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Iridium-Catalyzed Conversion of Alcohols into Amides via Oximes

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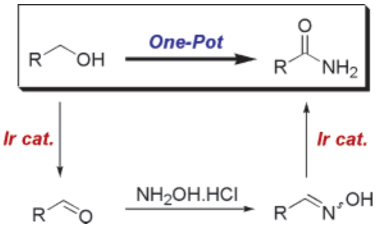
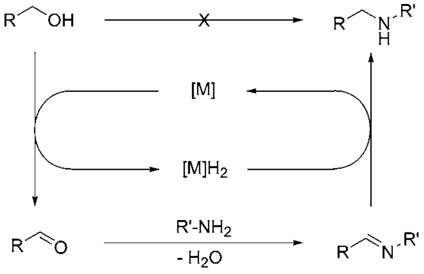
ABSTRACT



The iridium catalyst $[Ir(Cp^*)Cl_2]_2$ is effective for the rearrangement of oximes to furnish amides. The reaction has been combined with catalytic transfer hydrogenation between an alcohol and alkene to allow the conversion of alcohols into amides in a one-pot process.

Transition metal catalyzed transfer hydrogenation reactions have been used successfully for the interconversion of alcohols and carbonyl compounds.[1] Some catalysts also allow for the reduction of alkenes[2] or imines[3] using an alcohol as the stoichiometric reducing agent. Research from this group[4] and from others[5] has demonstrated that iridium and ruthenium catalysts can be used for the conversion of alcohols into amines, according to the pathway outlined in Scheme 1. The alcohol is oxidized into an aldehyde, which then undergoes simple imine formation in situ. These intermediates are reduced to the corresponding amine without any overall change in oxidation state. This "borrowing hydrogen" strategy has also been applied to the synthesis of C−C bonds from alcohols via the aldehyde and alkene.[6]

Scheme 1. C−N Bond Formation from Alcohols



We were interested in the possibility of converting alcohols into hydroxylamines using this catalytic pathway, although it is known that oximes are less amenable to reduction than are the equivalent imines.[7] We were unable to identify a catalyst that was able to reduce benzaldehyde oxime with isopropanol. However, the iridium catalyst $[Ir(Cp^*)Cl_2]_2$ gave an unusual rearrangement reaction leading to the corresponding amide. Neither alcohol nor base was required for the rearrangement reaction to be effective. Yamaguchi and co-workers have

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[1] Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045−2061.
[2] Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 4710−4712.
[3] Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917.
[4] (a) Cami-Kobeci, G.; Williams, J. M. J. *Chem. Commun.* **2004**, 1072. (b) Cami-Kobeci, G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Bioorg. Med. Chem.* **2005**, *15*, 535−537.
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[6] (a) Edwards, M. G.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4740−4743. (b) Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.: Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D. *Chem. Commun.* **2004**, 90−91.
[7] Jnaneshwara, G. K.; Sudalai, A.; Deshpande, V. H. *J. Chem. Res., Synop.* **1998**, 160−161.

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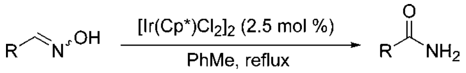
previously used this catalyst for a range of transfer hydrogenation reactions.[8] Transition metal complexes have been reported to dehydrate oximes to the corresponding nitriles,[9] but the only report of a catalytic rearrangement into amides required high temperatures (5 mol % $RhCl(PPh_3)_3$, 150 °C).[10]

We developed a standard set of conditions that was successful for the conversion of a range of oximes into the corresponding amides. Thus, treatment of oximes with $[Ir(Cp^*)Cl_2]_2$ in toluene provided the amides exceptionally cleanly upon heating at reflux for 4−16 h. The isolated yields of the amides after simple purification were consistently excellent (Table 1). Either the (*E*)- or (*Z*)- isomer of the oxime could be used,[11] although the interconversion of the (*Z*)-isomer into the (*E*)-isomer was more rapid than the rearrangement into the amide. Commercially available oximes are usually a mixture of the (*E*)- and (*Z*)-isomers, which were successfully employed for entries 5−10. Aromatic, aliphatic, and heteroaromatic oximes were all viable substrates for this rearrangement process.

