ORGANIC
LETTERS

2011
Vol. 13, No. 9
2184–2187

Palladium-Catalyzed Oxidative Coupling of Trialkylamines with Aryl Iodides Leading to Alkyl Aryl Ketones

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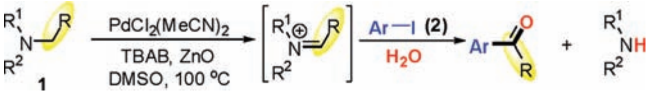
Received February 14, 2011

ABSTRACT



A new, simple method for selectively synthesizing alkyl aryl ketones has been developed by palladium-catalyzed oxidative coupling of trialkylamines with aryl iodides. In the presence of $PdCl_2(MeCN)_2$, TBAB, and ZnO, a variety of aryl iodides underwent an oxidative coupling reaction with tertiary amines and water to afford the corresponding alkyl aryl ketones in moderate to excellent yields. It is noteworthy that this method is the first example of using trialkylamines as the carbonyl sources for constructing alkyl aryl ketone skeletons.

Alkyl aryl ketones are a valuable class of compounds in chemistry and biology that have been widely used in the pharmaceutical, fragrance, dye, agrochemical, and functional material industries as well as in organic synthesis.[1] For these reasons, considerable effort has been made on the development of efficient methods for alkyl aryl ketone synthesis.[1−6] Among these methods, palladium-catalyzed coupling reactions are particularly attractive because they can avoid the use of both hazardous reagents and excess stoichiometric catalysts by comparison with the traditional Friedel−Crafts acylation,[2] as well as chelation assistance by comparison with hydroacylation of olefins and acylation of arenes.[3,4] However, the carbonyl sources for palladium-catalyzed coupling reactions with aryl halides are restricted with *N*-pyrazyl aldimines, *N-tert*-butylhydrazones,[5] or aldehydes.[6] Moreover, aldehydes often require a chelating auxiliary on them or the in situ generation of the enamine intermediates with pyrrolidine.[6] Here, we report a novel method for the synthesis of alkyl aryl ketones from palladium-catalyzed oxidative coupling of aryl iodides with trialkylamines (eq 1). To the best of our knowledge, it is the first example of using trialkylamines as carbonyl

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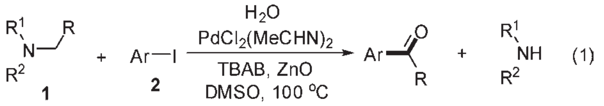
10.1021/ol200404z

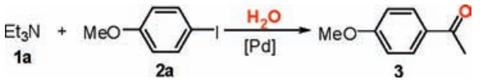
sources through an oxidative deaminization/hydrolyzation/oxidation process.



The reaction of triethylamine (**1a**) with 4-iodoansole (**2a**) was carried out to determine the optimal reaction conditions, and the results are summarized in Table 1.[7] To our delight, treatment of triethylamine (**1a**) with iodide **2a** and $PdCl_2(MeCN)_2$ (5 mol %) in DMSO at 100 °C for 16 h afforded the desired 1-(4-methoxyphenyl)ethanone (**3**) in 23% yield (entry 1).[8] Screening revealed that TBAB (n-Bu_4NBr) could improve the reaction: the yield was enhanced to 33% in the presence of 1.5 equiv of TBAB (entry 2). Prompted by the results, three other Pd catalysts, such as $PdCl_2$, $Pd(OAc)_2$, and $Pd(dba)_2$, were examined, and they were less effective than $PdCl_2(MeCN)_2$ (entries 3−5). Interestingly, ZnO was found to facilitate the reaction (entry 6). In light of these results, a mixture of additives was tested to enhance the yield of **3** (entries 7−17). As expected, the reaction displayed high activity in the presence of both TBAB and ZnO: the yield of **3** was increased sharply to 70% (entry 7). Subsequently, a series of other solvents, MeCN, DMF, and dioxane, were investigated, and they lowered the activity (entries 8−10) The results demonstrated that the amount of both TBAB and ZnO affected the reaction, and the reaction gave the best results using 1.5 equiv of TBAB and 1.3 equiv of ZnO (entries 11−14). Other additives, including $ZnBr_2$, $ZnCl_2$, ZnF, MgO, and KF, were used to replace ZnO (entries 15−19); however, the efficacy of these additives were lowered to some extent.[7] In particular, the reaction could not take place in the presence of KF.[7] Another controlled experiment showed that the reaction was also inert when both ZnO and KF were added (entry 20). These imply that ZnO is not used as a base to improve the reaction.[7] Among the amounts of $PdCl_2(MeCN)_2$ examined, it turned out that the reaction gave the best results at a loading of 5 mol % of $PdCl_2(MeCN)_2$ (entries 7, 21, and 22). It is noteworthy that the yield is reduced to 37% under argon atmosphere (entry 23). Surprisingly, the yield was lowered to 29% using 1 atm of O_2 instead of air, and the GC−MS analysis results showed that many byproducts were generated (entry 24). Gratifyingly, the optimal conditions were consistent with a 0.8 mmol scale of **1a** (entry 25).

