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Direct Acylation of Aryl Chlorides with Aldehydes by Palladium−Pyrrolidine Co-catalysis

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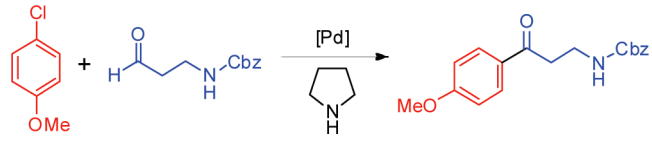
ABSTRACT



A palladium catalyst system has been developed that allows for the direct acylation of aryl chlorides with aldehydes. The choice of ligand, as well as the presence of pyrrolidine and molecular sieves is shown to be critical to the catalysis, which appears to proceed via an enamine intermediate. The reaction was successful for a wide range of aryl chlorides and tolerant of functionality on the aldehyde component, giving easy access to alkyl aryl ketones in modest to good yields.

Alkyl aryl ketones are extensively used in the pharmaceutical, fragrance, dye and agrochemical industries.[1] Such compounds are usually synthesized by the traditional Friedel−Crafts acylation, which involves handling hazardous reagents and fails with electron-deficient arenes.[2] In recent years, alternative methods have been developed, using catalysts and allowing easy-to-handle substrates to be employed. Notable examples include hydroacylation of olefins[3] and acylation of arenes,[4] although these reactions generally require chelation assistance. Acylation of aryl halides offers another attractive approach.[5−7] However, the initial reports were limited to aryl iodides in substrate scope and required bimetallic systems and a chelating auxiliary on the aldehydes. In related studies, aryl boronate salts have been acylated with aldehydes to give diaryl ketones,[8] which could also be obtained by coupling of aryl iodides with *N*-pyrazyl aldimines or *N*-*tert*-butylhydrazones followed by hydrolysis.[9,10]

We recently reported an efficient protocol for the direct acylation of aryl bromides with aldehydes, which uses palladium-amine cooperative catalysis, allowing a variety of alkyl aryl ketones to be readily synthesized.[11,12] This method

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(12) For similar acylation recently reported, see: (a) Zanardi, A.; Mata, J. A.; Peris, E. *Organometallics* **2009**, *28*, 1480. (b) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (c) Adak, L.; Bhadra, S.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 3811.

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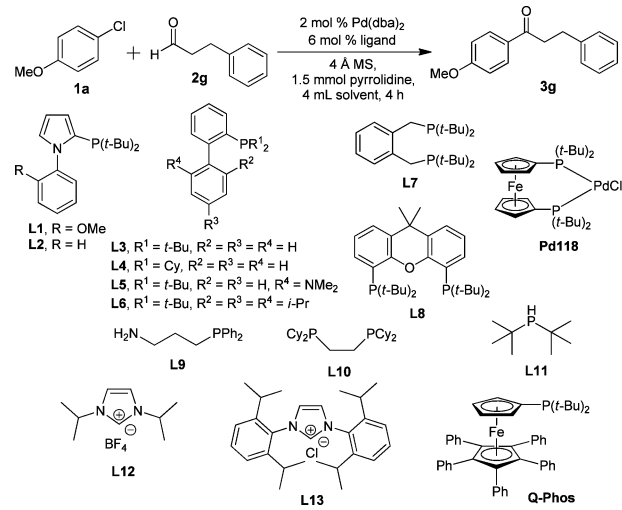
would be of even greater appeal if it were applicable to aryl chlorides, as they are cheaper and more widely available than their bromide or iodide counterparts. Unfortunately, aryl chlorides proved to be essentially inactive when subjected to the Pd-dppp catalysis we had developed for aryl bromides (*vide infra*).[11] Research from a number of pioneering groups has led to the discovery of palladium catalysts bearing bulky and electron-rich phosphine or carbene ligands that exhibit much enhanced activity toward aryl chlorides.[13] We thought that by ligating palladium with such a ligand we might be able to force aryl chlorides to enter the acylation reaction.

