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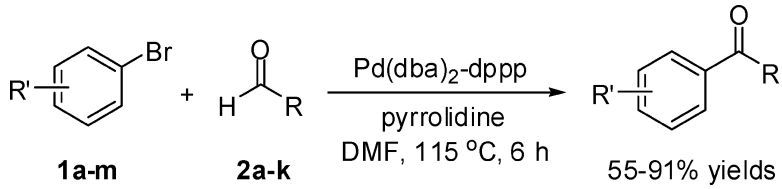

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Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis

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Alkyl aryl ketones are fundamental intermediates in the pharmaceutical, fragrance, dye, and agrochemical industries.[1] They are usually synthesized by the traditional Friedel−Crafts acylation, which involves handling hazardous reagents and fails with electron-deficient arenes.[2] Hydroacylation allows for direct access to these ketones from aldehydes and olefins, but generally requires chelation assistance for C−H activation and for inhibiting decarbonylation.[3] Acylation of aryl halides offers another direct approach. However, there are only a few reported examples of acylation of aryl iodides with aldehydes; these are catalyzed by bimetallic systems and require a chelating auxiliary on the aldehydes, affording alkyl aryl ketones in low yields.[4–6] In related studies, aryl boronate salts have been acylated with aldehydes to give diaryl ketones,[7] which could also be obtained by coupling of aryl iodides with *N*-pyrazyl aldimines or *N*-*tert*-butylhydrazones followed by hydrolysis.[8,9] Herein we disclose an efficient, palladium-catalyzed direct acylation reaction of aryl bromides with aldehydes, affording alkyl aryl ketones in one step.

The Heck reaction of aryl halides with the electron-rich olefin vinyl ethers or enamides provides yet another indirect method for accessing alkyl aryl ketones, where the aryl group inserts at the carbon α to the heteroatom and hydrolysis results in the ketone (Scheme 1).[10–12] As is known, under basic conditions or in the presence of a secondary amine, an aldehyde can equilibrate with an enolate or enamine, thus generating an olefin similar to that used in the well-established Heck reaction (Scheme 1). Enlightened by this, we reasoned that, if the enolate or enamine could be formed in situ, we might be able to obtain ketones directly from aryl halides and aldehydes via the Heck coupling.

With this hypothesis in mind, we set out to examine the acylation of 1-bromo-4-methoxybenzene (**1a**) with octanal (**2f**) in the presence

Scheme 1

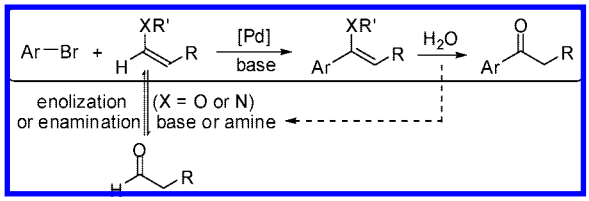
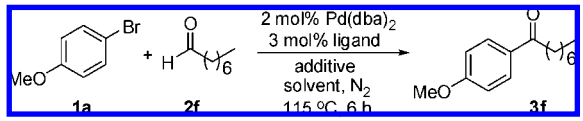


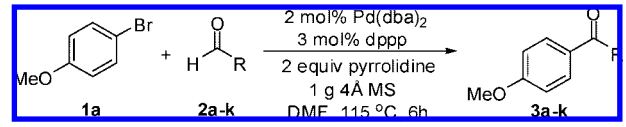
Table 1. Screening Conditions for the Acylation of **1a** with **2f**[a]



