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Iridium-catalyzed oxidative lactonization and intramolecular Tishchenko reaction of δ-ketoaldehydes for the synthesis of isocoumarins and 3,4-dihydroisocoumarins

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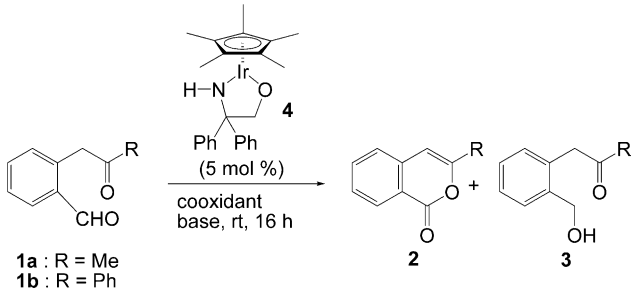
Abstract—Two new cyclizations of ketoaldehydes have been developed using an Ir-ligand bifunctional catalyst. Oxidative lactonization of δ-ketoaldehydes proceeded smoothly at room temperature to give coumarin derivatives in excellent yields. Intramolecular Tishchenko reaction of δ-ketoaldehydes afforded 3,4-dihydroisocoumarins in good yields.

Isocoumarins are useful synthetic intermediates to other heterocyclic and carbocyclic compounds.[1] Many studies on isocoumarin synthesis, including cyclization of keto acids and electrophilic cyclization of alkynylbenzoic acid derivatives, have been reported.[2] Although several catalytic methods using Pd,[3] Ag,[4] Ru,[5] and Ni[6] have been developed, there is no example of oxidative lactonization of ketoaldehydes. Recently, we have developed an Ir aminoalkoxide complex, which catalyzes the oxidative lactonization of diols and the Oppenauer oxidation of primary alcohols.[7,8] We present herein two Ir-catalyzed cyclizations of ketoaldehydes, which afford efficiently isocoumarins and 3,4-dihydroisocoumarins.

We first investigated the oxidative lactonization of 2-(2-oxopropyl)benzaldehyde (**1a**)[9](Scheme 1).

The reactions were performed in the presence of several cooxidants, bases, and 5 mol% of **4** at room temperature for 16 h. As shown in Table 1, 3-methylisocoumarin (**2a**) and alcohol **3a** were obtained in 58% and 42% yields, respectively, when the reaction was performed using a 0.1 M solution of acetone (136 equiv) as a cooxidant in the presence of K_2CO_3 (0.3 mol equiv) (entry 1).[10]



Scheme 1. Ir-catalyzed oxidative lactonization of **1**.

The ratio of isocoumarin to alcohol was improved by using only 3 mol equiv of pivalaldehyde in toluene, albeit the reaction was slow (entry 2). Higher yields of **2a** were obtained by increasing the amounts of K_2CO_3 and pivalaldehyde (entries 3 and 4). Finally, the best result was obtained by using Cs_2CO_3 (entry 5). The reaction of **1b** also proceeded without problems in 98% yield (entry 6).

A probable mechanism for the Ir-catalyzed oxidative lactonization is shown in Scheme 2. We believe that keto–enol equilibrium and aldehyde–hemiacetal equilibrium generate the hemiacetal intermediate from ketoaldehyde **1**, with the aid of a base. The iridium complex oxidizes the hemiacetal to give isocoumarin **2** and Ir hydride. The Ir complex **4** is regenerated by oxidation with pivalaldehyde. Alcohol **3** might be produced by the