With this hypothesis in mind, we set out to examine the acylation of 4-chloroanisole **1a** with 3-phenylpropanal **2g** by combining $Pd(dba)_2$ with various ligands under conditions previously developed for ArBr.[11] The results are summarized in Table 1. After screening several bidentate and monodentate ligands in DMF, we were delighted to find that the bulky, electron-rich monophosphine **L1** (entry 10)[14] led to the formation of the desired product in 19% isolated yield. The yield was increased to 53% by raising the reaction temperature to 140 °C (entry 11). A wider range of ligands were then tested at the increased reaction temperature in order to find the optimal catalyst system. Surprisingly, all other monophosphine ligands, except the structurally similar **L2** (entry 12), gave poor results, regardless of their steric and electronic characteristics. Likewise, all of the diphosphine ligands tested, including the previously successful dppp,[11] failed to yield any of the desired product! When investigating the use of ligands as their stable salts (entries 18, 25, and 26), a small amount of a strong base was added in the hope to release the free ligand in situ. Unfortunately, these ligands were also unable to catalyze the desired acylation reaction.

Changing the solvent from DMF to DMA (entry 28) further enhanced the acylation rate with Pd-**L1**, resulting in a 75% isolated yield of the desired ketone **3g**. It was found that 2 equiv of the aldehyde component were required in order to achieve full conversion of **1a**.[15] As in the case of ArBr,[11] the presence of the pyrrolidine and 4 Å MS was critical; no desired reaction occurred in the absence of either additive.

With the optimized conditions in hand, we then tested the acylation of **1a** with various aldehydes **2a**−**n**. As can be seen in Table 2, the reactions afforded moderate to good yields of ketones **3** when subjected to the Pd-**L1** catalysis in the presence of pyrrolidine and 4 Å MS. As in the case of ArBr, the reaction proved to be tolerant of functionalities on the aldehyde component (entries 10−13). The substrate scope was limited, however, to aldehydes without substitution on the α carbon, although β substitution did not pose a problem (e.g., entries 8 and 9). Thus, acylation of **1a** with 2-methylhexanal under the optimized conditions failed to yield any of the desired ketone.

Table 1. Optimizing Conditions for Acylation of **1a** with **2g**[a]



entry	ligand	solvent	temp (°C)	yield (%)[b]
1	−	DMF	115	0
2	dppp[c]	DMF	115	0
3	dppm[c]	DMF	115	0
4	dppe[c]	DMF	115	0
5	**L9**	DMF	115	0
6	**L10**[c]	DMF	115	0
7	**L11**	DMF	115	0
8	PCy_3	DMF	115	0
9	PPh_3	DMF	115	0
10	**L1**	DMF	115	19
11	**L1**	DMF	140	53
12	**L2**	DMF	140	50
13	**L3**	DMF	140	8
14	**L4**	DMF	140	0
15	**L5**	DMF	140	<5
16	**L6**	DMF	140	<5
17	Q-Phos	DMF	140	24
18	$P(t\text{-}Bu)_3{\cdot}HBF_4$[d]	DMF	140	18
19	dppf[c]	DMF	140	0
20	Binap[c]	DMF	140	0
21	4-OMe-dppp[e]	DMF	140	0
22	4-CF_3-dppp[f]	DMF	140	0
23	**L7**[c]	DMF	140	0
24	**L8**[c]	DMF	140	0
25	**L12**[d,g]	DMF	140	0
26	**L13**[d,g]	DMF	140	0
27[h]	**Pd118**	DMF	140	13
28	**L1**	DMA	140	75
29	**L1**	NMP	140	42
30	**L1**	toluene	140	10
31	**L1**	dioxane	140	<5
32	**L1**	DMSO	140	16

[a] All reactions were carried out with **1a** (1.0 mmol), **2g** (2.0 mmol), pyrrolidine (1.5 mmol), $Pd(dba)_2$ (2 mol %), ligand (6 mol %), and 4 Å MS (1 g) in 4 mL of solvent. [b] Isolated yields of ketone; zero indicates no or trace **3g** in the crude ^1H NMR spectrum. [c] 3 mol % of ligand was used. [d] 3 mol % of *t*-BuOK was added. [e] $(4\text{-}OMePh)_2PCH_2CH_2CH_2P(4\text{-}OMePh)_2$. [f] $(4\text{-}CF_3Ph)_2PCH_2CH_2CH_2P(4\text{-}CF_3Ph)_2$. [g] 2 mol % of ligand was used. [h] 2 mol % of **Pd118** was used as palladium source.

