Cite this: Chem. Commun., 2011, 47, 10629-10631

www.rsc.org/chemcomm

COMMUNICATION

Potassium *tert*-butoxide mediated Heck-type cyclization/isomerization-benzofurans from organocatalytic radical cross-coupling reactions[†]

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Received 16th July 2011, Accepted 18th August 2011 DOI: 10.1039/c1cc14297f

A transition metal-free Heck-type cyclization/isomerization reaction has been developed. Mediated by potassium *tert* but oxide and phenanthroline a variety of benzofuran derivatives have been synthesized.

Transition-metal catalyzed reactions hold a special place in organic synthesis due to their ability to promote C–C and C-heteroatom bond formation.¹ Despite major advances achieved in the field, critical issues deal with the presence of metal impurities in the final product, which may restrict their practical applicability. Hence, alternative transition-metal-free processes for the efficient construction of C–C and C-heteroatom bonds are attracting attention. In this context, a series of improved protocols for the direct C–H bond transformation, making use of strong inorganic bases like sodium or potassium *tert*-butoxide, have recently been established.

In late 2008, potassium tert-butoxide (KOtBu) was reported to promote C-C coupling of electron-deficient nitrogen heterocycles with haloarenes under microwave irradiation.^{2,3} Furthermore, in conjunction with peroxides, KOtBu was found to assist the formation of C-C bonds between nitrogen heteroaromatics and alkanes.⁴ More recently, transition metalfree coupling reactions mediated by KOtBu and leading to biaryl compounds were described by Shi and co-workers.⁵ Independently, similar results were reported by the groups of Hayashi^{6a} and Kwong and Lei.^{6b} In all cases, a catalytic system consisting of potassium or sodium tert-butoxide and a diamine such as DMEDA or phenanthroline promoted the reaction.^{5,6} Newly, in conjunction with KOtBu, quinoline-1-amino-2-carboxylic acid was also reported to promote the reaction between aryl halides and arenes.⁷ Along the same lines, Charette *et al.* described the KOtBu/pyridine mediated intramolecular arylation of various aryl halides under microwave irradiation.8 Moreover, KOtBu was also successfully applied in the coupling of aromatic compounds with alkenes.⁹ These newly developed reactions⁵⁻⁷

are supposed to follow a homolytic radical aromatic substitution mechanism. $^{10,11}\,$

The goal of our research was to extend this emergent coupling technique to intramolecular Heck-type reactions, as this would provide a transition metal-free synthetic pathway to bicyclic compounds.¹² Although intramolecular reactions are typically easier to perform, we were aware from the outset that the intramolecular Heck-type reaction, in contrast to the intermolecular variant, cannot be easily optimized by changing the reactant ratios and using large excess of one reactant.

To address these challenges, we chose the synthesis of benzofuran derivatives as a first target. Herein, we show that substituted allyl 2-iodophenyl ethers form benzofuran derivatives in the presence of KOtBu (3 equiv.) and 1,10-phenanthroline (0.4 equiv.) using mesitylene as a solvent (Scheme 1). To the best of our knowledge, this is the first example for a KOtBu mediated intramolecular reaction which connects an aromatic carbon with a carbon atom of an alkene.

Taking into account the recent mechanistic discussion, we propose a homolytic radical mechanism with a single electron



Scheme 1 A plausible reaction mechanism for the KO*t*Bu mediated Heck cyclization–isomerization reaction.

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[†] Electronic supplementary information (ESI) available: Extended screening table, experimental details and characterization data. See DOI: 10.1039/c1cc14297f

transfer process to the aryl halide as a first step (Scheme 1).^{10,11} The starting compound 1 is thereby reduced to radical anion 2 by the KO*t*Bu/diamine system.¹³ At this high energetic state, iodide leaves easily the molecule and the next ring closure step provides radical 4. The substitution pattern in the terminal alkene is essential for the ring closure as it stabilizes both the intermediate radical 4 and, more importantly, the double bond in 1 and 3, which would otherwise be easily isomerized to the vinyl ether under the reaction conditions employed.¹⁴

At this stage two different pathways can be rationalized. Radical 4 undergoes either deprotonation to yield radical anion 5 which reacts with the aryl halide 1 or is oxidized by the butoxide radical formed in the first step, and subsequently deprotonated to give 6. Base promoted isomerization leads to the final product 7.

Evaluation of various parameters revealed that only a balanced interplay of the base, diamine, halogen and solvent at temperatures between 150 and 170 °C results in promising yields. As intramolecular reactions cannot be optimized through different reactant ratios, avoiding decomposition was an additional challenge.¹⁵ Solvent screening revealed mesitylene, toluene, dioxane, and pyridine as potential reaction media for the KOtBu mediated Heck cyclization. In contrast, reactions in DMF and DMSO resulted in complete decomposition of the starting material 9 (X = I). Decomposition was observed also in the case of bromo- and chloro- substituted benzene derivatives 9 (X = Br, Cl, Table 1, entries 5 and 6). Here, a plausible explanation could be a lower compulsion of the halide to leave the activated radical anion, which results in side reactions of this highly active species. Sodium and lithium tert-butoxide did not mediate the reaction (Table 1, entries 7 and 8). In these cases, the starting material was completely recovered and we concluded that these weaker bases cannot form the reactive radical anion.

