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[Cp*IrCl$_2$]$_2$-Catalyzed Indirect Functionalization of Alcohols: Novel Strategies for the Synthesis of Substituted Indoles

Simon Whitney,[†] Ronald Grigg,*[,†] Andrew Derrick,[‡] and Ann Keep[§]

Molecular, Innovation, Diversity and Automated Synthesis (MIDAS) Centre,
Department of Chemistry, University of Leeds, Leeds LS2 9JT, United Kingdom

r.grigg@leeds.ac.uk

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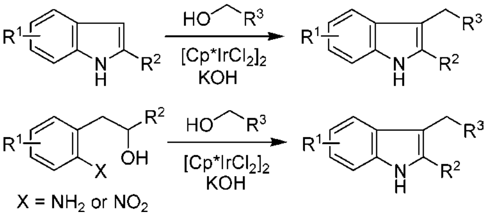
ABSTRACT



We report novel iridium(III)-catalyzed reactions that afford substituted indoles via the indirect functionalization of alcohols via C-3 selective alkylation of indoles with alcohols and a one-pot cascade strategy from amino- or nitro-phenyl ethyl alcohols, which incorporates oxidative cyclization and C-3 alkylation.

The indole ring is a privileged structure found in many structurally diverse natural products and pharmaceutical agents,[1] and new methods for indole synthesis and functionalization continue to attract attention.[2,3]

Increasing demand for environmentally benign processes has focused attention on transition metal catalyzed processes. We have a long-standing interest in direct catalytic alkylation with alcohols, which offers an attractive green chemistry solution due to its high atom efficiency.[4] Recent work in this area includes α-alkylation of ketones with alcohols,[5] indirect Wittig reactions with alcohols,[6] and several publications utilizing [Cp*IrCl$_2$]$_2$ in reactions of this type,[7a] including the direct β-alkylation of secondary alcohols with primary alcohols.[7b]

Previously we have shown the high activity of transition metal catalysts and in particular [Cp*IrCl$_2$]$_2$ in the monoalkylation of arylacetonitriles[8] and barbituric acid[9] with alcohols. As part of our ongoing interest in this area, we report two related [Cp*IrCl$_2$]$_2$-catalyzed cascade reactions that afford substituted indoles.

[†] University of Leeds.

[‡] Pfizer Ltd., Chemical Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, U.K.

[§] Johnson Matthey, Orchard Road, Royston, Hertfordshire SG8 5HE, U.K.

(1) Feniuk, W.; Humphrey, P. P. A. *Drug Dev. Res.* **1992**, *26*, 235.

(2) For reviews on the synthesis of indoles, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (d) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1. (e) Kuethe, J. T. *Chimia* **2006**, *50*, 543.

(3) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

(4) (a) Bibby, C. E.; Grigg, R.; Price, R. *J. Chem. Soc., Dalton Trans.* **1977**, 872. (b) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrrahedron Lett.* **1979**, *20*, 1067. (c) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611. (d) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrahedron* **1981**, *37*, 4313.

(5) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72.

(6) Edwards, M. G.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4740.

(7) (a) Fujita, K.; Yamaguchi, R. *Synlett.* **2005**, 560. (b) Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017.

(8) (a) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *Tetrahedron Lett.* **1981**, *22*, 4107. (b) Lofberg, C.; Grigg, R.; Whittaker, M.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023.

(9) Lofberg, C.; Grigg, R.; Keep, A.; Derrick, A.; Sridharan, V.; Kilner, C. *Chem. Commun.* **2006**, 5000.

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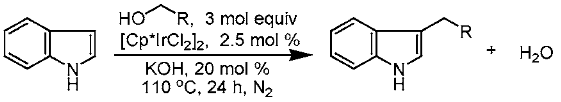
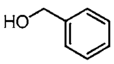
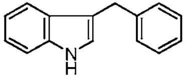
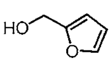
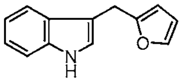
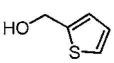
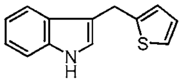
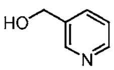
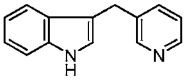
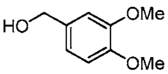
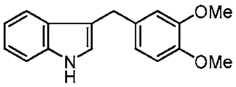
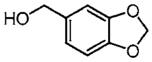
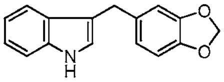
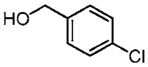
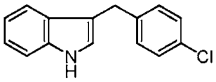
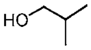
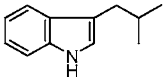
First we investigated the $[Cp^*IrCl_2]_2$-catalyzed alkylation of indole with alcohols under essentially solvent-free conditions using a slight excess of alcohol to achieve a stirrable mixture (Table 1). Indole was readily alkylated with aromatic, heteroaromatic, and aliphatic alcohols to give a variety of 3-substituted indoles in moderate to high yield. To the best of our knowledge this is the first reported hydrogen transfer mediated alkylation of indoles with alcohols using a transition metal catalyst.

