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Ruthenium-Catalyzed Alkylation of Oxindole with Alcohols

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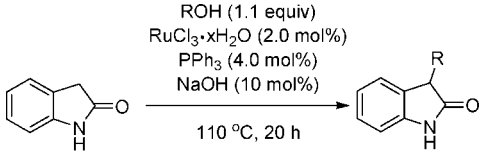
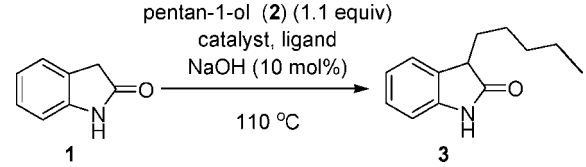


An atom-economical and solvent-free catalytic procedure for the mono-3-alkylation of oxindole with alcohols is described. The reaction is mediated by the in situ generated catalyst from $RuCl_3 \cdot xH_2O$ and PPh_3 in the presence of sodium hydroxide. The reactions proceed in good to excellent yields with a wide range of aromatic, heteroaromatic, and aliphatic alcohols.

The oxindole ring system is found in many natural products[1] and biologically active molecules.[2] Usually, the 3-position is substituted with one or two substituents which can be introduced from the parent molecule by alkylation with alkyl halides[2]/allylic esters[3] or by arylation with aryl halides.[4] Recently, alcohols have been used for alkylation of activated methylene compounds such as malonates,[5] barbiturates,[6] ketones,[7] and certain nitriles[8] where water is produced as the only byproduct. In all cases, the pK_a value of the methylene group is less than ~20 and the alkylation is achieved with a transition-metal catalyst and a base. The mechanism involves dehydrogenation of the alcohol to the carbonyl compound followed by addition of the activated methylene compound, elimination of water, and hydrogenation of the resulting C−C double bond.[9] Since the pK_a of the methylene group in oxindole is 18.2,[10] we speculated that this environmentally friendly alkylation reaction could also be used for introducing substituents in the 3-position of this motif.[11] Herein, we describe an expedient ruthenium-catalyzed procedure for alkylation of oxindoles with alcohols.

TABLE 1. Catalyst Screening for the Alkylation of Oxindole (1) with Pentan-1-ol (2)[a]



entry	catalyst	catalyst loading (mol %)	ligand	**3**[b] (%)
1	$[Cp^*IrCl_2]_2$	1.0		>95
2	$[IrCl(cod)]_2$	1.0	PPh_3	32[c]
3	$[RuCl_3 \cdot xH_2O]$	2.0	PPh_3	>95[c]
4	$[RuCl_3 \cdot xH_2O]$	2.0		0
5	$[RuCl_2(PPh_3)_3]$	2.0		>95
6	$[Ru(p\text{-cymene})Cl_2]_2$	1.0		47
7	$[Ru(p\text{-cymene})Cl_2]_2$	1.0	Xantphos	>95[d]
8	$[Ru(PPh_3)_3(CO)H_2]$	2.0		53
9	$[Ru(PPh_3)_3(CO)H_2]$	2.0	Xantphos	81[d]
10	Shvo's[14]	1.0		>95
11	$[Ru(acac)_3]$	1.0		0

[a] **1** (2.0 mmol) was reacted with **2** (2.2 mmol) under the influence of catalyst (1.0−2.0 mol %) and NaOH (10 mol %) at 110 °C for 20 h. [b] Conversion was estimated by ^1H NMR spectroscopy based on **1**. [c] PPh_3 (4.0 mol %). [d] Xantphos (2.0 mol %).

The studies began with investigating the direct catalytic alkylation of oxindole (**1**) with pentan-1-ol (**2**) (Table 1). We

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(5) Pridmore, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **2008**, *49*, 7413–7415.

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(11) Excess Raney nickel has been shown to mediate the alkylation of oxindole in alcohol solvent at 150−220 °C; see: Volk, B.; Mezei, T.; Simig, G. *Synthesis* **2002**, 595–597.