Table 1. Ir-Catalyzed Rearrangement of Oximes into Amides

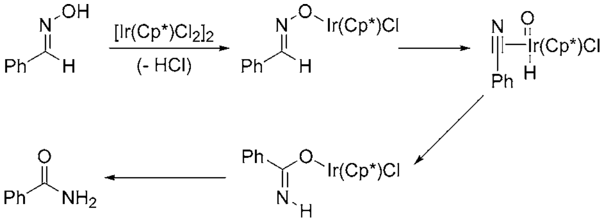


entry[a]	R[b]	*t* (h)	yield (%)[c]
1	*Z*-Ph	6	91
2	*E*-Ph	6	92
3	*Z*-(4-MeO)C_6H_4	6	90
4	*E*-(4-MeO)C_6H_4	6	92
5	(2,4-Cl)C_6H_3	8	88
6	(4-O_2N)C_6H_4	8	85
7	C_3H_7	4	97
8	$C_6H_5CH{=}CH$	4	94
9	2-furyl	12	82
10[d]	3-pyridyl	16	78

[a] Conditions: oxime (1.0 mmol), $[Ir(Cp^*)Cl_2]_2$ (2.5 mol %), PhMe (2 cm^3); 111 °C. [b] Unless specified, oximes are commercially available as mixed *E*/*Z* isomers. [c] Isolated yields after recrystallization or column chromatography. [d] DMF as solvent; 111 °C.

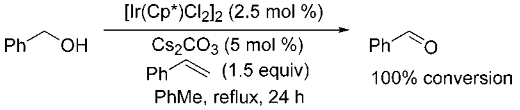
From a mechanistic standpoint, it was interesting to observe that O-alkylated oximes were inert to reaction, as were oximes derived from ketones. This suggested that the presence of both a hydrogen and a hydroxyl group was required for the transformation. In addition, nitrones were also resistant to rearrangement. Benzonitrile was inert to hydrolysis under these reaction conditions, suggesting that the reaction does not proceed via a free nitrile. Several mechanisms could be conceived for this process, with one option being that outlined in Scheme 2, where initial displacement of a chloride by oxime allows the iridium to remove the oxygen and the hydride, followed by replacing them in the isomeric form prior to the release of amide.

Scheme 2. Mechanistic Proposal for the Rearrangement

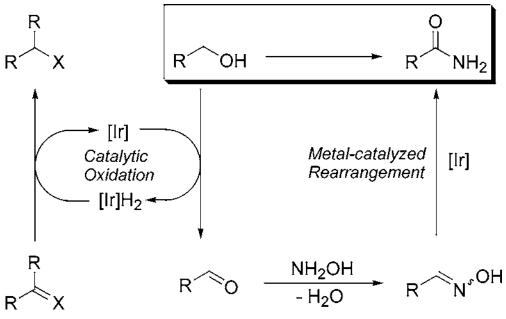


Since iridium complexes are known to be good catalysts for transfer hydrogenation reactions of alcohols and carbonyl compounds,[8] we investigated the use of alcohols as starting materials. We reasoned that in the presence of a suitable hydrogen acceptor, an alcohol would be transformed into an aldehyde which could be converted *in situ* to the corresponding oxime and then further transformed into an amide. This would then provide a one pot conversion of alcohols into amides, where the iridium complex would fulfill a dual role, acting as a catalyst in the two key steps. The total conversion of benzyl alcohol to benzaldehyde was readily achieved employing styrene (in slight excess) as the sacrificial acceptor, using $[Ir(Cp^*)Cl_2]_2$ as the catalyst in toluene at reflux over 24 h (Scheme 3). We chose to use an alkene as the oxidant to avoid having an additional carbonyl compound present that would cause complications in the oxime-forming step, although transfer hydrogenation reactions employing alkenes in this manner have remained

Scheme 3. Optimized Oxidation Conditions



Scheme 4. Novel Strategy for Converting Alcohols into Amides



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[8] (a) Review: Fujita, K.; Yamaguchi, R. *Synlett* **2005**, 560−571. (b) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* **2003**, *68*, 1601−1602.