The highest yield obtained for our initial target molecule **10** (Table 1, entry 10) was 38%. Next to the product, a considerable amount of a by-product was formed in which the double bond of the starting material was isomerized to the vinyl ether.

Hence, we turned our attention to substrate **1a** (Table 2). Here, yields up to 63% after column chromatography purification

Table 1 Survey of different solvents, halides and bases

Í		۸ 1,10-phe	IOtBu (3 enanthroli	equiv.) ne (0.4 equi	v.)	-0
	9 Ph		solvent,	t	10	Ph
Entry	Solvent	Х	М	$T/^{\circ}\mathrm{C}$	Time/h	Yield ^{a} (%)
1	Toluene	Ι	Κ	110	14	28
2	DMF	Ι	Κ	110	14	_
3	DMSO	Ι	Κ	110	14	_
4	Dioxane	Ι	Κ	110	14	30
5	Dioxane	Br	Κ	110	14	_
6	Dioxane	Cl	Κ	110	14	_
7	Dioxane	Ι	Na	110	14	_
8	Dioxane	Ι	Li	110	14	
9	Mesitylene	Ι	Κ	150	14	29
10	Mesitylene	Ι	Κ	150	2	38
11	Pyridine	Ι	Κ	160	2	21^{b}

^{*a*} Yield of the isolated product. ^{*b*} Determined by ¹H-NMR (internal standard: 1,3,5-trimethoxybenzene).

Table 2 Survey of temperatures, additives and concentrations

		0 1a	Ph Ph	KO <i>t</i> Bu 10-phenanthroline Mesitylene	7a Ph	-Ph
Entry	$T/^{\circ}\mathbf{C}$	Addi	tive (equiv.)	KOtBu (equiv.)	Time/min	Yield ^a (%)
1	80	Phen	(0.4)	3	120	16 ^b

1	80	Phen (0.4)	3	120	16^{b}
2	120	Phen (0.4)	3	120	25
3	160	Phen (0.4)	3	90	63
4	170	Phen (0.4)	3	120	58
5	160	Phen (0.2)	3	90	39^{b}
6	160	Phen (0.8)	3	90	49 ⁶
7	160	Phen-Me ₂ $(0.4)^{c}$	3	90	33^{b}
8	160	DMEDA $(0.4)^d$	3	90	40^{b}
9	150	Phen (0.4)	1.5	120	23^{b}
10	150	Phen (0.4)	5	120	43
11	155 ^e	Phen (0.4)	3	15	46

^{*a*} Yield of the isolated product. ^{*b*} Determined by ¹H-NMR (internal standard: 1,3,5-trimethoxybenzene). ^{*c*} 4,7-Dimethyl-1,10-phenanthroline. ^{*d*} N,N'-Dimethylethylenediamine. ^{*e*} Microwave reaction.

were obtained, supporting our proposed mechanism involving stabilized double bonds and radicals. The ideal temperature for this reaction was 160 °C (Table 2, entries 1-4). At higher temperatures fast decomposition of KOtBu and aryl iodide was observed; lower temperatures slowed down the reaction without leading to better yields even after extended reaction times. Decreasing the concentration of phenanthroline to 0.2 equiv. or increasing it to 0.8 resulted in lower yields (Table 2, entries 5 and 6). The use of phenanthroline was essential,¹⁶ but it could be replaced by 4,7-dimethyl-1,10-phenanthroline or by N,N'dimethylethylenediamine. However, the yields were significantly lower in both cases (Table 2, entries 7 and 8). The same result was observed for an increased base concentration of 5 equiv. (Table 2, entry 10). The use of 1.5 equiv. of the base resulted in a yield drop to 23%. Performing the reaction under microwave irradiation¹⁷ resulted in full conversion of the starting material and a yield of 46% after 15 minutes (Table 2, entry 11).

In previous publications on KOtBu mediated coupling reactions, researchers have taken every conceivable step to prove that the reactions work indeed transition metal-free.^{5,18} For our study we used sublimed KOtBu from Sigma Aldrich (99.99%) and conducted ICP-MS measurements to identify potential metal impurities.¹⁶ As previously reported by Shi *et al.*,⁵ traces of copper (0.34 ppm) were detected in the phenanthroline. One key experiment to probe the role of copper traces is to determine the yields after conducting the reaction with additional copper salts.¹⁹ However, no effect was observed in these cases.¹⁶

With the optimized conditions in hand, we evaluated various substrates **1a–o** as *cis/trans* isomers in the intramolecular Heck cyclization/isomerization reaction (Table 3). The method tolerates various electronic and substitution patterns on the aromatic moieties, affording benzofuran derivatives **7a–o** in moderate to good yields (Table 3).

The best yield was obtained in the case of substrate **1d** bearing electron donating groups on the aromatic ring directly involved in the reaction. Bis-coupling was also achieved leading to the corresponding product **7o** in 41% yield.

In summary, we have developed a transition metal-free intramolecular Heck-type cyclization/isomerization reaction







"Reactions were performed with **1a–o**, KO/Bu (3 equiv.), 1,10-phe nanthroline (0.4 equiv.) in mesitylene at 160 °C for 2 hours.

mediated by KOtBu.²⁰ A variety of benzofuran derivatives are accessible through a reaction pathway which involves aryl and stabilized tertiary benzhydryl radicals. Due to the operational simplicity, the method is expected to find further application in the synthesis of heterocyclic compounds of interest.

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