entry	ligand	additive	solvent	yield (%)[b]
1	dppp	KF	DMF	0
2	dppp	K_2CO_3	DMF	0
3	dppp	$KOBu^t$	DMF	0
4	dppp	Et_3N	DMF	<2
5	dppp	L-proline	DMF	<2
6	dppp	pyrrolidine	DMF	6
7	dppp	pyrrolidine, 4Å MS	DMF	87
8	dppp	*n*-$BuNH_2$, 4Å MS	DMF	<2
9	dppp	*n*-Bu_2NH, 4Å MS	DMF	20
10	dppp	morpholine, 4Å MS	DMF	60
11	dppp	piperidine, 4Å MS	DMF	50
12	dppp	L-proline, 4Å MS	DMF	<2
13	PPh_3	pyrrolidine, 4Å MS	DMF	80
14	dppf	pyrrolidine, 4Å MS	DMF	83
15	BINAP	pyrrolidine, 4Å MS	DMF	78
16	dppp	pyrrolidine, 4Å MS	dioxane	7
17	dppp	pyrrolidine, 4Å MS	toluene	6

[a] All reactions were carried out with **1a** (1.0 mmol), **2f** (1.2 equiv), 2 equiv of additive, $Pd(dba)_2$ (2 mol %), and ligand (3 mol %) in 4 mL of solvent at 115 °C for 6 h. 4Å MS: 4Å molecular sieves, 1 g when added; dppp: 1,3-bis(diphenylphosphino)propane; dppf: 1,1′-bis(diphenylphosphino)ferrocene; BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene. [b] Isolated yields of ketone.

Table 2. Acylation of **1a** with Various Aldehydes (**2a**−**k**)[a]



entry	aldehyde	product	yield (%)[b]
1[c]	**2a**	**3a**	55
2	**2b**	**3b**	81
3	**2c**	**3c**	91
4	**2d**	**3d**	90
5	**2e**	**3e**	88
6	**2f**	**3f**	87
7	**2g**	**3g**	75
8	**2h**	**3h**	65
9	**2i**	**3i**	89
10	**2j**	**3j**	85
11	**2k**	**3k**	78

[a] Reactions were carried out with **1a** (1.0 mmol), **2a**−**k** (1.2 equiv), pyrrolidine (2 equiv), 4Å MS (1 g), $Pd(dba)_2$ (2 mol %), and dppp (3 mol %) in 4 mL of DMF at 115 °C for 6 h. [b] Isolated yields. [c] Two equivalents of aldehyde used.

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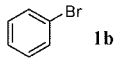
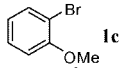
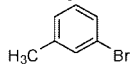
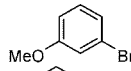
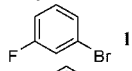
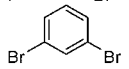
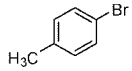
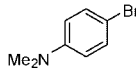
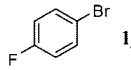
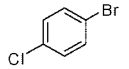
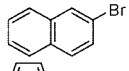
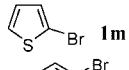
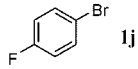
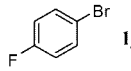
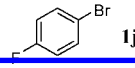
Table 3. Acylation of Aryl Bromides (**1b**−**m**) with **2d**,**i**−**k**[a]

entry	aryl bromide	aldehyde	product	yield (%)[b]
1	 **1b**	**2d**	**3l**	84
2	 **1c**	**2d**	**3m**	60
3	 **1d**	**2d**	**3n**	84
4	 **1e**	**2d**	**3o**	88
5	 **1f**	**2d**	**3p**	72
6	 **1g**	**2d**	**3q**	64[c]
7	 **1h**	**2d**	**3r**	90
8	 **1i**	**2d**	**3s**	61
9	 **1j**	**2d**	**3t**	83
10	 **1k**	**2d**	**3u**	81
11	 **1l**	**2d**	**3v**	71
12	 **1m**	**2d**	**3w**	58
13	 **1j**	**2i**	**3x**	82
14	 **1j**	**2j**	**3y**	78
15	 **1j**	**2k**	**3z**	72

[a] The conditions were the same as in Table 2. [b] Isolated yields. [c] Only one bromo group reacted.

of a base, using $Pd(dba)_2$-phosphine as catalyst precursor. The results are summarized in Table 1. The desired ketone **3f** was not obtained with inorganic bases (entries 1−3), and changing the base to Et_3N led to only a small amount of **3f** being formed (entry 4). We then turned attention to secondary amines, which are prone to forming enamines with the aldehyde.[13] To our delight, an encouraging result was obtained when pyrrolidine was used (entry 6). We then tested a range of other additives under various conditions. The results show that the combination of pyrrolidine and 4Å MS affords the best yield of ketone **3f** (entry 7). No reaction occurred using 4Å MS alone, and lower yields resulted with other amines (entries 8−12). While ligands show insignificant effects on the acylation (entries 13−15), solvents impact dramatically on the reaction (entries 16 and 17).

