## Iridium-Catalyzed Hydrogen Transfer: Synthesis of Substituted Benzofurans, Benzothiophenes, and Indoles from Benzyl Alcohols

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## ABSTRACT



An iridium-catalyzed hydrogen transfer has been developed in the presence of *p*-benzoquinone, allowing the synthesis of a diversity of substituted benzofurans, benzothiophenes, and indoles from substituted benzylic alcohols.

Oxidation is one of the most important reactions, and oxidation state adjustments are very frequent operations in

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organic synthesis. In green chemistry processes, heavy metal oxidants in stoichiometric quantities have to be avoided, and methods using nontoxic and recyclable reagents need to be developed. Transition metal catalysts such as palladium, copper, and ruthenium catalysts have been utilized to oxidize alcohols in the presence of  $H_2O_2$ and  $O_2$ <sup>1</sup> and oxidation/reduction sequences using hydrogen transfer induced by iridium, cobalt, and rhodium catalysts have been developed in the past 20 years.<sup>2</sup> Iridium complexes are more stable than rhodium and cobalt complexes under thermal conditions; therefore iridium catalysts are the catalysts of choice for hydrogen transfer processes.<sup>3</sup> Recently, we have reported that acetonitrile could be monoalkylated by primary alcohols through a one-pot oxidation/reduction sequence in the presence of iridium catalysts<sup>4</sup> and that intramolecular alkylation of nitriles by primary and secondary alcohols via a hydrogen transfer using [Ir(cod)Cl]<sub>2</sub> or [IrCp\*Cl<sub>2</sub>]<sub>2</sub> catalysts led to tetrahydronaphthalenes, chromanes, and thiochromanes

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in good yields.<sup>5</sup> These tandem reactions proceed with a concomitant liberation of hydrogen in the presence of Ir or Ru catalysts.<sup>6</sup> Some studies have also been developed using a co-oxidant to regenerate the Ir catalyst.<sup>7</sup>

Here, we would like to report that substituted benzofurans, benzothiophenes, and indoles of type **B** can be prepared from benzylic alcohols **A** using an iridium catalyst in the presence of *p*-benzoquinone as the co-oxidant (Scheme 1).<sup>8</sup>

Scheme 1. Cyclization of Benzylic Alcohols A to B



As substituted benzofurans are encountered in several bioactive molecules such as cicerfuran (antifungal),9 and machicendiol (asthma and rheumatism),<sup>10</sup> it is of interest to develop new methods to access benzofurans, and an attractive approach will start from the easily accessible compounds of type A(X = O). Compound 1 was prepared and treated under **Conditions I** {[IrCp\*Cl<sub>2</sub>]<sub>2</sub> (2.5 mol %), Cs<sub>2</sub>CO<sub>3</sub> (20 mol %), 1,4-dioxane, 110 °C, 20 h, MW},<sup>4</sup> **Conditions II** {[Ir(cod)Cl]<sub>2</sub> (2.5 mol %), PPh<sub>3</sub> (10 mol %), Cs<sub>2</sub>CO<sub>3</sub> (20 mol %), 1,4-dioxane, 110 °C, 20 h, MW},<sup>5</sup> and Conditions III {([IrLCp\*Cl]<sup>11</sup> (5 mol %), Cs<sub>2</sub>CO<sub>3</sub> (10 mol %), toluene, 110 °C, 20 h, MW)}. Under Conditions I and II, a 50% conversion of 1 and the formation of 2 and 3 in a ratio of 50/50 was observed. Under Conditions III, the conversion of 1 was low (13%) but benzofuran 2was the only observed product (Scheme 2).<sup>12</sup>

Scheme 2. Preliminary Results



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mediate [Ir]–H complex, resulting from the oxidation of the alcohol, the addition of *p*-benzoquinone in the reaction media was envisaged. If *p*-benzoquinone is reduced faster by [Ir]–H to hydroquinone than benzofuran **2** to dihydrobenzofuran **3**, the iridium catalyst would be regenerated (Scheme 3).

