ORGANIC LETTERS

2008
Vol. 10, No. 20
4673−4676

Potassium *t*-Butoxide Alone Can Promote the Biaryl Coupling of Electron-Deficient Nitrogen Heterocycles and Haloarenes

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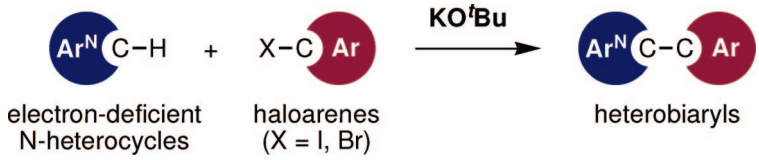
Received August 24, 2008

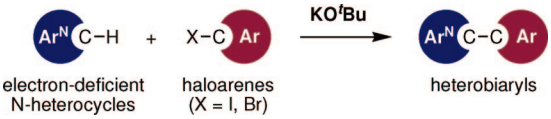
ABSTRACT



The biaryl coupling of electron-deficient nitrogen heterocycles and haloarenes can be promoted by potassium *t*-butoxide alone, without the addition of any exogenous transition metal species. Electron-deficient nitrogen heterocycles such as pyridine, pyridazine, pyrimidine, pyrazine, and quinoxaline are arylated with haloarenes. Control experiments support a radical-based mechanism. Taking these findings into account, radical processes may be partially involved in the reported transition-metal-catalyzed arylation reactions employing *t*-butoxide bases and haloarenes under elevated temperatures or under microwave irradiation.

The transition-metal-catalyzed arylation reactions of nucleophilic organic compounds with haloarenes are commonplace in modern organic synthesis.[1] Representative examples include the palladium-catalyzed arylation of organometallic reagents, amines, alcohols, and carbonyl compounds with haloarenes.[2] More recently, the C−H bond arylation of arenes with haloarenes has become a rapidly growing area of extensive research.[3] These arylation reactions occasionally employ strong bases such as *t*-butoxides and often proceed at high temperatures. Herein, we describe a surprising result from our laboratories, which demonstrates that the biaryl coupling of electron-deficient nitrogen heterocycles and haloarenes can be promoted *by potassium t-butoxide alone, without the addition of any exogenous transition metal species* (Scheme 1). Although the reaction is still in its infancy from a practical point of view, the discovered new reactivity of *t*-butoxides should raise concerns to the synthetic community. Considering the occasional employment of

Scheme 1. KO^{t}Bu-Promoted Biaryl Coupling of Electron-Deficient Nitrogen Heterocycles and Haloarenes



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(3) For recent reviews on biaryl synthesis through C−H bond arylation of aromatic compounds, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200.

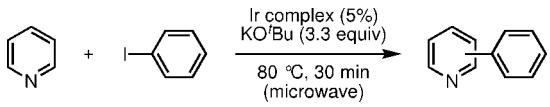
10.1021/ol8019764 CCC: $40.75
Published on Web 09/25/2008

t-butoxide bases and haloarenes in arylation reactions,[1−3] gauging the ability of these reagents to promote reactions in the absence of presumed metal catalysts is obviously critical.

Biaryls are ubiquitous in natural products and pharmaceuticals and are frequently used in organic materials or as ligands for metals.[4] Consequently, the development of new methods for making these privileged structures has been a topic of great importance in chemical synthesis. As a part of our program aimed at establishing a new catalytic biaryl coupling through C−H bond functionalization,[3] we recently reported that $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ can catalyze the C−H bond arylation of arenes with iodoarenes.[5] Since this rhodium catalysis is best with electron-rich arenes, the development of a protocol applicable for electron-deficient arenes such as pyridine has been our next goal.[6]

With the hypothesis that a "radical-type" transition metal mediated reaction might be optimal to achieve such a process,[7] we examined Fujita's iridium-based protocol, which has been assumed to be a radical process,[8] for the coupling of pyridine and iodobenzene. In fact, the C−H bond phenylation of pyridine with iodobenzene can be affected in the presence of $[Cp^*IrHCl]_2$ and KO^{t}Bu (C_5H_5N/C_6H_5I/Ir/KO^{t}Bu = 40:1:0.05:3.3 molar ratio) at 80 °C for 30 min under microwave irradiation to give phenylpyridine in 30% yield as a mixture of regioisomers (Table 1, entry 1). As

