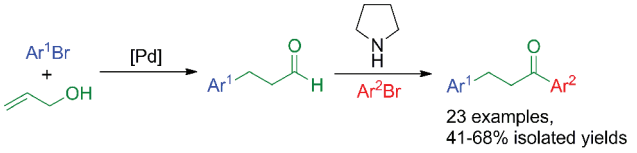
Received August 7, 2011

ABSTRACT



A one-pot, two-step catalytic protocol has been developed. A regioselective Heck coupling between aryl bromides and allyl alcohol leads to the generation of arylated allyl alcohols that *in situ* isomerize to give aldehydes, which then undergo an acylation reaction with a second aryl bromide. A variety of aryl bromides can be employed in both the initial Heck reaction and the acylation, providing easy access to a wide variety of substituted dihydrochalcones.

The Heck reaction is one of the most widely used methods for the construction of carbon–carbon bonds in modern organic chemistry.[1] Over the past few decades, improved catalytic systems have been developed to broaden its application, particularly toward electron-rich olefins.[2] In this context, our group recently disclosed a new catalytic method that allows the direct acylation of aryl halides with aliphatic aldehydes, which appears to occur via a Heck-type mechanism (Scheme 1).[3,4] In the presence of molecular sieves, the aldehyde condenses with pyrrolidine to give an electron-rich enamine, which undergoes a regioselective Heck coupling with aryl halides, most likely via a cationic mechanism.[5] During this work, some of the aldehyde substrates were synthesized by a Heck arylation–isomerization reaction of aryl halides with allylic alcohols.[6] We envisioned that it might be possible to develop a single palladium catalyst that is capable of generating aldehydes from aryl halides and allyl alcohol and, in the same reaction vessel, catalyzes the acylation of a second aryl halide (Scheme 2). This would broaden the scope of the acylation reaction beyond commercially available aldehydes, while circumventing the need for intermittent isolation and purification. The products of this one-pot

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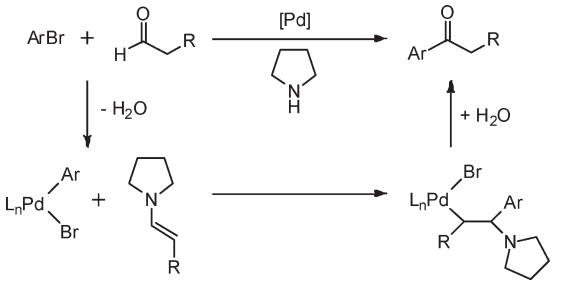
(6) For examples of Heck reaction with allylic alcohols, see: (a) Stone, M. T. *Org. Lett.* **2011**, *13*, 2326. (b) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2007**, *349*, 2572. (c) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (d) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629.

(7) For an alternative catalytic synthesis of DHCs, see: Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 1374.

10.1021/ol202144z
Published on Web 09/20/2011

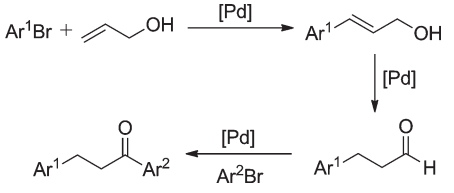
reaction would be substituted dihydrochalcones (DHCs),[7] which have been reported to demonstrate antioxidant properties[8] and have received considerable attention as food sweeteners.[9]

Scheme 1



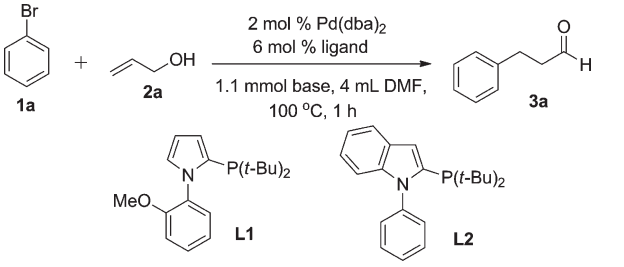
The acylation reaction necessiates a set of specific conditions.[3] We reasoned that, if the Heck arylation–isomerization sequence could be catalyzed under conditions suitable for the acylation, the one-pot process should be feasible. For aryl iodides, the Heck arylation of allylic/homoallylic alcohols is most commonly catalyzed by $Pd(OAc)_2$ in the presence of tetraalkylammonium salts.[6d,10] Such systems are particularly selective toward formation of the carbonyl product due to the high levels of isomerization generally observed but would not be effective toward aryl bromides. While the presence of a phosphine ligand can promote the arylation–isomerization reaction of aryl bromides, high temperatures are required to achieve sufficient activity.[11]

