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Synthesis of Benzazoles by Hydrogen-Transfer Catalysis

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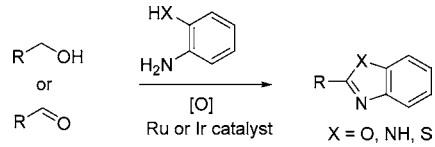
ABSTRACT



Transition-metal-catalyzed hydrogen-transfer reactions have been used for the conversion of alcohols into benzimidazoles and aldehydes into benzoxazoles and benzothiazoles.

Transition-metal-catalyzed hydrogen-transfer reactions have been widely used for the oxidation of a range of organic substrates.[1] In particular, the oxidation of alcohols to carbonyl compounds by hydrogen transfer to a suitable acceptor represents a useful alternative to other oxidation reactions.[2] The use of hydrogen transfer for the oxidation of aldehydes[3] and amines[4] has also been reported. Additionally, oxidation reactions in the absence of a hydrogen acceptor have been achieved in the presence of ruthenium catalysts for the conversion of primary alcohols into esters[5] or amides,[6] as well as the conversion of secondary alcohols into ketones.[7]

We wanted to explore oxidation reactions where aromatization could act as a driving force for loss of hydrogen. Herein, we report the first examples of catalytic hydrogen-transfer reactions for the formation of benzimidazoles, benzoxazoles, and benzothiazoles. These heteroaromatic systems are commonly encountered groups in natural products,[8] pharmaceuticals,[9] agrochemicals,[10] and other effect chemicals, and new methods for their preparation are in frequent demand.

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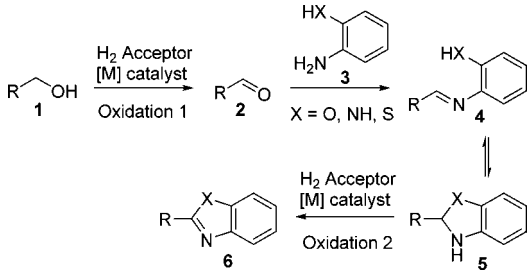
The proposed reaction pathway is described in Scheme 1. Starting from alcohol **1**, catalytic hydrogen transfer to an

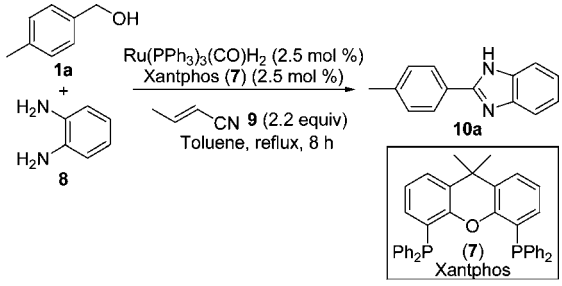
Scheme 1. Conversion of Alcohols or Aldehydes into Benzazoles



appropriate acceptor via "Oxidation 1" would lead to the formation of aldehyde **2**. Alternatively, aldehyde **2** could be used directly as the substrate. In either case, condensation of **2** with an ortho-heterosubstituted aniline **3** generates an intermediate imine **4**, which would be in equilibrium with dihydrobenzazole **5**. A second hydrogen-transfer process from **5** then provides a route to benzazole **6** via "Oxidation 2".

Two of us (J.M.J.W./M.I.H.) have recently reported the use of $Ru(PPh_3)_3(CO)H_2$ in combination with the bidentate ligand Xantphos **7**[11] for the oxidation of alcohols by hydrogen transfer.[12] We therefore chose to use this catalyst for our initial investigations. 4-Methylbenzyl alcohol **1a** was reacted with *o*-aminoaniline **8** in the presence of ruthenium catalyst and crotononitrile **9**, which led to the formation of benzimidazole **10a**, as shown in Table 1.