Table 1. Discovery of KO^{t}Bu-Promoted Biaryl Coupling[a]



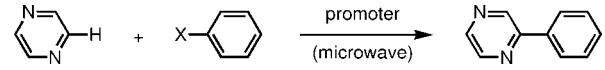
entry	Ir complex	yield (%)[b]
1	$[Cp^*IrHCl]_2$	30
2	$[Cp^*IrCl_2]_2$	32
3	$[IrCl(cod)]_2$	17
4	Ir(acac)(cod)	18
5	$IrH(CO)(PPh_3)_3$	29
6	$IrCl(CO)(PPh_3)_2$	41
7	$(NH_4)_3IrCl_6$	26
8	**none**	**39**

[a] Conditions: pyridine (16 mmol), iodobenzene (0.40 mmol), Ir complex (0.02 mmol), KO^{t}Bu (1.32 mmol), 80 °C, 30 min, under microwave irradiation. [b] As a mixture of regioisomers.

shown in Table 1, a variety of iridium sources were apparently able to catalyze this reaction in moderate yield. Struck by the similarity of reactions employing dramatically distinct iridium sources (entries 1−7), we carried out the coupling reaction in the absence of iridium and remarkably found that the coupling reaction proceeded to the same extent with KO^{t}Bu as the sole reagent (Table 1, entry 8).

With these unexpected results in hand, we further examined the reaction conditions (Table 2). For simplicity, pyrazine was chosen as a substrate for this study. When a mixture of pyrazine (20 mmol), iodobenzene (0.50 mmol), and KO^{t}Bu (0.75 mmol) is stirred in the dark at 50 °C for 5

Table 2. Phenylation of Pyrazine with Halobenzene[a]



entry	X	promoter	conditions	yield (%)
1	I	KO^{t}Bu	50 °C, 5 min	98
2[b]	I	KO^{t}Bu	120 °C, 13 h	79
3[c]	I	KO^{t}Bu	80 °C, 0.5 h (in DMAc)	54
4[c,d]	I	KO^{t}Bu	80 °C, 0.5 h (in DMAc)	35
5[b,c]	I	KO^{t}Bu	23 °C, 72 h (in DMAc)	26
6	Br	KO^{t}Bu	80 °C, 0.5 h	54
7	Cl	KO^{t}Bu	80 °C, 0.5 h	<1
8	F	KO^{t}Bu	80 °C, 0.5 h	<1
9	I	NaO^{t}Bu	50 °C, 5 min	<1
10	I	LiO^{t}Bu	50 °C, 5 min	<1
11	I	KOMe	50 °C, 5 min	<1
12	I	KOH	50 °C, 5 min	<1

[a] Conditions: pyrazine (20 mmol), halobenzene (0.50 mmol), promoter (0.75 mmol), under microwave irradiation. [b] Reaction was conducted without microwave irradiation. [c] 0.5 mL of *N*,*N*-dimethylacetamide (DMAc) was used as solvent. [d] 5.0 mmol of pyrazine was employed.

min under microwave irradiation, C−H bond phenylation takes place to afford 2-phenylpyrazine in 98% yield (Table 2, entry 1).[9] The reaction also takes place under conventional heating but requires higher temperatures and longer reaction times to achieve full conversion (79% at 120 °C, 13 h, entry 2). *N*,*N*-Dimethylacetamide (DMAc) can also be used as a solvent for this reaction (54% at 80 °C, 0.5 h, entry 3). Interestingly, the use of DMAc as a solvent allows the reaction to proceed at lower substrate loading (entry 4) or at room temperature (entry 5), albeit less efficiently. The reaction also takes place with bromobenzene at 80 °C (54%), but chlorobenzene and fluorobenzene are virtually unreactive

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(6) In the metal-catalyzed direct C−H bond arylation chemistry, electron-deficient nitrogen heterocycles are still challenging substrates. (a) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Baidossi, M.; Ponde, D. E.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1809. (b) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (c) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781.

