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Iridium-Catalyzed Direct Dehydroxylation of Alcohols

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Iridium-catalyzed direct dehydroxylation of alcohols with hydrazine was developed through a combination of the oxidation of alcohols and the Wolff–Kishner reduction. This protocol is simple to perform and highly efficient for a series of primary, benzylic and allylic alcohols.

Introduction

The dehydroxylation of alcohols is arguably one of the most fundamental transformations in organic chemistry and continuously plays an insurmountable role in the total synthesis of complex natural products bearing multifunctional groups.^[1] In addition, there is a great demand for more efficient dehydroxylation procedures in biomass conversions.^[2] The best known method for the dehydroxylation of alcohols was established by Barton and McCombie in 1975 through a radical synthetic procedure, which requires multistep conversions and proceeds with overall low atom efficiency.^[3] Many alternatives, including benzovl-ester-mediated^[4] and the phosphite-mediated^[5] variants, have since been developed. However, these strategies still require the conversion of an alcohol into the preactivated intermediate, which is subsequently transformed into the corresponding C-H bond by a radical process [Scheme 1, Eq. (1)].

The ever-increasing desire for efficient chemical transformations in the synthetic community calls for more direct dehydroxylation methods. Recently, two prominent attempts to achieve this challenging goal were reported. In 2010, Barrero and co-workers described the groundbreaking dehydroxylation of benzylic and allylic alcohols utilizing Nugent's reagent (Cp₂TiCl) to homolyze the C-O bond [Scheme 1, Eq. (2)].^[6] Very recently, Stephenson and coworkers developed visible-light-photoredox-catalyzed onepot dehydroxylation through an organic iodide intermediate, with a combination of the Garegg-Samuelsson reaction and flow chemistry [Scheme 1, Eq. (3)].^[7] Although these two procedures represent major ongoing efforts toward the direct dehydroxylation of alcohols, they still suffer from certain limitations: the substrate scope of the former is restricted to reactive candidates such as benzylic and allylic





Scheme 1. Conventional radical dehydroxylation methods versus efforts toward direct dehydroxylation. Cp = cyclopentadienyl, ppy = 2-phenylpyridinato, LED = light-emitting diode.

alcohols, and the latter is operationally complex, requiring a photoreactor with continuous flow. Thus, the development of a simple and versatile dehydroxylation approach is highly desirable.

The main challenge in the development of a one-step dehydroxylation reaction is the poor leaving group of the hydroxy group, owing to its large C–O bond dissociation energy, as well as the strongly basic hydroxide ion (OH⁻), which is generated. To overcome these intrinsic problems, most known tactics [Scheme 1, Eqs. (1) and (3)], are designed toward obtaining reactive intermediates with superior leaving groups from alcohols. Given that ways to generate such intermediates are generally compatible with many follow-up transformations, the direct dehydroxylation reac-

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tion can thus be achieved. For this matter, we planned to take advantage of the better reactivity of carbonyl compounds, which can be generated in situ by oxidation of alcohols using transition-metal catalysts. Compatible with this process is the Wolff-Kishner reduction, a classical textbook reaction, representing a powerful synthetic strategy to deoxygenate carbonyl groups in organic compounds.^[8] We envisaged that by employing hydrazine as a nucleophilic reducing reagent in addition a suitable transition-metal catalyst, the oxidation of alcohols might be combined with the Wolff-Kishner reduction to enable the direct dehydroxylation of alcohols. Herein, we report a simple and highly efficient method for the direct dehydroxylation of alcohols through an oxidation/Wolff-Kishner sequence [Scheme 1, Eq. (4)]. Remarkably, this reaction can even be carried out in water, albeit with a decreased yield.

Results and Discussion

To test our hypothesis, the pilot study was investigated between piperonyl alcohol (1a) and hydrazine hydrate (2, 2 equiv.) in H₂O in the presence of $[Cp*IrCI_2]_2$ (1.0 mmol-%, $Cp^* = C_5H_5$) and NaHCO₃ (1 equiv.) (Table 1, see the Supporting Information for full optimization data).^[9] To our delight, a trace amount of corresponding dehydroxylated product **3a** was detected after 12 h reaction at 120 °C (Table 1, entry 1). A slightly higher yield was obtained upon using the iridium pincer complex (PCP)IrH(Cl) {PCP = C_6H_3 -2,6-(CH₂PtBu₂)₂} as the catalyst (Table 1, entry 2).