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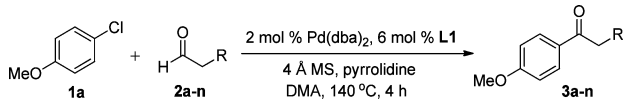
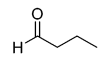
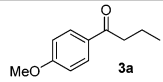
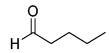
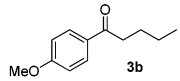
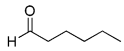
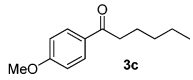
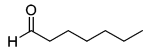
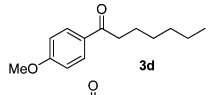
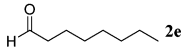
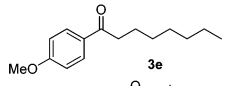
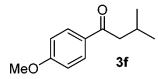
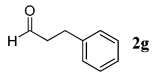
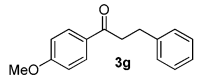
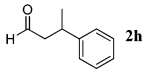
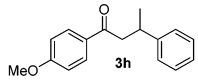
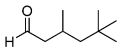
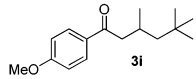
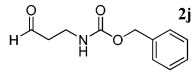
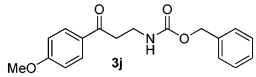
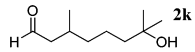
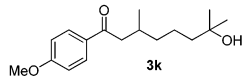
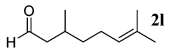
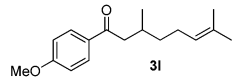
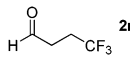
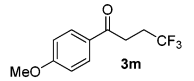
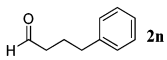
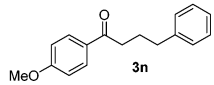
(15) This is due to the competing pathway of aldol condensation, as well as the limited stability of the aldehyde under the reaction conditions. Further increase in the amount of aldehyde used did not increase the product yield.

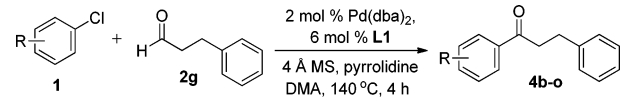
Table 2. Acylation of **1a** with Aldehydes **2a−n**[a]

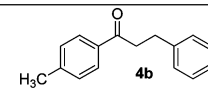
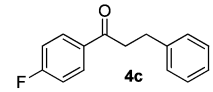
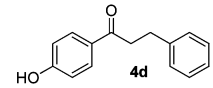
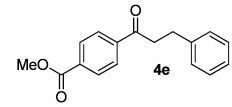
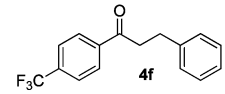
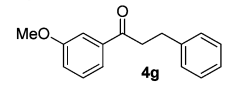
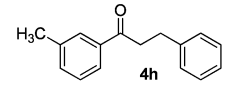
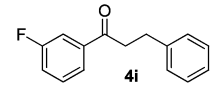
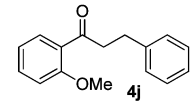
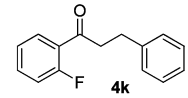


entry	aldehyde	product	yield (%)[b]
1	 2a	 3a	60
2	 2b	 3b	68
3	 2c	 3c	67
4	 2d	 3d	74
5	 2e	 3e	61
6	 2f	 3f	55
7	 2g	 3g	75
8	 2h	 3h	78
9	 2i	 3i	73
10	 2j	 3j	74[c]
11	 2k	 3k	72[c]
12	 2l	 3l	40
13	 2m	 3m	54
14	 2n	 3n	60

[a] Reactions were carried out with **1a** (1.0 mmol), **2a−n** (2.0 mmol), pyrrolidine (1.5 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (2 mol %), and **L1** (6 mol %) in 4 mL of DMA at 140 °C for 4 h. [b] Isolated yields. [c] 4 mol % of $Pd(dba)_2$ and 12 mol % of **L1** were used.

Table 3. Acylation of Aryl Chlorides **1b−o** with **2g**[a]



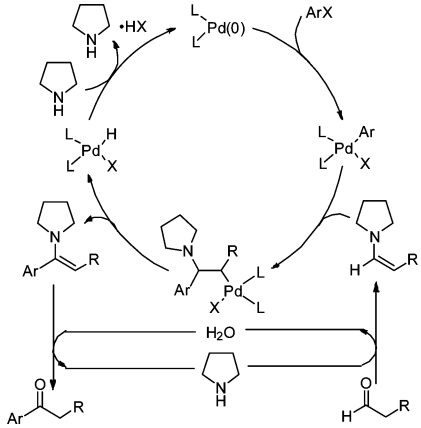
entry	R	product	yield (%)[b]
1	4-CH_3 **1b**	 4b	64
2	4-F **1c**	 4c	61
3	4-OH **1d**	 4d	50[c]
4	4-$COOCH_3$ **1e**	 4e	44
5	4-CF_3 **1f**	 4f	43
6	3-OCH_3 **1g**	 4g	73
7	3-CH_3 **1h**	 4h	61
8	3-F **1i**	 4i	55
9	2-OCH_3 **1j**	 4j	39
10	2-F **1k**	 4k	37
11	H **1l**	4l	73
12	3,5-OCH_3 **1m**	4m	50
13	2-napthyl **1n**	4n	74
14	3,4-dioxole **1o**	4o	59