With the optimal conditions in hand, the scope of both trialkylamines and aryl iodides was explored for the oxidative coupling reaction (Tables 2 and 3). As shown in Table 2, a number of trialkylamines **1** were first examined by reacting with 4-iodoansole (**2a**) in the presence of $PdCl_2(MeCN)_2$, TBAB, and ZnO. The results indicated that tributylamine (**1b**) and triheptylamine (**1c**) successfully underwent the oxidative coupling reaction with 4-iodoansole (**2a**) in good yield (entries 1 and 2). Notably, N-other unsymmetric tertiary amines, such as ethyl-N-isopropylpropan-2-amine (**1d**), N,N-diethylbut-3-en-1-amine (**1e**), and 2-(diethylamino)ethanol (**1f**), selectively furnished 1-(4-methoxyphenyl)ethanone (**3**) in moderate yields (entries 3−5). It was interesting to find that another twice-coupled product **6**, 1,2-bis(4-methoxyphenyl)ethanone, was isolated from the reaction between 2-(diethylamino)ethanol (**1f**) and iodide **2a** (entry 5). However, 1-butylpyrrolidine (**1g**) was not a suitable substrate for the reaction under the optimal conditions (entry 6). For N-benzyl-N-butylbutan-1-amine (**1h**), only 1-(4-methoxyphenyl)ethanone (**3**) was isolated in 50% yield (entry 7).

Table 1. Palladium-Catalyzed Oxidative Coupling of Triethylamine (**1a**) with 4-Iodoansole (**2a**)[a]



entry	[Pd] (mol %)	additive (equiv)	solvent	yield[b] (%)
1	$PdCl_2(MeCN)_2$ (5)		DMSO	23
2	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)	DMSO	33
3	$PdCl_2$ (5)	TBAB (1.5)	DMSO	11
4	$Pd(OAc)_2$ (5)	TBAB (1.5)	DMSO	21
5	$Pd(dba)_2$ (5)	TBAB (1.5)	DMSO	9
6	$PdCl_2(MeCN)_2$ (5)	ZnO (1.3)	DMSO	39
7	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	DMSO	70
8	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	MeCN	42
9	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	DMF	43
10	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	dioxane	28
11	$PdCl_2(MeCN)_2$ (5)	TBAB (0.5)/ZnO (1.3)	DMSO	41
12	$PdCl_2(MeCN)_2$ (5)	TBAB (3)/ZnO (1.3)	DMSO	32
13	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (0.5)	DMSO	45
14	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (2)	DMSO	68
15	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/$ZnBr_2$ (1.3)	DMSO	49
16	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/$ZnCl_2$ (1.3)	DMSO	52
17	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnF_2 (1.3)	DMSO	50
18	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/MgO (1.3)	DMSO	45
19	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/KF (1.3)	DMSO	trace
20[c]	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO_2 (1.3)	DMSO	trace
21	$PdCl_2(MeCN)_2$ (10)	TBAB (1.5)/ZnO (1.3)	DMSO	64
22	$PdCl_2(MeCN)_2$ (2)	TBAB (1.5)/ZnO (1.3)	DMSO	39
23[d]	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	DMSO	37
24[e]	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	DMSO	29
25[f]	$PdCl_2(MeCN)_2$ (5)	TBAB (1.5)/ZnO (1.3)	DMSO	71

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [Pd], additive, and solvent (2 mL) at 100 °C for 16 h under air atmosphere. [b] Isolated yield. [c] In the presence of KF (1 equiv). [d] Under argon atmosphere. [e] Under O_2 (1 atm). [f] Substrate **1a** (0.8 mmol) and **2a** (2.0 mmol) for 32 h.