Subsequently, a variety of bases were examined and Et₃N was found to be the best (Table 1, entries 3 and 4; Supporting Information, Table S1, entries 1-4). Screening of transition-metal catalysts revealed that iridium complexes displayed higher catalytic activity than ruthenium complexes (Table 1, entries 5–8; Table S1, entries 5–8), whereas neither rhodium nor iron complexes showed any catalytic activity (Table S1, entries 9 and 10). Among all the iridium catalysts tested, Vaska's complex [(PPh₃)₂IrCl(CO)] gave the best result, and desired product 3a was detected in 32% yield (Table 1, entry 5). Encouraged by these results, we next investigated the influence of solvents, with MeOH providing the highest yield (Table 1, entries 9 and 10; Table S1, entries 11–22). A further increase in yield was obtained by replacing Et_3N (1 equiv.) with KOH (2 equiv.) as the base (Table 1, entry 11); this was attempted in view of KOH being commonly used in the Wolff–Kishner reduction. While optimizing the conditions, we discovered that this reaction was insensitive to air. Moreover, all of the signals in the ¹H NMR spectrum of the crude reaction mixture could be ascribed to either 1a or 3a, which indicated that it was possible to entirely consume 1a. On the basis of the above observations, our attention was turned to the reaction temperature. A higher reaction temperature was found to be beneficial (59 and 70% at 120 and 160 °C, respectively; Table 1, entry 11 vs. entry 12). Notably, an increased reaction concentration resulted in a shorter reaction time and nearly quantitative yield of the product (Table 1, entry 13);



Table 1. Optimization of reaction conditions.[a]

0~	\sim	cataly	st, base			
	OH + NH ₂ NH ₂ •H	2 ^O sol temp	lvent erature 2 h			
Entry	Catalyst	Base	Solvent ^[b]	<i>Т</i> [°С]	Yield [%] ^[c]	
1 2	[Cp*IrCI ₂] ₂ (PCP)IrH(Cl)	NaHCO ₃ NaHCO ₃	H ₂ O H ₂ O	120 120	<5 8	
3 4	(PCP)IrH(Cl) (PCP)IrH(Cl)	Cs ₂ CO ₃ Et ₃ N	H ₂ O H ₂ O	120 120	15 29	
5 6	$\frac{(PPh_3)_2 IrCl(CO)}{[(C_8H_{12})Ir(OMe)]_2}$	Et ₃ N Et ₃ N	H ₂ O H ₂ O	120 120	32 31	
7 8	$(PPh_3)_3Ru(CO)H_2$ $(PPh_3)_3Ru(CO)(Cl)H$	Et ₃ N Et ₃ N	H ₂ O H ₂ O	120 120	9 15	
9 10 11[d]	$(PPh_3)_2IrCl(CO)$ $(PPh_3)_2IrCl(CO)$ $(PPh_3)_2IrCl(CO)$	Et ₃ N Et ₃ N	MeOH	120 120	29 38	
$12^{[d]}$ 12 ^[d]	$(PPn_3)_2IrCl(CO)$ $(PPh_3)_2IrCl(CO)$ $(PPh_3)_2IrCl(CO)$	KOH	MeOH MeOH	120 160	59 70 00[f]	
1.J. [d-f,h]	$(PPh_{3})_{2} IICl(CO)$	KOH	MeOH	160	96 ^[g]	
15 ^[d]	(PPh ₃) ₂ IrCl(CO)	KOH	neat MeOH	160 160	50 0	
17 ^[d-f,i] 18 ^[d-f]	(PPh ₃) ₂ IrCl(CO) (PPh ₃) ₃ Ru(CO)(Cl)H	KOH KOH	MeOH MeOH	160 160	0 92	

[a] Reaction conditions: **1a** (15 mg, 0.1 mmol), **2** (10 mg, 0.2 mmol), catalyst (1 mol-%), base (0.1 mmol), under an air atmosphere. [b] Solvent (0.1 mL) was used (c = 1 M), unless otherwise noted. [c] Determined by ¹H NMR spectroscopy by using nitromethane as an internal standard. [d] 0.2 mmol KOH was used. [e] 10 μ L MeOH was used (c = 10 M). [f] Reaction time: 3 h. [g] Reaction time: 2 h. [h] Under an atmosphere of Ar. [i] Without **2**.

this yield was unaffected by an argon atmosphere (Table 1, entry 14). The product was obtained in only 50% yield under solvent-free conditions even after 10 h (Table 1, entry 15). Furthermore, control experiments demonstrated that both the iridium catalyst and hydrazine hydrate were indispensable for this dehydroxylation, as no reaction occurred in the absence of either reagent (Table 1, entries 16 and 17). It is noteworthy that the use of (PPh₃)₃Ru(CO)-(Cl)H also afforded the product, albeit in a slightly lower yield relative to that obtained with (PPh₃)₂IrCl(CO) (Table 1, entry 18).