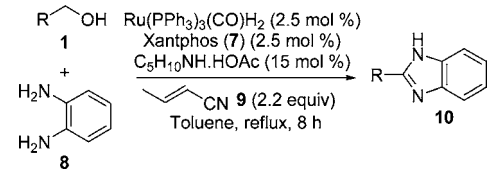
Table 1. Catalyst Optimization for the Formation of Benzimidazole **10a**

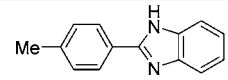
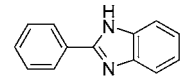
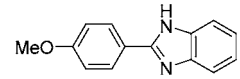
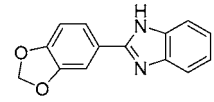
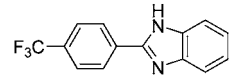
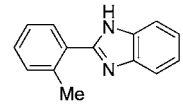
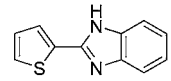
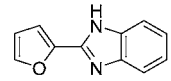
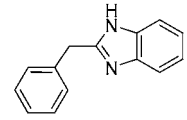
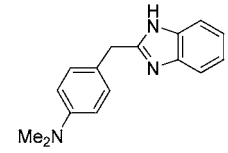
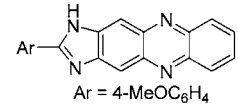


entry	catalyst (2.5 mol %)[a]	additive[b]	conversion (%)
1	$Ru(PPh_3)_3(CO)H_2$	none	48
2	$Ru(PPh_3)_3(CO)H_2$	5 mol % of **A**	97
3	$Ru(PPh_3)_3(CO)H_2$	10 mol % of **A**	6
4	$Ru(PPh_3)_3(CO)H_2$	10 mol % of **B**	75
5	$Ru(PPh_3)_3(CO)H_2$	15 mol % of **B**	98
6	$Ru(PPh_3)_3(CO)H_2$	20 mol % of **B**	98
7	$[Ru(p\text{-cymene})Cl_2]_2$[c] dppe	none	0
8	$[Cp^*IrCl_2]_2$[d]	none	0

[a] Entries 7 and 8 were run at 1.25 mol % of the catalyst dimer (i.e., 2.5 mol % in Ru or Ir). [b] Additive **A** is *p*-TsOH. Additive **B** is piperidinium acetate. [c] Acetone was used as the acceptor in place of **9**. [d] Styrene was used as the acceptor in place of **9**

Table 2. Benzimidazoles Prepared in Scheme 3



entry	benzimidazole product[a]	isolated yield (%)
1		73
2		72
3		79
4		78
5		65
6		43
7		71
8		68
9		70
10		60
11[b]	 Ar = 4-MeOC$_6$H$_4$	85

[a] Conditions: alcohol (1.0 mmol), *o*-aminoaniline (1.2 mmol), crotononitrile (2.2 mmol), piperidinium acetate (15 mol %).

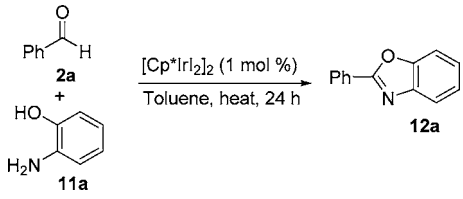
In the absence of any further additive, we were pleased to observe a reasonable conversion into product (Table 1, entry 1). However, the addition of either 5 mol % of *p*-TsOH (entry 2) or piperidinium acetate (entries 4−6) provided an improved conversion. We believe that *p*-TsOH reacts with the ruthenium dihydride to form a ditosylate and that

(11) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

piperidinium acetate may promote addition of *o*-aminoaniline **8** to the intermediate aldehyde by temporary iminium ion formation.