Subsequently, the scope of aryl iodides was investigated in the presence of $PdCl_2(MeCN)_2$, TBAB, and ZnO (Table 3). The results disclosed that a variety of aryl halides **2b**−**e** and **2g**−**k** were suitable for the reaction (entries 1−5 and 7−11), but a bulky iodide **2f** (entry 6) and aryl bromides were inert. 4-Iodoaniline, for instance, was reacted with triethylamine (**1a**) or tributylamine (**1b**) smoothly to afford the corresponding products **7** and **8** in 96% and 87% yields, respectively (entries 1 and 2). Other iodides, bearing p-Me, m-Me, NHAc, Cl, or CO_2Et groups on the aryl ring, were compatible with the optimal conditions (entries 4, 5 and 7−10). However, substrate **1f** with an o-Me group was not suitable only providing a trace of the desired product **12** (entry 6). It is noteworthy that the

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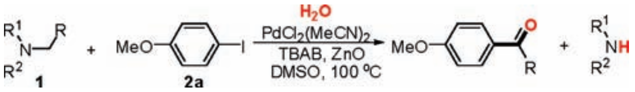
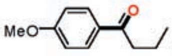
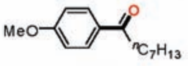
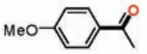
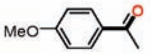
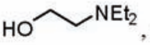
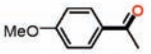
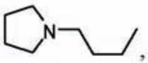
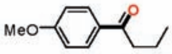
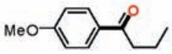
[7] Detailed data is available in Table S1 of the Supporting Information.

[8] Diethylamine was determined by GC−MS analysis.

Table 2. Palladium-Catalyzed Oxidative Coupling of Trialkylamines (**1**) with 4-Iodoanisole (**2a**)[a]



entry	amine (**1**)	time (h)	product/isolated yield (%)
1	(n-Bu)$_3$N, **1b**	16	 **4**/73
2	(n-C$_7$H$_{13}$)$_3$N, **1c**	90	 **5**/71
3	(i-Pr)$_2$NEt, **1d**	50	 **3**/31
4	 , **1e**	41	 **3**/38
5[b]	 , **1f**	40	 **3**/41
6	 , **1g**	48	 **4**/trace
7	(n-Bu)$_2$NBn, **1h**	48	 **4**/50

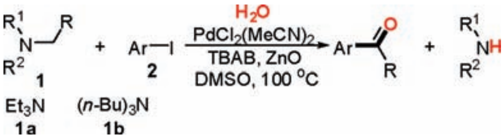
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), $PdCl_2(MeCN)_2$ (5 mol %), TBAB (1.5 equiv), ZnO (1.3 equiv), and DMSO (2 mL) at 100 °C under air atmosphere. [b] 1,2-Bis(4-methoxyphenyl)ethanone (**6**) was obtained in 12% yield.

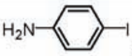
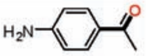
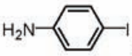
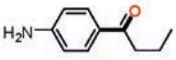
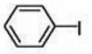
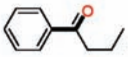
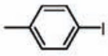
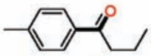
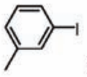
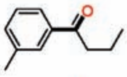
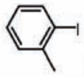
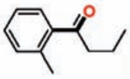
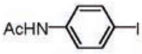
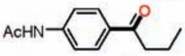
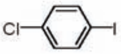
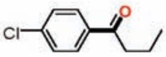
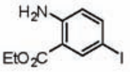
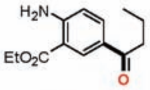
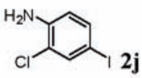
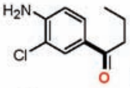
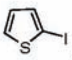
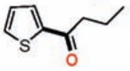
amino group favors the reaction: while 1-chloro-4-iodobenzene (**2h**) provided the desired product **14** in 31% yield (entry 8), substrate **2j** bearing both a chloro group and a amino group furnished the corresponding target product **16** in 72% yield (entry 10). It was noted that the reaction of heteroaryl iodide **2k** with amine **1b** was also successful to afford the desired product **17** in moderate yield (entry 11).

The ^{18}O-labeled experiment was carried out to understand the mechanism (Scheme 1, eq 2). Treatment of amine **1b** with iodide **2b**, $H_2{}^{18}O$ (0.1 mL), $PdCl_2(MeCN)_2$, TBAB, and ZnO in anhydrous DMSO afforded a ^{18}O-contained product **8-O-18**, suggesting that the oxygen atom of products is from water. However, treatment iodide **2a** with butyraldehyde (**18**) afforded the desired product **3** in a low yield (Scheme 1, eq 3). Interestingly, product **3** was obtained in 58% yield from the reaction between iodide **2a** with butyraldehyde (**18**) in the presence of dibutylamine (Scheme 1, eq 4). It is noteworthy that no butyraldehyde is observed by GC−MS analysis without aryl iodides (Scheme 1, eq 5). These results suggest that imine intermediates are generated in situ, which requires the aid of aryl iodides.