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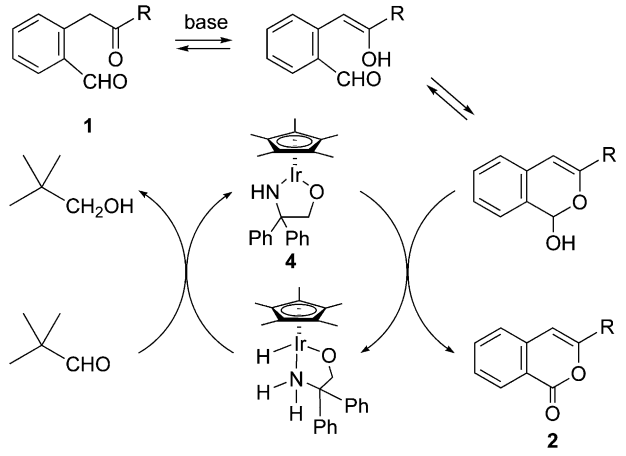
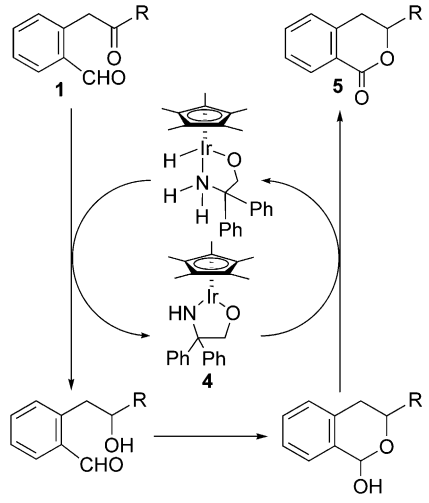
Table 1. Catalytic oxidative lactonization of **1** by an Ir complex **4**[a]

Entry	Substrate	Base (mol equiv)	Cooxidant (equiv)	Yield (%)[b]		
				2	**3**	**1**
1[c]	**1a**	K_2CO_3 (0.3)	Acetone (136)	58	42	0
2	**1a**	K_2CO_3 (0.3)	$(CH_3)_3CCHO$ (3)	30	6	55
3	**1a**	K_2CO_3 (3)	$(CH_3)_3CCHO$ (3)	81	15	4
4	**1a**	K_2CO_3 (3)	$(CH_3)_3CCHO$ (10)	92	4	0
5	**1a**	Cs_2CO_3 (1)	$(CH_3)_3CCHO$ (10)	98	0	0
6	**1b**	Cs_2CO_3 (1)	$(CH_3)_3CCHO$ (3)	98	0	0

[a] Unless otherwise stated, the reaction was carried out using **1** (0.36 mmol), Ir catalyst **4** (0.018 mmol, 5 mol%), base, and cooxidant in toluene (3.6 mL) at room temperature for 16 h.
[b] Isolated yield.
[c] Acetone (3.6 mL) was used as the solvent in place of toluene.



Scheme 2. Possible mechanism for the Ir-catalyzed oxidative lactonization of **1**.

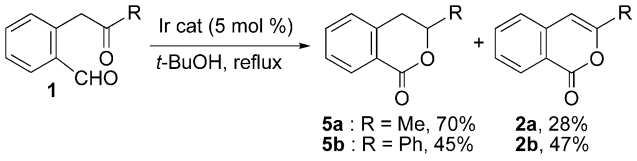


Scheme 3. Working hypothesis for the Ir-catalyzed intramolecular Tishchenko reaction of **1**.

reaction between the iridium hydride and the substrate aldehyde **1**.

Next, we turned our attention to the development of other catalytic systems utilizing the Ir hydride species. We investigated the intramolecular Tishchenko reaction of ketoaldehydes **1**.[11] Some intramolecular Tishchenko reactions of ketoaldehydes using Sm (10–50 mol%),[12] and Al[13] have been reported.[14] However, there is no example of intramolecular Tishchenko reaction of ketoaldehydes using an iridium catalyst. A working hypothesis for the intramolecular Tishchenko reaction is shown in Scheme 3. The first step is the reduction of **1** by Ir hydride to give the hydroxyaldehyde and Ir complex **4**, which oxidizes the lactol generated from the hydroxyaldehyde to give the 3,4-dihydroisocoumarin **5**.

After several attempts, using in situ-generated Ir hydride catalyst, we were very pleased to find that the reaction of **1a** proceeded in *t*-BuOH under reflux using 5 mol% of Ir catalyst, leading to the formation of 3,4-dihydroisocoumarin **5a** in 70% yield (Scheme 4).[15,16] Interestingly isocoumarin **2a** was also obtained in 28% yield under the conditions, although no extra cooxidant was added to the reaction mixture.[19] Similarly, the reaction with the more enolizable **1b** gave **5b** and **2b** in 45% and 47% yields, respectively.



