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Iridium-catalyzed stereoselective [3+2] annulation of α -oxocarboxylic acids with 1,3-dienes[†]

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The stereoselective annulation of α -oxocarboxylic acids with 1, 3-dienes proceeded in the presence of a hydroxoiridium catalyst to give α -hydroxy- γ -lactones in good yields with high 3,5-*trans* relative stereochemistry. The use of a chiral diene ligand for a cationic iridium complex enabled asymmetric annulation with high enantioselectivity.

The transition metal-catalyzed annulation reaction has become a method of choice for the synthesis of heterocyclic compounds such as lactones and lactams, which are widely found in natural products and biologically active molecules such as medicinal and agricultural chemicals.¹ In particular, the atom-economical synthesis of these compounds is highly desirable in pharmaceutical and industrial fields.² In this context, we have recently reported the iridiumcatalyzed annulation of α -oxocarboxamides with 1.3-dienes giving α -hydroxy- γ -lactams, whose relative stereochemistry is 3,5-cis (Scheme 1a).³ The reaction is proposed to proceed via an amidoiridium(1) species intramolecularly coordinated with a carbonyl oxygen. We next focused on the use of α-oxocarboxylic acids for the synthesis of γ -lactones.⁴ The acid-catalyzed reaction of α-oxocarboxylic acids with 1,1-disubstituted alkenes was reported by Jarvis and co-workers.⁵ The reaction gave α -hydroxy- γ butyrolactones in the presence of concentrated H₂SO₄, where no diastereoselectivity of the products was observed.⁶ Herein we report that a hydroxoiridium complex catalyzes the annulation of α oxocarboxylic acids with 1,3-dienes giving α-hydroxy-γ-lactones with high stereoselectivity (Scheme 1b). The 3,5-trans stereochemistry of the product observed in the present reaction is different from the reaction of α -oxocarboxamides.³ The preliminary results of asymmetric annulation using the chiral diene ligand⁷ are also described.

† Electronic supplementary information (ESI) available: Experimental procedures, and compound characterization data. See DOI: 10.1039/d1cc02003j

An initial trial of the reaction of an α -oxocarboxylic acid with a 1,3-diene failed under the reaction conditions that efficiently promoted the annulation of α -oxocarboxamides. As shown in Table 1, the treatment of phenylglyoxylic acid (1a) with isoprene (2a) in the presence of [Ir(OH)(cod)]₂ (5 mol % of Ir and cod = 1,5-cyclooctadiene) in toluene at 30 °C for 48 h did not give any annulation products (entry 1). The solvents such as 1,4dioxane and dichloromethane were ineffective as well (entries 2 and 3). The formation of the annulation product 3aa was observed in the reaction in methanol, albeit a low yield (5% yield, entry 4) was obtained. The use of H₂O as an additive led to a dramatic increase of the yield (58% yield, entry 5), where very high diastereoselectivity of the product was observed (99:1).^{8,9} The relative stereochemistry of the major product was determined to be 3,5-trans by NOE NMR experiments. The presence of N-methylpyrrolidone (NMP) also slightly improved the yield (entry 6). Other amides such as



Scheme 1 Ir-catalyzed annulation reactions.

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Table 1 $\$ Ir-catalyzed annulation of phenylglyoxylic acid (1a) with isoprene (2a)^a



^{*a*} Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), and $[Ir(OH)(cod)]_2$ (5 mol % of Ir) in solvent (0.4 mL) at 30 °C for 48 h. ^{*b*} Determined by ¹H NMR. ^{*c*} 20 Equiv. ^{*d*} 1.5 equiv. ^{*e*} Performed with $[IrCl(cod)]_2$ (5 mol % of Ir), NaBAr^F₄ (10 mol %), and NMP (0.5 equiv.). ^{*f*} Without $[Ir(OH)(cod)]_2$.

N,*N*-dimethylformamide and *N*,*N*-dimethylacetamide were also effective (the results are not shown). The reaction in toluene was also found to proceed with a cationic iridium complex generated from $[IrCl(cod)]_2$ and $NaBAr_4^F [Ar^F = 3,5-(CF_3)_2C_6H_3]$ in the presence of NMP, although diastereoselectivity was rather low (70:30, entry 7). The present annulation reaction did not proceed without the iridium catalyst (entry 8).

The results obtained from the diastereoselective annulation of a variety of α -oxocarboxylic acids 1 with isoprene (2a) catalyzed by the hydroxoiridium complex are summarized in Scheme 2. The reaction of α -oxocarboxylic acids bearing the *para-* (**1b-f**) and *meta-*substituted phenyl groups (**1g-i**) proceeded well to give the corresponding 3,5-trans lactones 3ba-ia in good yields with high diastereoselectivity. By contrast, the reaction of ortho-substituted 1j was slow, giving 3ja in 24% yield after 96 h. α -Oxocarboxylic acids substituted with 3, 5-dimethoxyphenyl 1k, 3,5-bis(trifluoromethyl)phenyl 1l, 2-naphthyl 1m, and 2-benzothiophenyl 1n are also good substrates giving the corresponding lactones 3ka-na in good yields. The alkyl-substituted α -oxocarboxylic acids, such as pyruvic acid (10), 2-oxobutyric acid (1p), 2-oxododecanoic acid (1q), and 2-cyclohexyl-2-oxoacetic acid (1r), also participated in the present annulation reaction to give 30a-ra in moderate to good yields with high diastereoselectivity.