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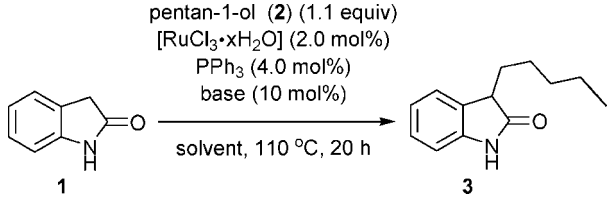
TABLE 2. Influence of Base and Solvent on the Catalytic Alkylation of Oxindole (1) with Pentan-1-ol (2)[a]



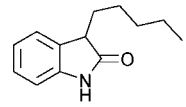
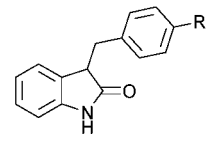
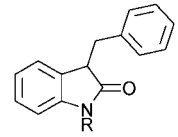
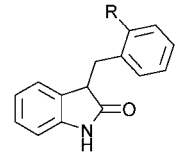
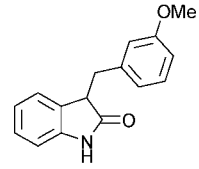
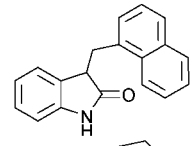
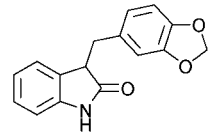
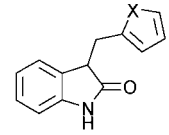
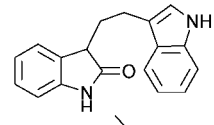
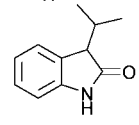
entry	base	solvent	3[b] (%)
1	NaOH		>95
2	KOH		>95
3	Na_2CO_3		58
4	K_2CO_3		80
5	Cs_2CO_3		>95
6	Et_3N		39
7			0
8	NaOH	toluene	>95[c]
9	NaOH	*p*-dioxane	92[c]
10	NaOH	water	58[c]

[a] **1** (2.0 mmol) was reacted with **2** (2.2 mmol) under the influence of $RuCl_3 \cdot xH_2O$ (2.0 mol %), PPh_3 (4.0 mol %), and base (10 mol %) at 110 °C for 20 h. [b] Conversion was estimated by ^1H NMR spectroscopy based on **1**. [c] Solvent (1.0 mL) added.

decided to employ the commercially available trivalent iridium complex $[Cp^*IrCl_2]_2$[12] for the first experiments since this catalyst has previously shown high reactivity in the alkylation of barbiturates and arylacetonitriles with primary alcohols.[6,8a] After surveying a small range of bases and reaction temperatures, it was found that the alkylation of **1** with **2** proceeded cleanly to provide the 3-alkylation product in almost quantitative yield when the reaction was performed under neat conditions at 110 °C. Surprisingly, the catalyst system based on $[IrCl(cod)]_2$ and PPh_3 only provided the desired product in low yield (Table 1, entries 1 and 2). With these encouraging results in hand, we decided to examine the performance of a range of different catalysts in the alkylation reaction in order to find a cheaper ruthenium-based catalyst system. The in situ generated catalyst based on $[RuCl_3 \cdot xH_2O]$ and PPh_3 as well as the preformed $[RuCl_2(PPh_3)_3]$ complex afforded the desired product in high yield (entries 3 and 5). The addition of PPh_3 proved to be essential since the absence of PPh_3 resulted in complete recovery of the starting materials. A selection of other ruthenium-based catalysts were tested in the reaction. $[Ru(p\text{-cymene})Cl_2]_2$ and $[Ru(PPh_3)_3(CO)H_2]$ in combination with Xantphos[13] as well as Shvo's catalyst[14] provided the product in high yields while $[Ru(acac)_3]$ and $[Ru(p\text{-cymene})Cl_2]_2$ with no additional ligand added gave either no reaction or low conversion (entries 6−11). We did not in any case observe dialkylation of the C-3-position, nor did we observe any *N*- or *O*-alkylation. Based on this initial screening, we decided to use $[RuCl_3 \cdot xH_2O]$ in combination with PPh_3 for the further studies.

A number of experiments were carried out to investigate the influence of the base and the solvent (Table 2). Sodium hydroxide and potassium hydroxide seemed to perform equally well leading to complete conversion of the starting material (entries 1 and 2). Lower yields were observed when sodium or potassium carbonate as well as triethylamine were employed, while cesium carbonate afforded full conversion of **1** (entries 3−6). Not surprisingly no reaction was observed in the absence of a base, and the starting materials were recovered quantitatively (entry 7). The reaction performed very well in toluene or dioxane while water gave a slightly lower yield (entries 8−10). However, for general use we decided to use sodium hydroxide as the additive under neat reaction conditions.

TABLE 3. Catalytic Alkylation of Oxindole (1) with Various Alcohols[a]

entry	product		yield[b]
1			89
2		R = H	89
3		F	83
4		CF_3	86
5		Cl	89
6		Me	92
7		OMe	83
8		NHPiv	74[c]
9		Bn	91
10		PMB	92
11		F	81
12		Cl	88
13		Me	90
14		OMe	85
15			84
16			87
17			79
18		X = O	71[c]
19		S	81
20			72[c]
21			73[d]

[a] **1** (2.0 mmol) was reacted with **2** (2.2 mmol) under the influence of $RuCl_3 \cdot xH_2O$ (2.0 mol %), PPh_3 (4.0 mol %), and base (10 mol %) at 110 °C for 20 h. [b] Isolated yield. [c] Toluene (1.0 mL) used as cosolvent. [d] Stirred for 48 h with 5 equiv (10 mmol) of the alcohol.