The use of $[Ru(p\text{-cymene})Cl_2]_2$/dppe with acetone as an acceptor[13] and the use of $[Cp^*IrCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) with styrene as the acceptor[14] gave no formation of product, and therefore, the conditions identified in entry 5, Table 1, were used for further reactions. A range of alcohols **1** was converted into the corresponding benzimidazoles **10** as shown in Table 2. The benzimidazole product precipitated from the reaction mixture upon cooling. Benzylic alcohols were converted into benzimidazoles in good yield including electron-rich (entries 3 and 4) and electron-deficient (entry 5) substrates, although the *o*-methyl-substituted benzyl alcohol gave a lower isolated yield (entry 6). The 2-thienyl and 2-furyl substrates (entries 7 and 8) were also found to be effective, as were nonbenzylic substrates (entries 9 and 10). The reaction is not limited to simple *o*-aminoanilines, with heterocyclization also being effected upon 2,3-diaminophenazine in good yield (entry 11).

Table 3. Ir-Catalyzed Conversion of Benzaldehyde into 2-Phenylbenzoxazole

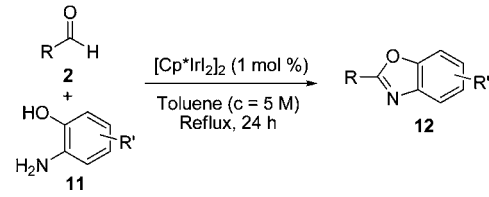


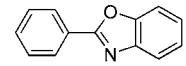
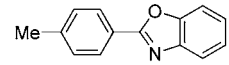
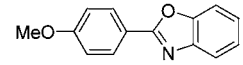
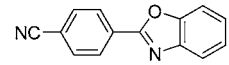
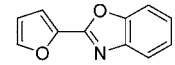
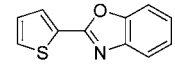
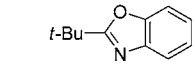
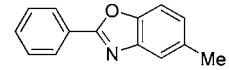
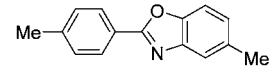
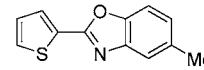
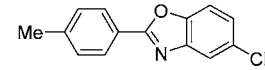
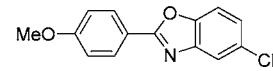
entry	reaction conditions[a]	conversion[b] (%)
1	80 °C	15
2	80 °C, styrene (1.5 equiv)	12
3	80 °C, $MeCO_2H$ (1.0 equiv)	13
4	reflux	52
5	reflux, c = 5 M	100
6	reflux, styrene (1.5 equiv)	50
7	reflux, $[Cp^*IrCl_2]_2$ as catalyst	17
8	reflux, 0.1 mol % of $[Cp^*IrI_2]_2$	17
9	reflux, no catalyst	<5

[a] Conditions: benzaldehyde (1.0 mmol), *o*-aminophenol (1.0 mmol), toluene, c = 0.5 M, 24 h. [b] Conversion determined by NMR ratio of Schiff base to benzoxazole product.

We next examined the formation of benzoxazoles. However, the reaction of benzyl alcohol or benzaldehyde with *o*-aminophenol **11a** using the $Ru(PPh_3)_3(CO)H_2$/Xantphos combination led to a complex mixture of products from which benzoxazole **12a** could not be isolated. The iridium complex $[Cp^*IrI_2]_2$ (SCRAM catalyst) has previously been shown by one of us (A.J.B.) to be effective for the racemization of α-branched amines via temporary oxidation to an achiral imine,[15] and we therefore examined the use of this catalyst for benzoxazole formation. Although no reaction took place between benzyl alcohol and *o*-aminophenol **11a**, we were pleased to find that by starting at the aldehyde oxidation state, the reaction of benzaldehyde **2a** with **11a** led to the formation of benzoxazole **12a** using $[Cp^*IrI_2]_2$ under a range of conditions (Table 3).