Table 1. Alkylation of Indole with a Variety of Alcohols Using $[IrCp^*Cl_2]_2$ and KOH[a]



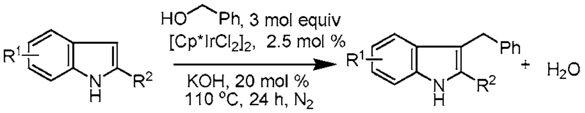
entry	alcohol	product	yield (%)[b]
1			80
2			84
3			54
4			83
5			70
6			78
7			81[c]
8			35[d]

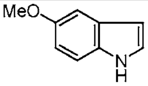
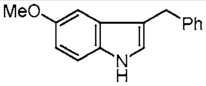
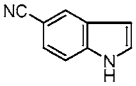
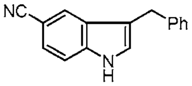
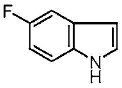
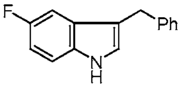
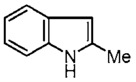
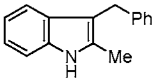
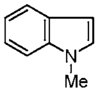
[a] Reactions were carried out in a sealed tube at 110 °C for 24 h with indole (1.0 mmol), alcohol (3.0 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH (0.2 mmol). Bis-indolylmethane byproducts 11−20% (Scheme 2) were observed by ^{1}H NMR. [b] Isolated yield. [c] Reaction time 48 h. [d] Reaction time 48 h, ratio of product : bis-indolylmethane byproduct was 3.5:1.

Next we investigated the alkylation of substituted indoles (Table 2). Introduction of electron-donating and electron-withdrawing groups was tolerated as was substitution in the 2-position. However *N*-methyl indole failed to undergo alkylation (Table 2, entry 6), implicating the indole anion in the alkylation (Scheme 1).

Scheme 1 is supported by the formation of minor bis-indolylmethane byproducts arising from Michael addition of indole to the intermediate **A** (Scheme 2).[10]

Table 2. Alkylation of Substituted Indoles with Benzyl Alcohol Using $[IrCp^*Cl_2]_2$ and KOH[a]

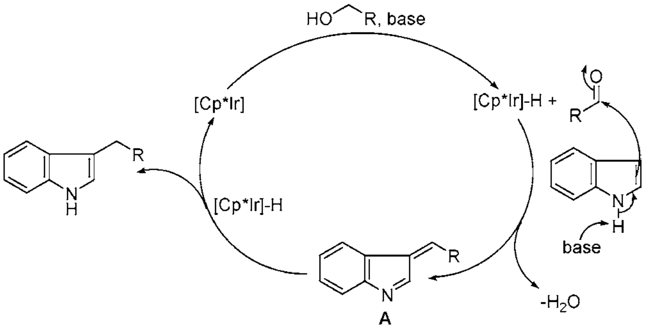


entry	indole	product	yield (%)[b]
1			65[c]
2			60[d]
3			73
4			69
5		-	-[e]

[a] Reactions were carried out in a sealed tube at 110 °C for 24 h with the indole (1.0 mmol), benzyl alcohol (3.0 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH (0.2 mmol). [b] Isolated yield. [c] Ratio of desired:bis-indolylmethane byproduct was 6:1. [d] Reaction time was 48 h. [e] No product was observed after 72 h.

The use of transition metal catalysts for the oxidative cyclization of 2-aminophenyl ethyl alcohols to give indoles has been reported,[11] and it was therefore of interest to investigate a $[Cp^*IrCl_2]_2$-catalyzed/oxidative cyclization/alkylation cascade of 2-aminophenyl ethyl alcohol and benzyl alcohol (Table 3).