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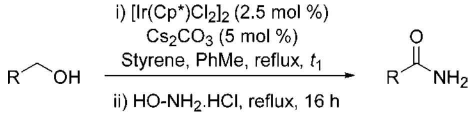
[11] For examples, see: (a) Albrecht, M. R.; Crabtree, R. H.; Mata, J.; Peris, E. *Chem. Commun.* **2002**, 32. (b) Tani, K.; Iseki, A.; Yamagata, T. *Chem. Commun.* **1999**, 1821. (c) Hillier, A. C.; Lee, H. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 4246.

Table 2. One-Pot Synthesis of Amides from Alcohols



entry[a]	R	t_1 (h)	yield (%)[b]
1	Ph	24	87
2	(4-Me)C_6H_4	24	90
3	(4-F)C_6H_4	24	84
4	(4-Br)C_6H_4	30	79
5	(4-Cl)C_6H_4	30	83
6	(4-MeO)C_6H_4	24	91
7	(4-BnO)C_6H_4	24	90
8	(4-O_2N)C_6H_4	36	48
9	(4-F_3C)C_6H_4	36	56

[a] Conditions: alcohol (1.0 mmol), [Ir(Cp*)Cl_2]$_2$ (2.5 mol %), PhMe (2 mL); 111 °C. [b] Isolated yields after recrystallization or column chromatography.

comparatively poorly developed.[11] Styrene is a convenient oxidant as it is cheap and benign, and both itself and the reduced product (ethylbenzene) can be removed by simple evaporation.

We established the procedure shown in Scheme 4 for the conversion of alcohols into amides. The alcohol was oxidized into the corresponding aldehyde using the iridium catalyst in the presence of base over 24−36 h. Hydroxylamine hydrochloride was added to the reaction mixture, and the reaction was heated at reflux to allow the oxime to form and then undergo rearrangement into the amide, which was isolated in moderate to excellent yield. Kanno and Taylor have reported a tandem oxidation/oxime-forming process[12] and a related process in which amides can be formed via aldehydes[13] using stoichiometric manganese(IV) oxide.

The amides formed from alcohols are identified in Table 2, along with the isolated yields and time required for the oxidation step. These reactions were successful for a range of benzylic alcohols, although those with electron-withdrawing groups gave rise to more sluggish oxidations and lower yields. The reaction proved to be unsuccessful for aliphatic alcohols, as no oxidation to the aldehyde was observed under the conditions employed. Further studies into metal-mediated oxidations of this type are ongoing.

In summary, we have identified a novel iridium-catalyzed rearrangement of oximes into amides, which has also been used in a sequential process that permits the conversion of alcohols into amides in good yield and with minimal purification.[14] Further studies into this and other metal-mediated tandem and sequential reactions will be reported in due course.

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

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[12] Kanno, H.; Taylor, R. J. K. *Synlett* **2002**, 1287−1290.

[13] Foot, S. J.; Kanno, H; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055−1064.

[14] **Representative Procedure for Formation of Amides from Alcohols via a Sequential Process.** To an oven-dried, nitrogen-purged Schlenk tube charged with [Ir(Cp*)Cl_2]$_2$ (0.025 mmol) and cesium carbonate (16.4 mg, 0.05 mmol) were added alcohol (1 mmol), styrene (172 μL, 1.5 mmol), and degassed anhydrous toluene (2 cm^3) via syringe, and the mixture was heated at reflux. The reaction was allowed to cool to room temperature and hydroxylamine hydrochloride (36.2 mg, 1 mmol) added. The vessel was flushed with nitrogen and the mixture further refluxed for 16 h. The reaction was allowed to cool to room temperature, diluted with dichloromethane, and filtered through a short plug of silica gel, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel or recrystallization from suitable solvent