[a] The conditions were the same as in Table 2. No **4a**, which would be the same as **3g**. [b] Isolated yields. [c] 4 mol % of $Pd(dba)_2$ and 12 mol % of **L1** were used.

We next extended the acylation to a series of aryl chlorides coupling with the aldehyde **2g**. As summarized in Table 3, the reaction afforded moderate to good yields of ketones **4**, particularly when electron-rich aryl chlorides were used. However, as previously found for ArBr,[11] the presence of *ortho* (entries 9 and 10) or electron-withdrawing substituents (entries 4 and 5) on the aryl ring resulted in lower yields. It should be noted that the moderate success of the electron-deficient substrates **1e** and **1f** is a significant improvement, as the equivalent ArBr were completely inactive under the previously reported Pd-dppp catalysis.[11] Unfortunately, acylation of heterocyclic chlorides, such as 2-chlorothiophene and 2-chloropyridine, did not occur under the same conditions.

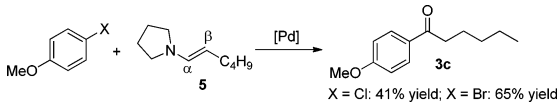
We previously suggested that the acylation may take place via a Heck-type pathway.[11] A possible catalytic cycle is depicted in Scheme 1. Pyrrolidine plays two roles in the

Scheme 1. Proposed Acylation Mechanism



reaction: one is to form an enamine in a catalytic fashion and the other to neutralize the acid HX.[11] The *in situ* formation of the enamine from the aldehyde is a key element of the catalytic cycle. If instead pyrrolidine deprotonated the aldehyde, α arylation might result.[16] To determine if the enamine is involved in the acylation, we carried out a reaction starting from a preformed enamine **5**. Under the conditions established (Table 2), the ketone **3c** was indeed formed (Scheme 2), thus supporting the intermediacy of enamine.

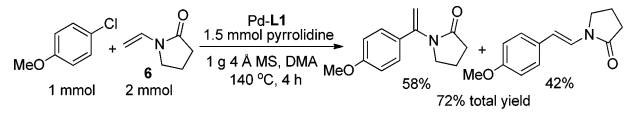
Scheme 2. Arylation of Preformed Enamine **5**



A higher yield was obtained when using bromoanisole under the previously developed conditions.[11] In both cases, however, the isolated yield was somewhat lower than starting with hexanal. As with the acylation of ArBr,[11] the coupling of ArCl with aldehydes becomes catalytic in the amine in the presence of an additional base. Thus, the ketone **3g** could be obtained by reacting **1a** with **2g** using 20 mol % pyrrolidine and 1 equiv KF under otherwise identical conditions to those above (Table 2);[17] this resulted in a 51% isolated yield of **3g**.

The pyrrolidinyl moiety of the enamine is critical for the desired acylation. It polarizes the C=C double bond, which facilitates the β carbon coordination to Pd(II) and the migration of the aryl group to the α carbon, thereby furnishing the α arylated product.[18] In line with this view, the arylation of **6** led to a mixture of α and β arylated enamides (Scheme 3). The formation of these relatively stable

Scheme 3. Arylation of Enamide **6**



regioisomers is most likely a result of the electron-withdrawing effect of the carbonyl group, which renders the C=C double bond less polarized. When using a bidentate ligand under ionizing conditions, however, the α product can be exclusively obtained from **6**.[19]

In summary, we have discovered a catalyst system that allows for the direct acylation of a wide range of aryl chlorides with various aldehydes, including those bearing functionalities. In contrast to the acylation of ArBr effected by Pd-dppp and pyrrolidine, the reaction of ArCl necessitates an electron-rich monophosphine ligand and a higher temperature.

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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.

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(17) A prolonged reaction time of 6 h was required to achieve full conversion with respect to **1a**.

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