Scheme 4. Synthesis of 3,4-dihydroisocoumarin by intramolecular Tishchenko reaction of **1**.

In conclusion, we have succeeded in the development of the first oxidative lactonization of ketoaldehyde for the synthesis of isocoumarin using an Ir catalyst. Moreover, 3,4-dihydroisocoumarins were obtained from the same substrates, via intramolecular Tishchenko reaction. This simple and environmentally friendly process should be useful for contemporary organic synthesis. Further studies including structural elucidation of active species are in progress.

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10. General procedure for the oxidative lactonization of 1. A 10 mL test tube equipped with a magnetic stirring bar was charged with 97.7 mg (0.3 mmol) of Cs_2CO_3 and 9.7 mg (0.02 mmol, 5 mol%) of Ir complex **3**. A solution of **1** (0.36 mmol) in toluene (3.6 mL) and pivalaldehyde (117 μL, 1.08 mmol) was added to the above mixture and the whole was stirred at room temperature for 16 h. The reaction mixture was passed through a short silica gel column (12 g, ethyl acetate) to remove the catalyst and then concentrated under reduced pressure. The products of **2a**,**b** were purified by silica gel column chromatography (hexane–ethyl acetate, 4:1). 3-Methylisocoumarin (**2a**)[3b] ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 6.28 (s, 1H), 7.34–8.25 (m, 4H). 3-Phenylisocoumarin (**2b**)[3b] ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.97 (s, 1H), 7.42–7.54 (m, 5H), 7.70–7.76 (m, 1H), 7.86–7.92 (m, 2H), 8.30–8.34 (m, 1H). 1-(2-Hydroxymethylphenyl)-2-propanone (**3a**) ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.49 (s, 3H), 2.56 (br s, 1H), 2.89 and 3.02 (ABq, J = 16.2 Hz, 2H), 4.75 and 5.00 (ABq, J = 15.0 Hz, 2H), 6.92–7.18 (m, 4H). IR (NaCl) ν_{max} (cm^{-1}): 3399 (OH), 1705 (C=O). MS *m/z*: 164 (M^+), 145, 115, 104, 91, 78, 65, 51, 43, 39. HRMS *m/z*: (M^+) Calcd for $C_{10}H_{12}O_2$: 164.0837. Found: 164.0862.
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15. The reaction using other solvents such as THF, dichloroethane, CH_3CN, toluene, and 2-butanone gave unsatisfactory results.
16. General procedure for the intramolecular Tishchenko reaction of **1**. To a 10 mL test tube containing $[Cp^*IrCl_2]_2$ (7.2 mg, 0.009 mmol), 2,2-diphenylglycinol[17] (3.8 mg, 0.018 mmol), and KOH (5.0 mg, 0.09 mmol) was added CH_2Cl_2 (1.8 mL). The mixture was stirred for 2 h at room temperature, and the insoluble materials were removed by filtration. 2-Propanol (0.3 mL, 3.92 mmol) was added to this catalyst solution, and stirred at room temperature for 30 min, then volatile materials were removed under vacuum, and a solution of **1** (0.36 mmol) in *t*-BuOH was added. The mixture was refluxed for 16 h. After cooling to room temperature, the mixture was passed through a short silica gel column (12 g, ethyl acetate) to remove the catalyst and the eluate was concentrated under reduced pressure. The products were purified by preparative TLC (hexane–ethyl acetate). In the case of the reaction of **1b**, the product was obtained as an inseparable mixture and the yield was determined by 270 MHz ^{1}H NMR. 3,4-Dihydro-3-methylisocoumarin (**5a**)[18a] ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.52 (d, J = 6.3 Hz, 3H), 2.87–3.04 (m, 2H), 4.62–4.75 (m, 1H), 7.24–8.10 (m, 4H). 3,4-Dihydro-3-phenylisocoumarin (**5b**)[18b] ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.14 (dd, J = 16.4, 3.2 Hz, 1H), 3.36 (dd, J = 16.4, 11.9 Hz, 1H), 5.57 (dd, J = 11.9, 3.2 Hz, 1H), 7.2–7.9 (m, 8H), 8.16 (d, J = 7.6 Hz, 1H).
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