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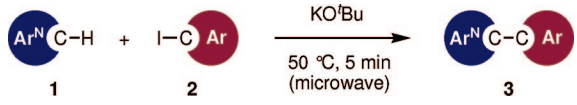
(8) Fujita, K.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926.

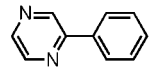
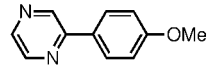
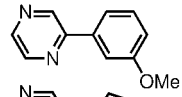
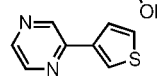
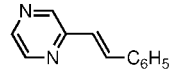
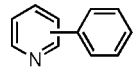
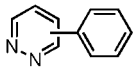
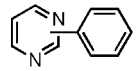
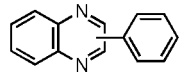
(9) Although we hold the temperature at 50 °C, this is the bulk temperature of the reaction mixture. As well documented, we assume that the reaction is taking place at high-temperature "hotspots" that are generated by microwave irradiation. For reviews on the use of microwave in organic synthesis, see: (a) de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

under these conditions (entries 6−8). Other potential promoters related to KO^{t}Bu were also examined (entries 9−12). The use of NaO^{t}Bu or LiO^{t}Bu instead of KO^{t}Bu does not give the product under these conditions (50 °C, 5 min). However, it should be noted that, at temperatures above 80 °C, NaO^{t}Bu also promotes the biaryl coupling. In addition to the nature of the metal cation (K), the *t*-butoxide moiety is also crucial, as KOMe and KOH exhibited nearly no reactivity.

Next the scope of the reaction with respect to the iodoarene and nitrogen heterocycle was examined. Representative results are summarized in Table 3. Various iodoarenes react with pyrazine to give the corresponding nitrogen-containing biaryls in good yields (entries 1−4). These reactions take place exclusively at the C−I bond of iodoarenes, and regioisomers with respect to the iodoarene are not detected.[10]

Table 3. Substrate Scope of KO^{t}Bu-Promoted Biaryl Coupling[a]



entry	1	2	3 (yield, %)[b]	
1	pyrazine	C_6H_5I		98
2[c]	pyrazine	4-$CH_3OC_6H_4I$		83
3[c]	pyrazine	3-$CH_3OC_6H_4I$		64
4[c]	pyrazine	3-iodothiophene		71
5[c]	pyrazine	β-iodostyrene		33
6	pyridine	C_6H_5I		63[d]
7	pyridazine	C_6H_5I		56[e]
8[c]	pyrimidine	C_6H_5I		59[f]
9	quinoxaline	C_6H_5I		75[g]

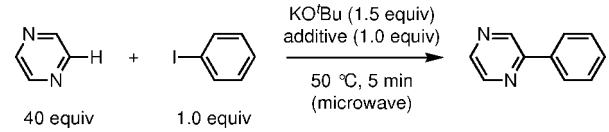
[a] Molar ratio: **1/2**/KO^{t}Bu = 40:1.0:1.5. [b] Isolated yield. [c] Molar ratio: **1/2**/KO^{t}Bu = 40:1.0:2.0. Conditions: 80 °C, 30 min. [d] Isomer ratio: 2-/3-/4- = 36:21:43. [e] Isomer ratio: 3-/4- = 24:76. [f] Isomer ratio: 2-/4-/5- = 23:52:25. [g] Isomer ratio: 2-/5- = 64:36.

Other than iodoarenes, iodoalkenes such as β-iodostyrene also react with pyrazine (entry 5). A range of electron-deficient nitrogen heterocycles other than pyrazine undergo arylation with iodoarenes. For example, pyridine, pyridazine, pyrimidine, and quinoxaline react with iodobenzene to afford the coupling products in good yields, albeit with poor regioselectivity with respect to the heteroarene (entries 6−9).