Table 4. Acceptorless Oxidation of Aldehydes to Benzoxazoles



entry	benzimidazole product[a]	isolated yield (%)
1		74
2		77
3		85
4		36
5		61
6		80
7		52
8		77
9		80
10		69
11		63
12		68

[a] Conditions: aldehyde (1.0 mmol), *o*-aminophenol (1.2 mmol), $[Cp^*IrI_2]_2$ (1 mol %), PhMe (0.2 cm^3), 111 °C, 24 h.

At 80 °C, only small amounts of product were formed (entries 1−3); however, when the reaction was performed

(12) (a) Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2006**, *47*, 6787. (b) Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal.* **2008**, *350*, 1975. (c) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Chem. Commun.* **2008**, 624.

(13) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725.

(14) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73.

(15) (a) Blacker, A. J.; Stirling, M. J. WO2004046059, Avecia Pharmaceuticals Ltd., 2004. (b) Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Proc. Res. Dev.* **2007**, *11*, 642. (c) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247.

(16) Nakajima, T.; Inada, T.; Igarishi, T.; Sekioka, T.; Shimizu, I. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1941.

at reflux, a higher conversion was obtained (entries 4−6), and quantitative conversion was observed when the reaction was carried out at the higher concentration of 5 M (entry 5). Notably, the reactions were equally effective in the presence or absence of styrene as a sacrificial hydrogen acceptor (entries 1 and 4 versus entries 2 and 6). This suggests that the aromatizing oxidation is ultimately mediated by loss of hydrogen gas from an intermediate (di)hydridoiridium complex. The liberation of hydrogen has previously been observed accompanying the oxidative self-dimerization of primary amines by $[Cp^*IrI_2]_2$.[15b]

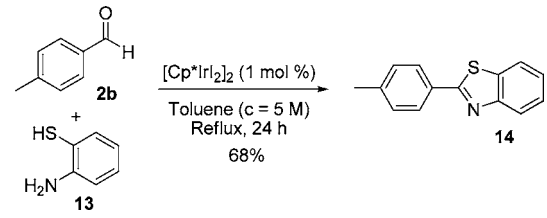
The diiodide $[Cp^*IrI_2]_2$ was found to be a superior catalyst to the corresponding dichloride $[Cp^*IrCl_2]_2$ (entry 7), as expected from their known relative effectiveness as catalysts for amine oxidation.[13] Conversion was too slow to be synthetically useful at a 0.1 mol % catalyst loading (entry 8). Finally, as a control we verified that in the absence of catalyst essentially no product was formed (entry 9).

We then applied these reaction conditions to the conversion of a range of aldehydes **2** into benzoxazoles **12** (Table 4).

Good isolated yields were obtained in the majority of cases. Benzaldehyde (entry 1) and electron-rich benzaldehydes (entries 2 and 3) were good substrates, although the electron-deficient *p*-cyanobenzaldehyde (entry 4) and aliphatic aldehyde (entry 7) only gave moderate yields, consistent with a mechanism involving a hydride abstraction with associated buildup of partial cation character. The use of heterocyclic aldehydes (entries 5 and 6) and substituted *o*-aminophenols (entries 8−11) was successful in all cases. Enolizable aliphatic aldehydes were not suitable substrates, however, giving rise instead to hydroxyquinoline derivatives via enamine condensation/cyclization pathways.[16]

Finally, the reaction conditions used for benzoxazole synthesis were also successfully applied to the synthesis of a benzothiazole. Thus, *p*-tolualdehyde **2b** and *o*-aminothiophenol **13** underwent oxidative cyclization to generate benzothiazole **14** (Scheme 2).

Scheme 2. Formation of a Benzothiazole



In summary, ruthenium-catalyzed hydrogen-transfer reactions have been used for the conversion of alcohols into benzimidazoles using crotononitrile as a hydride acceptor, while iridium-catalyzed acceptorless oxidation has been used for the highly atom economic conversion of aldehydes into benzoxazoles and benzothiazoles.

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Supporting Information Available: Details of experimental procedures and characterization data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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