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We then turned our attention to other alcohols in order to investigate the scope of the 3-alkylation procedure (Table 3). The reaction proceeded in high yield when benzylic alcohols with either electron-donating or electron-withdrawing groups present in the 2-, 3-, or 4-position were employed (entries 2−8 and 11−15). It is interesting that chloro substituents are tolerated under the reactions conditions (entries 5 and 12) since they will allow for further functionalization of the alkylated product through cross-coupling chemistry. The use of 4-bromobenzyl alcohol or 4-(hydroxymethyl)benzonitrile led to complex product mixtures probably due to hydrodehalogenation and hydrolysis, respectively. It should be noted that several protecting groups such as amide, benzyl, and *p*-methoxybenzyl were compatible with the reaction conditions (entries 8−10). Some steric hindrance ortho to the benzyl alcohol is well-tolerated (entries 11−14 and 16), while the highly congested 2,4,6-trimethylbenzyl alcohol and 2,6-dimethoxybenzyl alcohol afforded the desired alkylated product in less than 25% yield as judged by ^{1}H NMR. A variety of pharmacophoric functionalities such as catechol, thiophene, furan, and unprotected indole also proved successful in the catalytic alkylation (entries 17−20). Notably, the attempt to alkylate **1** with 2-hydroxymethylfuran under neat conditions mainly led to decomposition while the addition of toluene provided a clean alkylation (entry 18).

The reaction in entry 21 required longer reaction time and excess alcohol (5 equiv) to reach full conversion of the oxindole which shows that secondary alcohols react significantly slower than the corresponding primary alcohols. Attempts to use cyclohexanol and cyclopentanol gave inseparable mixtures of the α,β-unsaturated aldol product and the desired product. Thus for secondary alcohols the reduction of the putative intermediate α,β-unsaturated carbonyl species seems to be the rate-limiting step. When 4-penten-1-ol was employed in the alkylation procedure, a 2:1 mixture of **3** and the corresponding α,β-unsaturated oxindole was obtained in a modest 27% yield.

In conclusion, we have developed a convenient, cheap, and very effective catalytic system for the selective mono 3-alkylation of unprotected and protected oxindoles with a range of aromatic, heteroaromatic, and aliphatic alcohols. This catalytic hydrogen transfer reaction constitutes a highly atom-economical transformation that can be performed under neat conditions and only produces water as the byproduct.

Experimental Section

General Procedure for 3-Alkylation of Oxindole. [$RuCl_3 \cdot xH_2O$] (8.3 mg, 0.04 mmol), PPh_3 (21.0 mg, 0.08 mmol), NaOH (8.0 mg, 0.2 mmol), oxindole (266 mg, 2.0 mmol), and the alcohol (2.2 mmol) were placed in a 7-mL thick-walled screw-cap vial. The vial was purged with Ar and sealed with a screw-cap. The mixture was placed in an aluminum block preheated to 110 °C and stirred for 20 h or until ^{1}H NMR of the crude reaction mixture showed complete consumption of the oxindole. The reaction mixture was allowed to cool to room temperature followed by dilution with CH_2Cl_2 (10 mL). SiO_2 was added, and the suspension was concentrated under reduced pressure to afford a powder that was purified by use of silica gel chromatography (3 × 15 cm SiO_2, 9:1 → 4:1 → 3:7 *n*-hexane/EtOAc).

3-Pentyl-1,3-dihydroindol-2-one (3) (Table 3, entry 1). Isolated yield 89%; colorless oil; R_f = 0.18 (heptane/EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (bs, 1H), 7.26−7.17 (m, 2H), 7.08−6.98 (m, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.48 (t, J = 5.9, 1H), 2.28−1.86 (m, 2H), 1.55−1.16 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 141.6, 129.9, 127.7, 124.1, 122.2, 109.7, 46.1, 31.8, 30.5, 25.4, 22.4, 14.0; IR (neat) 3211, 3094, 3060, 3031, 2955, 2928, 2858, 1701, 1620, 1470, 1338, 1219, 1100, 749 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{21}N_2O$ ([M + H + MeCN]$^+$) 245.1654, found 245.1649.

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Supporting Information Available: General experimental methods, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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