Considering that trace transition metals present in sodium carbonate have been shown to catalyze coupling reactions such as the Suzuki−Miyaura reaction when performed under forcing conditions,[11] all reagents were purified extensively before use, including sublimation for KO^{t}Bu.[12] All reaction glassware and equipment were thoroughly cleaned prior to use. Finally, the quantitative elemental analysis of KO^{t}Bu was conducted by ICP−AES (inductively coupled plasma−atomic emission spectrometry).[13] Though very low in concentration, the most abundant exogenous elements found to be present in the KO^{t}Bu used in this study are Si (0.92 ppm), Al (0.38 ppm), and Ca (0.048 ppm). These elements are unlikely to be promoters for the present coupling since there is no correlation between the yield of coupling product and the concentration of these elements in the promoters listed in Table 2.[13] More importantly, the concentration of all transition metals in the KO^{t}Bu employed in our study is less than 0.50 ppm. In particular, Pd, Rh, and Ru, which one might suspect as potential catalysts for such biaryl couplings,[3] were not found in concentrations above the detection limits (Pd: <0.06 ppm, Rh: <0.20 ppm, Ru: <0.30 ppm). Although the possibility of transition metal mediation in this reaction cannot be completely excluded, such a catalyst, if any, must be effective at low parts per billion concentrations.[11]

Although the precise mechanism of this reaction remains to be determined, our current hypotheses favor either homolytic aromatic substitution[14] or $S_{RN}1$ reaction,[15] both of which involve the generation of an aryl radical from iodoarene as a key step. While other possibilities such as S_NAr and aryl cation[16] mechanisms cannot be rigorously excluded at this stage, the radical nature of the present reaction is supported by control experiments performed in the presence of radical scavengers. For example, the addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), galvinoxyl, or acrylonitrile to the reaction of pyrazine, iodobenzene, and KO^{t}Bu completely shuts down the otherwise efficient biaryl coupling (Scheme 2).

Scheme 2. KO^{t}Bu-Promoted Coupling with Radical Scavengers



additive	*yield*
none	*98%*
galvinoxyl	*<1%*
TEMPO	*<1%*
acrylonitrile	*<1%*

(10) These results imply that our reaction does not proceed through aryne intermediates, although such a mechanism cannot be rigorously excluded at this stage. (a) Bates, R. B.; Janda, K. D. *J. Org. Chem.* **1982**, *47*, 4374. (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3389.

In summary, the arylation of electron-deficient nitrogen heterocycles with iodoarenes promoted by potassium *t*-butoxide has been described. Although further mechanistic studies and a systematic optimization of the reaction conditions are warranted for this reaction to reach its full synthetic potential, the discovered new reactivity of *t*-butoxides should raise concerns to the synthetic community. Given the occasional use of *t*-butoxide bases and haloarenes in transition-metal-catalyzed arylation reactions (e.g., C−H bond functionalization and amination),[17,18] the ability of these bases to promote coupling reactions is of significant importance. Taking our findings into account, radical processes may be partially involved in the reported transition-metal-catalyzed arylation reactions employing these *t*-butoxide bases and haloarenes under elevated temperatures or under microwave irradiation. Thus, great care is urged in the analysis and interpretation of such reactions.

Acknowledgment. This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday. This work was supported by the PRESTO program of Japan Science and Technology Agency (JST), and a Grant-in-Aid for Scientific Research from MEXT and JSPS. S.Y. is a recipient of the JSPS Predoctoral Fellowships for Young Scientists. We thank Prof. Cathleen M. Crudden (Queen's University, Canada) and Dr. Jean Bouffard (Nagoya University) for critical comments and discussion.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The reaction also takes place with commercial unsublimed KO^{t}Bu similarly.

(13) See Supporting Information for details.

(14) Studer, A.; Bossart, M. *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 62.

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(16) (a) Dichiarante, V.; Fagnoni, M. *Synlett* **2008**, 787. (b) Dichiarante, V.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6495.

(17) For the selected examples using *t*-butoxides and haloarenes in C−H bond arylation reactions, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Proch, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3135. (c) Reference 8. (d) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (e) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310. (f) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (g) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (h) Wang, D.; Wu, Z. *Chem. Commun.* **1999**, 529. (i) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (j) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.

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