Scheme 1. Proposed Mechanism for the $[Cp^*IrCl_2]_2$-Catalyzed Alkylation of Indole with Alcohols



Initial trials using 5 molar equiv of benzyl alcohol to aid solubility gave a mixture of *N*- and 3-benzyl indole due to similar rates of intramolecular cyclization and intermolecular *N*-alkylation. However at higher base concentration the

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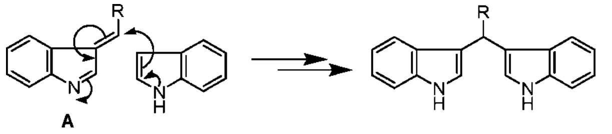
(10) Gibbs, T. J. K.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2005**, *3*, 4043.

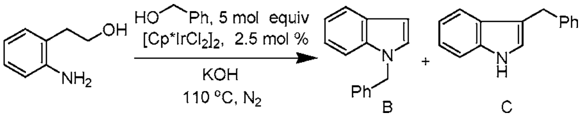
(11) (a) Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *4*, 2691. (b) Aoyagi, Y.; Mizusaki, T.; Ohta, A. *Tetrahedron Lett.* **1996**, *37*, 9203. (c) Tsuji, Y.; Kotachi, S.; Huh, K.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580. (d) Tsuji, Y.; Huh, K.; Yokoyama, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1575.

Scheme 2. Proposed Mechanism for the Formation of Minor Bis-indolylmethane Byproducts



reaction was highly selective for 3-benzylindole, which was isolated in 78% yield (Table 3, entry 5).

Table 3. Oxidative Cyclization/Alkylation of 2-Aminophenyl Ethyl Alcohol with Benzyl Alcohol Using $[Cp^*IrCl_2]_2$ and Varying Amounts of KOH[a]



entry	KOH (mmol)	conversion[b] (%)	ratio[b] B:C
1	0.1	60	50:50
2	0.2	>95	50:50
3	0.5	>95	33:67
4	1.0	>95	13:87
5	2.0	>95	1:99 (78%)[c]

[a] Reactions were carried out in a sealed tube at 110 °C for 24 h with amino alcohol (1.0 mmol), benzyl alcohol (5.0 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH. [b] Estimated from ^1H NMR. [c] Isolated yield of 3-benzylindole (C).

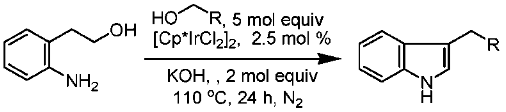
The synthesis of C-3 substituted indoles from 2-aminophenyl ethyl alcohol and a variety of alcohols was investigated using the optimized conditions (Table 4). Moderate to high yields were achieved for aromatic, heteroaromatic, and aliphatic alcohols. The high yielding synthesis of *N*,*N*-dimethyltryptamine (Table 4, entry 7) is of particular interest as analogues of this compound form a class of commercially important anti-migraine drugs.[2a]

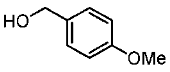
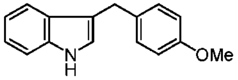
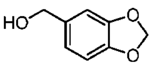
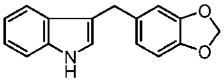
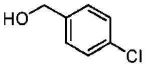
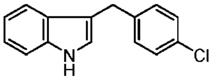
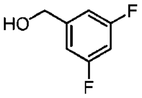
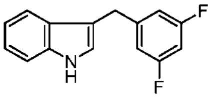
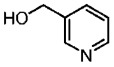
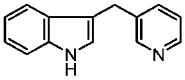
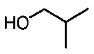
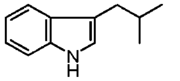
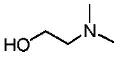
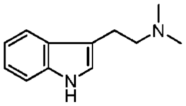
Next we investigated the effect of substitution on the amino alcohol (Table 5). Good yields of disubstituted indoles were achieved with substitution tolerated on the aromatic ring (Table 5, entries 1 and 2) and also on the ethanol side chain to give 2-methyl-3-benzyl indole in 71% yield (Table 5, entry 3).

The overall catalytic sequence consists of two interlocking $[Cp^*IrCl_2]_2$-catalyzed cycles (Scheme 3). The first cycle is the oxidative cyclization of the amino alcohol to generate the indole component.[11a] The second is the C-3 alkylation of the in situ formed indole as described in Scheme 1.

Fujita et al. reported the use of $[Cp^*IrCl_2]_2$ in the reduction of 2-nitrophenyl ethyl alcohol in the presence of propan-2-ol as a sacrificial hydrogen donor to give indole.[11a] In order to incorporate the reduction of the nitro group into our chemistry, we explored the reaction of 2-nitrophenyl ethyl alcohol and benzyl alcohol (Scheme 4).