Therefore, a possible mechanism as outlined in Scheme 2 was proposed on the basis of the present results[7] and the reported mechanism.[3−6,9] Intermediate **A** can be generated with the aid of Pd, air, and ZnO.[9] Intermediate **A** reacted with ArPdI, which forms from the oxidative addition of

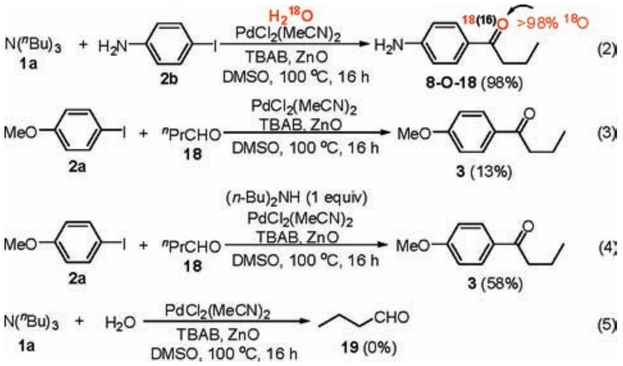
Table 3. Palladium-Catalyzed Oxidative Coupling of Trialkylamines (**1**) with Aryl Iodides (**2**)[a]



entry	1	aryl halide 2	time (h)	product/isolated yield (%)
1	**1a**	 **2b**	16	 **7**/96
2	**1b**	 **2b**	20	 **8**/87
3	**1b**	 **2c**	22	 **9**/76
4	**1b**	 **2d**	16	 **10**/84
5	**1b**	 **2e**	36	 **11**/76
6	**1b**	 **2f**	26	 **12**/trace
7	**1b**	 **2g**	30	 **13**/77
8	**1b**	 **2h**	46	 **14**/31
9	**1b**	 **2i**	36	 **15**/76
10	**1b**	 **2j**	23	 **16**/72
11	**1b**	 **2k**	40	 **17**/53

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), $PdCl_2(MeCN)_2$ (5 mol %), TBAB (1.5 equiv), ZnO (1.3 equiv), and DMSO (2 mL) at 100 °C under air atmosphere.

Scheme 1. ^{18}O-Labeled Experiment and Controlled Experiments



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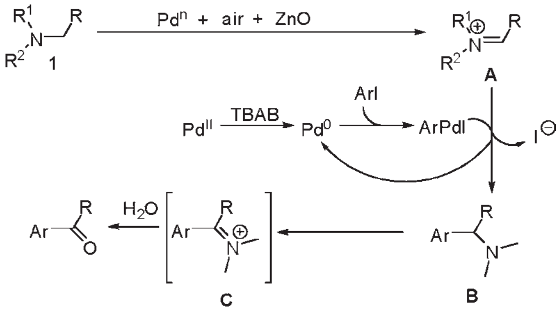
(9) For selected reviews and paper on enamine catalysis, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Kim, J. W.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9249. (d) Murahashi, S. I.; Zhang, D. Z. *Chem. Soc. Rev.* **2008**, *37*, 1490. (e) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

Scheme 2. Possible Mechanism



Pd(0) to ArI, to afford intermediate **B** and regenerate the active Pd(0) species through an eductive elimination process.[5] Intermediate **B** undergoes the reaction with Pd, air and ZnO leading to intermediate **C**,[9] followed by hydrolyzation/oxidation reaction of intermediate **C** furnish the desired product.[5] We deduce that TBAB may play as a ligand to stabilize the active Pd intermediates. The occurrence of the reductive elimination of intermediate **B** is difficult in the case of bulky aryl groups, which results in no reaction for the bulky substrate **1f**.

In summary, we have described a new and simple protocol for the synthesis of alkyl aryl ketones by palladium-catalyzed oxidative coupling of trialkylamines with aryl iodides. Importantly, this method uses commercial available tertiary amines as the carbonyl sources, which makes it more attractive for organic synthesis and industry. However, the catalytic system is inert to 1-iodo-2-methylbenzene and aryl bromides. Thus, work to develop new efficient catalytic system extending this protocol in organic synthesis and study the detailed mechanism is currently underway.

Acknowledgment. We thank the Program of Science and Technology of Wenzhou (Nos. Y20090243 and G20090080), National Natural Science Foundation of China (Nos. 20872112 and 21002070), and Zhejiang Provincial Natural Science Foundation of China (Nos. Y407116 and Y4080169) for financial support. Y.L. also thanks Wenzhou University (No. 3160601010943) for financial support.

Supporting Information Available. Analytical data and spectra (^{1}H and ^{13}C NMR) for all products; typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.