To avoid the reduction of 2 to 3 by the formal inter-





A screening of the conditions (base, solvent) was realized to transform 1 to 2 in good yields. Using 0.2 equiv of  $Cs_2CO_3$  in toluene led, after 60 h, to aldehyde 4 as the major product (85%) and to 5% of the desired benzofuran 2 (Table 1, entry 1). Increasing the quantity of base (1.5 equiv) produced, after 40 h, aldehyde 4 (45%) and benzofuran 2 (39%) (Table 1, entry 2). The best conditions were the use of [IrCp\*Cl<sub>2</sub>]<sub>2</sub> (2.5 mol %), *p*-benzoquinone (1.1 equiv), and  $Cs_2CO_3$  (1.5 equiv) in 1,4-dioxane instead of toluene at 110 °C for 20 h (**Conditions IV**), as 1 was fully converted to 2 and isolated in 92% yield (Table 1, entry 3). We have to point out that when *t*-BuOK was used instead of  $Cs_2CO_3$ , whatever the solvent (toluene or 1,4-dioxane),

Table 1. Screening of the Reaction Conditions

		Cp*Cl <sub>2</sub> ] <sub>2</sub> (2.5 mol %) nzoquinone (1.1 equiv) base olvent, time, 110 °C sealed tube		)—cn + ((		
	base					
entry	(equiv)	solvent	time	$ au_{ m c}{}^a$	$2^{a}$	$4^{a}$
1	$Cs_2CO_3$	toluene	60 h	90%	5%	85%
	(0.2 equiv)					
<b>2</b>	$Cs_2CO_3$	toluene	40 h	84%	39%	45%
	(1.5 equiv)					
3	$Cs_2CO_3$	1,4-dioxane	$20 \ h$	100%	100%	/
	(1.5 equiv)				$(92\%)^{b}$	
4	t-BuOK	toluene	$20 \ h$	100%	87%	13%
	(1.5 equiv)					
<b>5</b>	t-BuOK	1,4-dioxane	$20 \ h$	100%	70%	30%
	(1.5 equiv)					

<sup>*a*</sup> Determined by GC/MS. <sup>*b*</sup> Isolated yield.

a mixture of aldehyde **4** and benzofuran **2** was obtained (Table 1, entries 4 and 5).

Having determined a useful set of reaction conditions, the scope and limitation of the transformation of benzylic alcohols of type **A** to benzofurans of type **B** was examined. In this transformation, the presence of various electronwithdrawing groups was not detrimental to the process, as benzofurans **2**, **8**, **9**, and **10** were obtained with good to excellent yields (Scheme 4).





The substitution of the aromatic ring was then studied, and benzofurans 13 and 14 were obtained in good to excellent yields from the corresponding benzylic alcohols 11 and 12 possessing electron-donating or electron-withdrawing groups on the aromatic ring. However, when the aromatic ring of benzylic alcohols 11 and 12 was substituted by a methoxy group at C5, no cyclized product (13c and 14c) was observed but only degradation of the alcohols occurred (Scheme 5).

Scheme 5. Influence of the Substitution of the Aromatic Ring of the Benzylic Alcohol on the Formation of Benzofurans



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To introduce structural diversity into the benzofuran, secondary benzylic alcohols **15** and **16** were subjected to the reaction conditions and, after 20 h, a complete conversion of the starting material was observed. To our delight, we were able to isolate the corresponding benzofurans **17** and **18** in good to excellent yields (60% to 92%). A diversity of functional groups was tolerated; however no conversion was observed in the case of the dithianyl derivative **15e** as the steric hindrance prevents oxidation of the alcohol to the intermediate ketone, and treatment of **15f** with [IrCp\*Cl<sub>2</sub>]<sub>2</sub> [*p*-benzoquinone,  $Cs_2CO_3$ , 1,4-dioxane] led only to the degradation of this alcohol (Scheme 6).



Scheme 6. Cyclization of Secondary Benzylic Alcohols, Scope, and Limitations

With an efficient synthesis of benzofurans established, we turned our attention to the synthesis of benzothiophenes





**21** and indoles **22** (Scheme 7). For that purpose, we have examined the reactivity of **19** and **20** toward the standard reaction conditions (**Conditions IV**). We were able to isolate benzothiophenes **21** and indoles **22** in yields ranging from 40% to 86%. Surprisingly, *N*-tosylbenzyl alcohol **20d** (X = NTs, EWG = CO<sub>2</sub>t-Bu) was transformed to **22d** in 80% yield (Scheme 7).

The transformation of **20d** to **22d** can be explained by the oxidation of **20d** to aldehyde **23** which cyclized to **24**, probably *via* an aldolization. After cleavage of the *N*-tosyl group under basic conditions, the hydroxyimine **25** could be formed, and this latter transformed to **22d** through a tautomeric equilibrium (Scheme 8).

In conclusion, we have developed an efficient chemoselective hydrogen transfer method catalyzed by  $[IrCp*Cl_2]_2$  which, in the presence of *p*-benzoquinone, allows the synthesis of diversely substituted benzofurans, benzothiophenes, and indoles from substituted benzylic alcohols.

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Scheme 8. Supposed Mechanism for the Formation of 22d



**Supporting Information Available.** Experimental procedure and characterization data and NMR spectra of benzylics alcohols and heterocyclic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.