Under the optimized conditions, the substrate scope was explored using 2 (2 equiv.) as the reagent, $(PPh_3)_2$ -IrCl(CO) (1 mol-%) as the catalyst, KOH (2 equiv.) as the base in MeOH (c = 10 M) at 160 °C under an air atmosphere for 3 h (Table 2). In general, benzylic alcohols showed excellent reactivity, including those with both electron-donating and electron-withdrawing substituents on the benzene rings (Table 2, entries 1–12); nearly quantitative yields were obtained for electron-rich benzylic alcohols in almost all cases (Table 2, entries 1–3 and 7). Interestingly, the yield decreased significantly (99 to 58%) upon moving the methoxy group from the *para* position to the *ortho* position, whereas the meta isomer remained unaffected (Table 2, entries 3-5). The decrease in the yield of the product obtained through the use of the ortho isomer can possibly be attributed to the ready chelation of the ortho-methoxy and

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hydroxy groups to the iridium catalyst; this chelation occupies the empty coordination site, which is required for activation of the β C–H bond. Moreover, this chelation effect was not observed with the more sterically bulky benzoxy substituent (Table 2, entry 6). Next, primary alcohols other than benzylic alcohols were tested and most of them gave satisfactory results (Table 2, entries 13–19). To our delight, the reaction scope was extended to heteroaromatic, heterocyclic, and aliphatic alcohols and diols, as the direct dehydroxylation of these candidates has not been previously reported (Table 2, entries 14–18).^[6,7] Significantly, both the hydroxy group and the C=C bond can be efficiently reduced by employing this dehydroxylation strategy (Table 2, en-

try 19), whereas the C=C bond remains intact in the previous Ti^{III}-promoted strategy.^[6] However, only a moderate yield was observed for secondary cyclic alcohol **1t** (Table 2, entry 20), possibly as a result of increased steric hindrance, which offers potential regioselective dehydroxylation of molecules bearing multiple hydroxy groups.

This new (PPh₃)₂IrCl(CO)/NH₂NH₂·H₂O dehydroxylation protocol exhibits many appealing practical features: (1) All reactions take place either in air or under inert gas atmosphere. (2) Reactions can be simply performed by adding all chemicals into the sealed Ace pressure glass tube and then heated. (3) The workup procedure is very straightforward and only requires filtration through a silica plug.

		R' R	+ NH	(PP) 2NH2•H2O 2	h ₃) ₂ IrCl(CC <u>KOH (2 e</u> MeOH, 1 3 h	D) (1 mol-%) equiv.) 60 °C	R′ R → H 3a–t	1		
Entry	Substrate 1	Product 3		Yield [%] ^[b]	Entry	Substrate 1		Product 3		Yield [%] ^[b]
1	ОДОН	CH ₃	3a	99 (89)	11	OH		CH ₃	3k	77 (74)
2	ОН	CH ₃	3b	98	12 ^[c]		ОН	H ₂ N	31	60 (51)
3	МеО	CH3	3c	99 (90)	13	MeO		MeO	3m	98 (88)
4	ОМе	CH ₃	3d	58 (50)	14	П ОН	∕_он		3n	87 (62)
5	ОМе	CH ₃	3e	93 (86)	15	СЛОН		SCH3	30	66 (55)
6	OBn	OBn	3f	80 (75)	16		`он		3p	72
	Ц ОН МеО	CH ₃			17 ^[d,e]	HO	∕ОН	H ₃ C N CH ₃	3q	77 (64)
7	МеО	MeO CH ₃	3g	99 (93)	18 ^[d,e]	HO	OH		3r	48
8	MeSOH	MeS CH ₃	3h	90 (82)	19 ^[f]		∕ОН	ССН3	3s	96 (81)
9	СОН	CH3	3i	82 (73)	20 ^[f]			$\langle \rangle \rangle$	3t	46 (43)
10	Орон	С	3j	92 (88)						

Table 2. Scope of the Ir-catalyzed direct dehydroxylation.^[a]

[a] Reaction conditions: 1 (0.3 mmol), 2 (30 mg, 0.6 mmol), (PPh₃)₂IrCl(CO) (2.3 mg, 1 mol-%), KOH (34 mg, 0.6 mmol), MeOH (30 μ L), 160 °C, 3 h, under an air atmosphere. [b] Determined by ¹H NMR spectroscopy by using nitromethane as an internal standard; yields of the isolated products are given in parentheses. [c] MeOH (90 μ L) was used (*c* = 3 M). [d] Reaction conditions: 1 (0.3 mmol), 2 (60 mg, 1.2 mmol), (PPh₃)₂IrCl(CO) (1 mol-%), KOH (68 mg, 1.2 mmol), MeOH (30 μ L), 160 °C, 3 h, under an air atmosphere. [e] A trace amount of mono-dehydroxylated product was detected. [f] Reaction time: 12 h.