The reactions of several 2-substituted 1,3-dienes with 1a are shown in Table 2. The 2-alkyl-substituted 1,3-dienes 2b and 2c were suitable for diastereoselective annulation with 1a to give 3ab and 3ac, respectively, with high diastereoselectivity (entries 1 and 2). Functional groups such as ether (2d), C–C double bond (2e), hydroxy (2f), and ester (2g) were compatible in the reaction (entries 3–6). Unfortunately, however, certain 1,3-dienes such as 2,3-dimethyl-1,3-butadiene, 3-methyl-1,3-pentadiene, and cyclohexadiene were not applicable to the reaction.



Scheme 2 Annulation of α -oxocarboxylic acids with isoprene. Reaction conditions: α -oxocarboxylic acids **1** (0.20 mmol), isoprene (0.60 mmol), NMP (0.30 mmol), H₂O (4.0 mmol), and [Ir(OH)(cod)]₂ (5 mol % of Ir) in anhydrous MeOH (0.4 mL) at 30 °C for 48 h. The isolated yields are shown. The ratios of diastereomers are shown in parentheses. ^aFor 72 h. ^bFor 96 h.

Lactone **3aa** obtained with high diastereoselectivity was transformed into several compounds (Scheme 3). The dehydration of **3aa** by treatment with mesyl chloride and triethylamine followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave bute-nolide **4** in 65% yield. The treatment of **3aa** with lithium aluminium hydride in THF gave triol **5**, which consisted of two *tert*-alcohol and a *pri*-alcohol moieties, in 62% yield. The ring-opening reaction of **3aa** with methylamine in methanol gave amide **6** in 99% yield.

Because the present annulation reaction was catalyzed by the iridium complex coordinated with 1,5-cyclooctadiene as the ligand and the use of external bidentate phosphine ligands such as binap and segphos inhibited the reaction, we next examined the enantioselective annulation of **1a** with **2a** by using chiral diene ligands (Table 3). Recently, we have developed chiral diene ligands with a tetrafluorobenzobarrelene (tfb) framework for the Rh- and Ir-catalyzed asymmetric reactions.^{7b,10} The treatment of **1a** with **2a** in the presence of $[Ir(OH)(L1)]_2$ (5 mol % of Ir), NMP (1.5 equiv.), and H₂O (20 equiv.) in methanol at 30 °C for 48 h (condition A) gave **3aa** in 30% yield with high diastereoselectivity (entry **1**). ChemComm



 a Reaction conditions: 1a (0.20 mmol), 2 (0.60 mmol), $[Ir(OH)(cod)]_2$ (5 mol % of Ir), NMP (0.30 mmol), and H₂O (4.0 mmol) in anhydrous MeOH (0.4 mL) at 30 $^\circ C$ for 48 h. b Isolated yields. c Determined by $^1 H$ NMR. d For 72 h.



Unfortunately, however, the ee of **3aa** was only 8%. Other chiral tfb ligands such as Ph-tfb* (**L2**) and Me-tfb* (**L3**) displayed 26% and 37% ee, respectively (entries 2 and 3). The use of ligand **L4**, which displayed high enantioselectivity in the annulation of α -oxocarboxamides with 1,3-dienes, gave **3aa** with 52% ee (entry 4). After screening of the reaction conditions, it was found that high enantioselectivity was obtained in the reaction in toluene in the presence of a chiral cationic Ir complex. Thus, the treatment of **1a** with **2a** in the presence of [IrCl(**L1**)]₂ (5 mol % of Ir), NMP (0.5 equiv.), and NaBAr^F₄ (10 mol %) in toluene at 30 °C for 48 h (condition B) gave a mixture of diastereomers **3aa** in 63% yield (*trans:cis* = 75:25, entry 5), whose enantioselectivities were 92% and 89% ee, respectively.¹¹

Although the control over both the high diastereo- and enantioselectivity has not been yet achieved at this stage, the preliminary results of asymmetric annulation obtained with the cationic Ir/L1 complex are listed in Table 4.¹² Several

Table 3Asymmetric annulation of phenylglyoxylic acid (1a) with isoprene(2a)



Conditions A: **1a** (0.20 mmol), **2a** (0.60 mmol), [Ir(OH)L*]₂ (5 mol% Ir), NMP (1.5 equiv.), H₂O (20 equiv.), MeOH (0.25 M).

Conditions B: **1a** (0.20 mmol), **2a** (0.60 mmol), [IrClL*]₂ (5 mol% Ir), NMP (0.5 equiv.), NaBArF₄ (10 mol%), toluene (0.25 M).



Entry	Ligand	Conditions	Yield ^a (%)	ee^b (%)
1	L1	Α	30	8
2	L2	Α	62	26
3	L3	Α	58	37
4	L4	Α	63	52
5	L1	В	63	92,89 $(75:25)^c$

^a Isolated yields. ^b Determined by HPLC analysis with chiral stationary phase columns. ^c Diastereoselectivity (*trans:cis*) determined by ¹H NMR.

 α -oxocarboxylic acids participated in the reaction with **2a** to give the corresponding annulation products in high yields with good diastereo- and enantioselectivity.

In summary, we have developed a highly diastereoselective annulation of α -oxocarboxylic acids with 1,3-dienes catalyzed by a hydroxoiridium/cod complex. This reaction displayed high *trans*-selectivity of the products. In addition, the use of the



^{*a*} Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), [IrCl(((*s*,*S*)-Fc-tfb*)]₂ (5 mol % of Ir) and NMP (0.10 mmol) in toluene (0.4 mL) at 30 °C for 48 h. ^{*b*} Isolated as inseparable mixtures of diastereomers. ^{*c*} Determined by ¹H NMR. ^{*d*} The ee values (*trans:cis*) were determined by HPLC analysis with chiral stationary phase columns.

chiral diene ligand enabled the asymmetric reaction to give the products with good enantioselectivity.

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Conflicts of interest

There are no conflicts to declare.

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