Scheme 2



More recent catalyst systems employ oxime-derived palladacycles, which have proven to be highly active and selective catalysts for the arylation of aryl halides with a variety of allylic alcohols.[6b] However, the catalysis takes place in aqueous/organic media, which would be incompatible with the molecular sieves needed for the acylation reaction.[3]

Table 1. Optimizing Conditions for Heck Arylation–Isomerization Reaction of **1a** with **2a**[a]



entry	ligand	base	yield (%)[b]
1	–	Et_3N	<2
2	PPh_3	Et_3N	<5
3	dppp[c]	Et_3N	<2
4	$P(t\text{-Bu})_3.HBF_4$	Et_3N	37
5	**L1**	Et_3N	59
6	**L2**	Et_3N	62
7	**L2**	Pyrrolidine	<2
8	**L2**	Cy_2NMe	74
9	**L2**	K_2CO_3	22

[a] All reactions were carried out with **1a** (1.0 mmol), **2a** (1.1 mmol), base (1.1 mmol), $Pd(dba)_2$ (0.02 mmol), and ligand (0.06 mmol) in 4 mL of DMF at 100 °C for 1 h. [b] Isolated yields. [c] 3 mol % of ligand was used.

Table 1 shows our attempt for the formation of hydrocinnamaldehyde **3a** from a model reaction of bromobenzene **1a** and allyl alcohol **2a**. Commonly employed phosphine ligands such as PPh_3 and dppp resulted in poor conversion, as did the ligand-free condition (entries 1–3). However, the use of bulky, electron-rich monophosphines $P(t\text{-Bu})_3$, **L1**, and **L2**[12] led to selective formation of the desired aldehyde, with the latter two affording better yields (entries 4–6); no internal arylation was observed. **L1** was previously demonstrated to be effective in the acylation of aryl chlorides.[3a] The reaction conditions were further optimized by changing the base (entries 7–9). The tertiary amine Cy_2NMe afforded the best result, with **3a** being isolated in 74% yield (entry 8). It was hoped that pyrrolidine would be a suitable base for the reaction, as its presence is critical to the acylation step that follows in the overall one-pot process.[3] Unfortunately, use of pyrrolidine as the base yielded very little of the aldehyde product (entry 7).

To test the utility of the newly developed reaction conditions, we examined the Heck–isomerization reaction of a range of aryl bromides with allylic/homoallylic alcohols (Table 2). Functional groups on the aryl bromides were easily tolerated, posing no signifcant effect on the isolated yield of the aldehyde products (entries 2–4).

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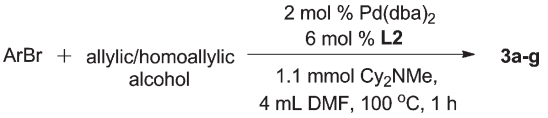
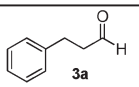
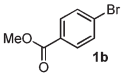
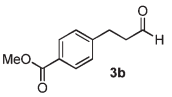
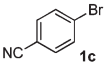
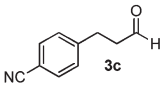
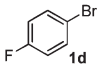
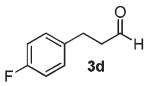
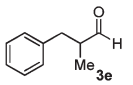
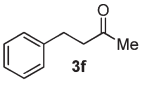
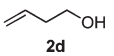
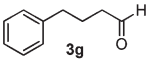
Table 2. Arylation–Isomerization Reaction of Aryl Bromides with Allylic Alcohols[a]



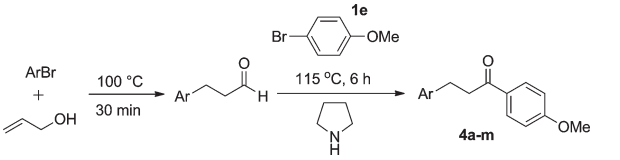
entry	ArBr	allylic/homo-allylic alcohol	product	yield (%)[b]
1	 1a	2a	 3a	74
2	 1b	2a	 3b	68
3	 1c	2a	 3c	67
4	 1d	2a	 3d	71
5	 1a	 2b	 3e	66[c]
6	 1a	 2c	 3f	81
7	 1a	 2d	 3g	43