To explore the mechanism of this dehydroxylation reaction, some control experiments were conducted under the optimized conditions (Scheme 2). Tertiary 2-phenyl-2-propanol (4) did not react with hydrazine hydrate (2) due to its lack of a β -H (Scheme 2, a). In addition, an intermolecular reaction between piperonyl alcohol (1a) and styrene (6) provided corresponding dehydroxylated product 3a and ethylbenzene (7), both in quantitative yield. This implies that hydrogen gas generated in situ can participate in the hydrogenation of the double bond catalyzed by Vaska's complex (Scheme 2, b). Anticipating two key intermediates (the aldehyde and the hydrazone) in the overall dehydroxylation process, we also carried out an NMR spectroscopy experiment in deuterated benzene (Scheme 2, c). As expected, a small amount of piperonyl aldehyde (8) was detected by ¹H NMR spectroscopy upon treatment of piperonyl alcohol (1a) with (PPh₃)₂IrCl(CO) (1 equiv.) and KOH (1 equiv.) at 65 °C for 1 h. However, 8 was not observed in the absence of base even if the reaction mixture was heated. The subsequent addition of 2 (1 equiv.) to that reaction mixture led to the formation of a trace amount of piperonyl hydrazone (9). Moreover, a quartet was observed in ¹H NMR spectrum around 10 ppm ($J_{P,H}$ = 21.6 Hz), which can be assigned to the Ir-H bond (see the Supporting Information for more details).



Scheme 2. Investigation of the mechanism for the dehydroxylation.

On the basis of the obtained experimental results as well as literature studies on the "borrowing hydrogen" strategy^[10] and the Wolff–Kishner reduction, a tentative mechanism for this iridium-catalyzed direct dehydroxylation of alcohols is proposed in Scheme 3. Given that the activation of the alcohol does not occur without involvement of a base, we postulate an initial equilibrium between Vaska's complex and hydroxy-substituted derivative **A** in the presence of KOH. Then, alcohol **1** replaces the hydroxy group in complex **A** to generate complex **B**, which is subsequently converted into complex **C** through β -H elimination. The carbonyl derivative coordinating to **C** dissociates from the iridium metal center to give rise to corresponding alkane **3** following the Wolff–Kishner reduction. After ligand dissociation of the carbonyl compound from **C**, iridium hydride complex **D** is protonated by H_2O to regenerate the active species **A**, with concomitant release of hydrogen gas. Interestingly, the presence of hydrogen acceptors in this catalytic system results in simultaneous reduction of their double bonds through an insertion and protonation sequence (Table 2, entry 9 and Scheme 2, b). However, the role of iridium complexes other than Vaska's complex in the catalytic cycle is still unclear at this stage and needs further investigation.



Scheme 3. Tentative mechanism for the Ir-catalyzed direct dehydroxylation of alcohols.

Conclusions

In summary, we have reported herein an unprecedented iridium-catalyzed direct alcohol dehydroxylation reaction to form C–H bonds in a simple and efficient fashion. This reaction is proposed to proceed through an oxidation/ Wolff–Kishner reduction sequence. The present approach highlights a useful alternative to the classical multistep dehydroxylation strategy of alcohols, especially for benzylic and allylic primary alcohols. Notably, even water can be used as a solvent for this reaction. Further efforts to expand the reaction scope, clarify the reaction mechanism, and explore the synthetic applications of this reaction are currently in progress in our laboratory.

Experimental Section

General Procedure: An Ace pressure glass tube (4 cm) was charged with (PPh₃)₂IrCl(CO) (2.3 mg, 0.003 mmol), KOH (34 mg, 0.6 mmol), the alcohol (0.3 mmol), NH₂NH₂·H₂O (29 μ L, 0.6 mmol), and MeOH (30 μ L) under an air atmosphere. The Ace tube was sealed, and the reaction mixture was stirred at 160 °C for 3 h. After that, the reaction mixture was cooled to room temperature and filtered through a short column made of a silica plug by flushing it with CH₂Cl₂ (10 mL). The filtrate was dried with Na₂SO₄ and concentrated under reduced pressure to give a residue, which was first subjected to analysis by ¹H NMR spectroscopy by

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using nitromethane (5.4 μ L, 0.1 mmol) as an internal standard and then further purified by preparative TLC or flash chromatography on silica gel to afford the desired product.

Supporting Information (see footnote on the first page of this article): Full optimization data, synthesis, and copies of the ¹H NMR and ¹³C NMR spectra of all isolable compounds.

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