Having established the optimized conditions, we then tested the acylation of **1a** with various aldehydes **2a**−**k**. The results are shown in Table 2. As can be seen, the reactions afforded good to excellent yields of ketones **3**. In particular, very good results were obtained for the functionalized aldehydes **2j**,**k** (entries 10 and 11), providing a better way for preparing functionalized alkyl aryl ketones, synthetically useful intermediates for pharmaceutical compounds, such as Fluoxetine and analogues.[14] However, due to the low boiling point and self-condensation, a low yield was obtained with propionaldehyde (entry 1).

We next extended the acylation to a series of aryl bromides (**1b**−**m**) coupling with hexanal (**2d**) and the functionalized aldehydes **2i**−**k**. As summarized in Table 3, the reactions afforded moderate to excellent yields of ketones **3**. As may be expected,[10c] *ortho* substitution on the arene ring decreases the yield (entry 2). It appears that aryl bromides with electron-withdrawing or very electron-donating groups also tend to furnish lower yields. Good results were again obtained when using the aldehydes **2i**−**k** (entries 13−15). We also examined the acylation of 2-bromothiophene (**1m**); a moderate yield was recorded (entry 12).

The hypothesis in Scheme 1 implies that, in the case of an enamine, the overall acylation can be catalytic in the amine since it should be regenerated following hydrolysis of the Heck coupling product. To further probe the mechanism, we then studied the acylation of **1a** with **2f** by using 20 mol % of pyrrolidine and 1 equiv of K_2CO_3 as base under otherwise identical conditions to those above. **3f** was obtained in 85% isolated yield.[15] This compares well with the result in Table 2, suggesting that pyrrolidine indeed acts as a catalyst, presumably converting the aldehyde into a highly reactive electron-rich olefin for palladium to seize and as a base under the conditions of Tables 2 and 3 to neutralize the HBr released from the Heck reaction, as hypothesized in Scheme 1. It is interesting to note that, under similar conditions but without pyrrolidine and 4Å MS added, the coupling reaction of aldehydes with aryl bromides led to α-arylated aldehydes instead of ketones, as shown by Hartwig very recently.[16]

In summary, we have developed an efficient protocol for the direct acylation of aryl bromides with various aldehydes, obtaining alkyl aryl ketones in moderate to excellent yields. The reaction appears to involve cocatalysis of palladium and amine. Studies into the mechanism and further application of the reaction will be the focus of future work.

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

References

(1) (a) Franck, H. G.; Stadelhofer, J. W. *Industrial Aromatic Chemistry*; Springer-Verlag: Berlin, 1988. (b) Surburg, H.; Panten, J. *Common Fragrance and Flavor Materials*, 5th ed.; Wiley-VCH: Weinheim, Germany, 2006.
(2) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley: New York, 1973.
(3) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222.
(4) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823.
(5) Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 1682.
(6) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455.
(7) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356.
(8) Ishiyama, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 12043.
(9) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 14800.
(10) (a) Hyder, Z.; Ruan, J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 5555. (b) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152. (c) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751.
(11) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217.
(12) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
(13) Recent reviews of enamine catalysis: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580.
(14) Review of antidepressants Fluoxetine and its analogues: Wong, D. T.; Perry, K. W.; Bymaster, F. P. *Nat. Rev. Drug Discovery* **2005**, *4*, 764.
(15) Under the same conditions but in 10 h reaction time, **3k**, **3l**, **3t**, and **3u** were obtained in 75, 78, 75, and 79% isolated yield, respectively.
(16) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127.

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