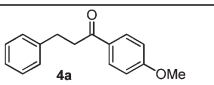
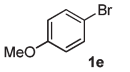
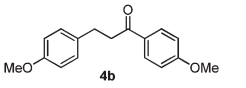
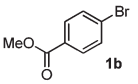
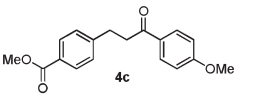
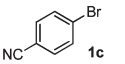
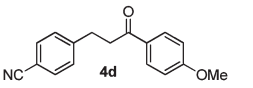
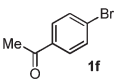
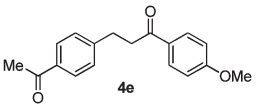
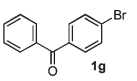
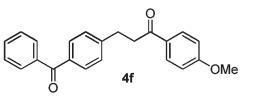
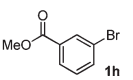
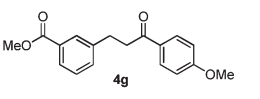
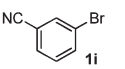
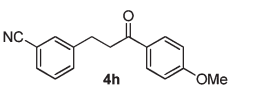
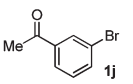
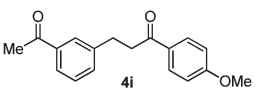
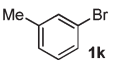
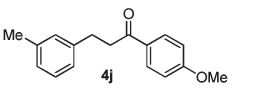
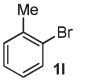
[a] Reactions were carried out with **1a**–**d** (1.0 mmol), **2a**–**d** (1.1 mmol), Cy_2NMe (1.1 mmol), $Pd(dba)_2$ (0.02 mmol), and **L2** (0.06 mmol) in 4 mL of DMF at 100 °C for 1 h. [b] Isolated yields. [c] Reaction time was 2 h.

Internal substitution of the double bond of the allylic alcohol was also tolerated (entry 5); however, the reaction became sluggish and nonselective when terminally substituted allylic alcohols were employed. Secondary allylic alcohol **2c** was also a very effective substrate, giving access to the corresponding ketone in high yield (entry 6). In contrast, the homoallylic alcohol **2d** furnished a lower yield, due to incomplete isomerization (entry 7).

Armed with conditions that enable the facile formation of aldehydes from aryl bromides and allyl alcohol, we turned our attention to the one-pot synthesis of DHCs. Bearing in mind that pyrrolidine is necessary for the acylation but inhibits the arylation–isomerization reaction, an aryl bromide was first allowed to react with 1 equiv of allyl alcohol at 100 °C for 30 min, at which point a second aryl bromide was added together with pyrrolidine and the reaction temperature was raised to 115 °C for 6 h. The molecular sieves, another critical additive for the acylation reaction, were present from the beginning and did not impact the initial aldehyde formation.[3b] It was also found that the presence of potassium carbonate accelerates the acylation reaction, giving cleaner products and higher yields. As can be seen in Table 3, the one-pot reaction

Table 3. One-Pot Arylation, Isomerization, and Acylation Reactions Varying the Initial Aryl Bromides[a]

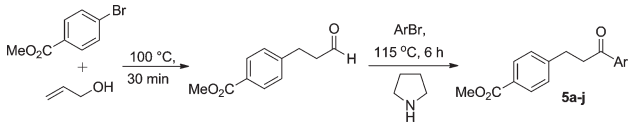


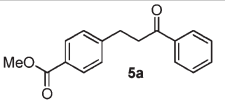
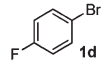
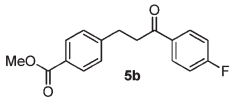
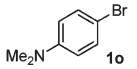
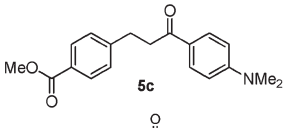
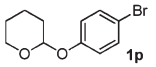
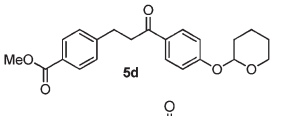
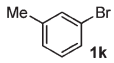
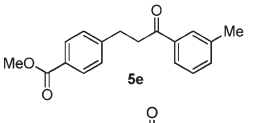
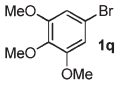
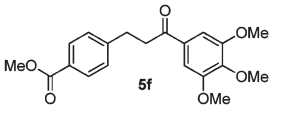
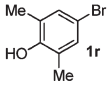
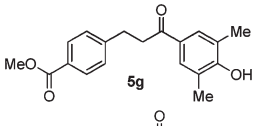
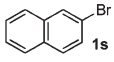
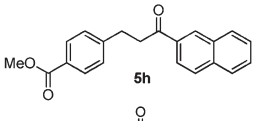
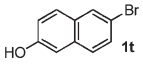
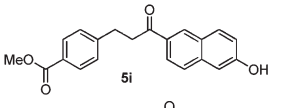
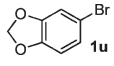
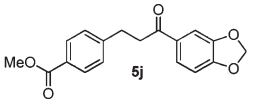
entry	ArBr	product	yield (%)[b]
1	 1a	 4a	64
2	 1e	 4b	43
3	 1b	 4c	66
4	 1c	 4d	58
5	 1f	 4e	63
6	 1g	 4f	52
7	 1h	 4g	55
8	 1i	 4h	57
9	 1j	 4i	54
10	 1k	 4j	56
11	 1l	4k	51
12	1m	4l	51[c]
13	1n	4m	48[c]