Table 4. One-Pot Synthesis of Substituted Indoles from 2-Aminophenyl Ethyl Alcohol and Primary Alcohols[a]

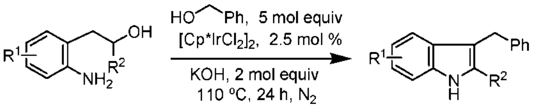


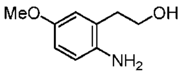
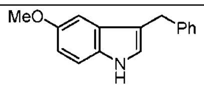
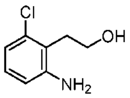
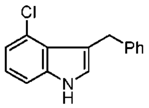
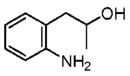
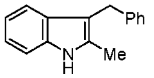
entry	alcohol	product	yield (%)
1			75
2			71
3			68[c]
4			71[c]
5			68[c]
6			53[c]
7			74[c]

[a] Reactions were carried out in a sealed tube at 110 °C for 24 h with amino alcohol (1.0 mmol), alcohol (5.0 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), and KOH (2.0 mmol). [b] Isolated yield. [c] Reaction time 48 h.

Using 10 molar equiv of benzyl alcohol, we obtained 3-benzylindole in 49% yield. This result is significant as it demonstrates the ability to incorporate further steps into the already complex catalytic cascade, which is dependent on the relative rates of the individual steps in the sequence. In this reaction $[Cp^*IrCl_2]_2$ is performing multiple oxidation and reduction steps. In Tables 4 and 5 and Scheme 4 little,

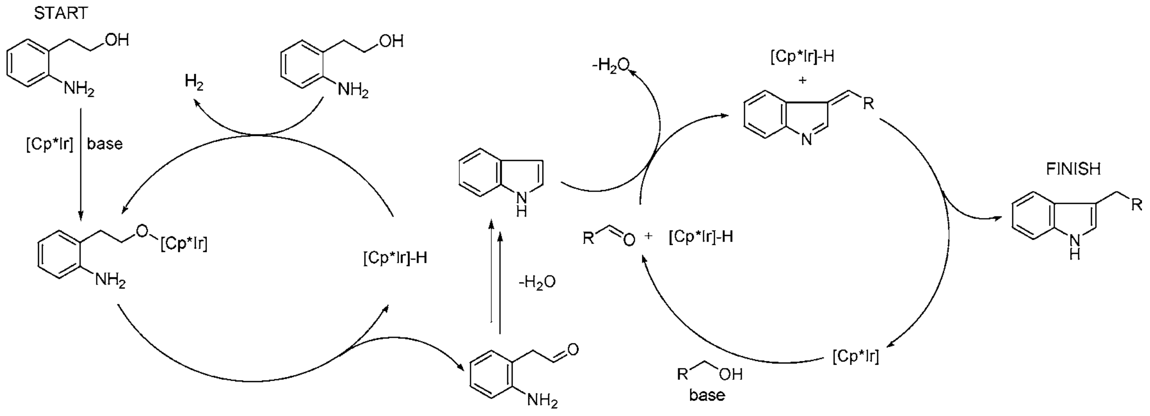
Table 5. One-Pot Synthesis of 3-Benzylindoles from Amino Alcohols and Benzyl Alcohol[a]



entry	amino alcohol	product	yield[b] (%)
1			74
2			65
3			71

[a] Reaction conditions as for Table 3. [b] Isolated yield

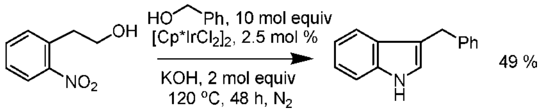
Scheme 3. Proposed Mechanism for the One-Pot, Tandem Oxidative Cyclization/Alkylation of 2-Aminophenyl Ethyl Alcohol and Primary Alcohols To Afford Substituted Indoles



if any, bis-indolylmethane byproducts were evident, highlighting indole concentration as the key factor in the generation of these species.

In conclusion, two novel $[Cp^*IrCl_2]_2$-catalyzed methods for the synthesis of substituted indoles have been developed, utilizing the indirect functionalization of alcohols. These allow one-pot access to a wide range of key building blocks. Work continues on the development and application of this methodology.

Scheme 4. One-Pot Synthesis of 3-Benzylindole from 2-Nitrophenyl Ethyl Alcohol and Benzyl Alcohol



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

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