[a] Reactions were carried out with **1a**–**c**,**e**–**n** (2.0 mmol), **2a** (2.0 mmol), Cy_2NMe (2.0 mmol), K_2CO_3 (1.0 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (0.02 mmol), and **L2** (0.06 mmol) in 4 mL of DMF at 100 °C for 30 min, followed by addition of **1e** (1.0 mmol) and pyrrolidine (1.0 mmol) at 115 °C for 6 h. [b] Isolated yields based on **1e**. [c] 0.04 mmol of $Pd(dba)_2$ and 0.12 mmol of **L2** were used.

proved capable of forming a variety of DHCs in moderate to good isolated yields. In particular, functional groups on

Table 4. One-Pot Arylation, Isomerization, and Acylation Reactions Varying the Second Aryl Bromides[a]



entry	ArBr	product	yield (%)[b]
1	 1a	 5a	53
2	 1d	 5b	52
3	 1o	 5c	50
4	 1p	 5d	57
5	 1k	 5e	55
6	 1q	 5f	57
7	 1r	 5g	61[c]
8	 1s	 5h	41
9	 1t	 5i	66[c]
10	 1u	 5j	68

[a] Reactions were carried out with **1b** (2.0 mmol), **2a** (2.0 mmol), Cy_2NMe (2.0 mmol), K_2CO_3 (1.0 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (0.02 mmol), and **L2** (0.06 mmol) in 4 mL of DMF at 100 °C for 30 min, followed by addition of **1a,d,k,o–u** (1.0 mmol) and pyrrolidine (1.0 mmol) at 115 °C for 6 h. [b] Isolated yields based on ArBr. [c] 0.04 mmol of $Pd(dba)_2$ and 0.12 mmol of **L2** were used.

the initial aryl bromides, such as ester, nitrile, and ketone, were tolerated by the multistep catalysis (entries 3–9). In steric terms, *meta* and *para* substitution did not pose any significant problem, but unfortunately *ortho* substitution with any group of steric bulk greater than that of methyl (entry 11) dramatically inhibited the initial Heck coupling. Furthermore, some heterocyclic aryl bromides were successfully employed (entries 12 and 13).

We next examined the efficiency of the one-pot process by varying the second aryl bromide, which undergoes the acylation reaction. The results are seen in Table 4. We were happy to observe that the acylation step in the one-pot process appears to behave in the same way as it does in isolation.[3] As such, the aryl bromide can be broadly functionalized in the *meta* and *para* positions and the reaction runs smoothly, affording the DHCs in moderate yields.

As a general trend, the arylation step appears to favor aryl bromides bearing electron-withdrawing substituents, while the acylation reaction works better with those having electron-donating groups (Tables 3 and 4). This is probably because the oxidative addition in the arylation and the insertion step in the acylation are facilitated by these electron-withdrawing and -donating groups, respectively. In addition, when **2a** was replaced with **2b**, the one-pot reaction was unsuccessful due to the failure of the acylation with α-substituted aldehydes.[3] Similarly, replacement of **2a** with **2d** gave poor results as a result of incomplete isomerization.

In conclusion, a one-pot protocol has been developed, which allows highly functionalized DHCs to be easily synthesized from readily available substrates. The palladium catalyzed Heck arylation–isomerization reaction of aryl bromides and allyl alcohol first leads to the formation of aldehydes which, under the intervention of pyrrolidine and the same palladium catalyst, undergo an acylation reaction with an additional aryl bromide, affording the DHCs.

Acknowledgment. Financial support from the EPSRC (EP/F000316) and AstraZeneca is gratefully acknowledged. We also thank the EPSRC National Mass Spectrometry Service Centre for analytical support.

Supporting Information Available. Experimental details and analytical data (NMR, IR, MS). This material is available free of charge via the Internet at http://pubs.acs.org.