Asymmetric Annulation

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Hydroxoiridium/Chiral Diene Complexes as Effective Catalysts for Asymmetric Annulation of α-Oxo- and Iminocarboxamides with 1,3-Dienes

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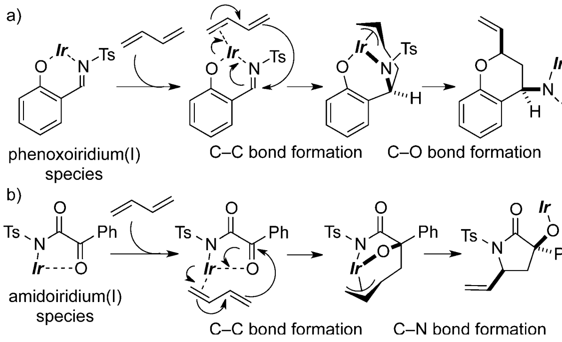
Abstract: *The asymmetric [3+2] annulation of α-oxo- and α-iminocarboxamides with 1,3-dienes catalyzed by hydroxoiridium/chiral diene complexes was realized, giving high yields of the corresponding γ-lactams with high enantioselectivity.*

Recent progress of transition-metal-catalyzed cycloaddition reactions has met the requirements of cost saving and environmental friendliness.[1] Catalytic enantioselective cycloaddition reactions are one of the most powerful and atom-efficient methods of a direct enantioselective construction of functionalized carbo- and heterocycles without formation of the extra waste.[1,2] In this context, we recently reported the iridium-catalyzed annulation of salicylimines with 1,3-dienes giving 4-aminochromane derivatives, for which the reaction proceeds via a phenoxoiridium(I) species intramolecularly coordinated with the imine moiety (Scheme 1a).[3] The phenoxoiridium(I) undergoes oxidative cyclization with a 1,3-diene to form a π-allyliridium(III) species, and the following reductive elimination gives a six-membered heterocycle.[4,5] We next focused on the synthesis of five-membered lactams starting from α-oxocarboxamides, which potentially have both an electrophilic and a nucleophilic part in the same molecule. The strategy for the synthesis of the lactams is as follows: 1) Oxidative cyclization of an amidoiridium(I) species coordinated with a carbonyl oxygen forms a π-allyliridium(III) species including a C–C bond formation. 2) Reductive elimination forming a C–N bond gives a five-membered lactam with an alkoxoiridium(I) species. Here we report that a hydroxoiridium complex coordinated with a chiral diene ligand can catalyze the asymmetric annulation of α-oxocarboxamides or an α-iminocarboxamide with 1,3-dienes giving γ-lactams with high enantioselectivity.



Scheme 1. Iridium-catalyzed annulation with 1,3-dienes.

The 2-pyrroridone core unit is found in many pharmaceuticals and natural products possessing various biological activities such as proteasome inhibitors,[6] antiphlogistics,[7] and antidepressants.[8] Although many synthetic methods for the synthesis of 2-pyrrolidone derivatives have been developed,[9] the reports on the catalytic enantioselective direct formation of the γ-lactams in an intermolecular manner is limited.[10] Enders and co-workers reported the organocatalytic aza-Michael/aldol domino reaction leading to functionalized 1,3,5-triarylpyrrolidin-2-ones.[10b] Okamura, Onitsuka, and co-workers reported the synthesis of γ-lactams by ruthenium-catalyzed sequential allylic amidation and atom-transfer radical cyclization.[10d] In this context, we found that the direct synthesis of γ-lactams from α-oxocarboxamides and 1,3-dienes is achieved by use of a hydroxoiridium complex (Table 1). Treatment of α-oxocarboxamide **1a** with isoprene (**2a**) in the presence of $[\{Ir(OH)(cod)\}_2]$ in toluene at 50 °C for 3 h gave α-hydroxy-γ-lactam **3aa** in 96 % yield (entry 1). The formation of **3aa** was highly regio- and stereoselective; a more substituted alkene moiety of isoprene participated in the reaction to give **3aa** with 3,5-*cis* relative stereochemistry. The reaction using $[\{IrCl(cod)\}_2]$ combined with bases (K_2CO_3 or KOH_{aq}) gave a much lower yield of **3aa** than the hydroxoiridium complex (entries 2 and 3). A rhodium complex $[\{Rh(OH)(cod)\}_2]$ did not promote the present annulation (entry 4). An electron-deficient substituent on the amine nitrogen of **1** was essential for the present reaction; *p*-toluenesulfonyl (**1a**) displayed higher reactivity than methanesulfonyl (**1b**), and a simple amide **1c** did not give the annulation product at all (entries 5 and 6). These results indicate that the formation of the amidoiridium species from the hydroxoiridium species requires a high acidity of the N–H proton of **1**. On the other hand, the present reaction was not promoted by use of a bisphosphine ligand such as (*R*)-binap (entry 7). These results prompted us to use chiral diene ligands[11] for the development of an asymmetric variant of the reaction. Recently, we have developed chiral diene ligands with a tetrafluorobenzobarrelene (tfb) framework,[12] and they have been successfully applied to the Rh- and Ir-catalyzed asymmetric reactions. The reported tfb-ligands substituted with Me, Ph, and ferrocenyl (Fc) were less

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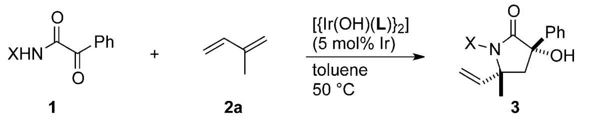
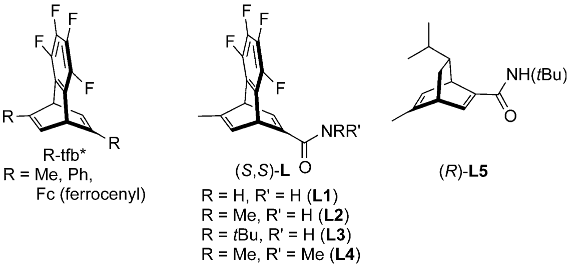
Table 1: Iridium-catalyzed asymmetric annulation of α-oxocarboxamides **1** with isoprene (**2a**).[a]

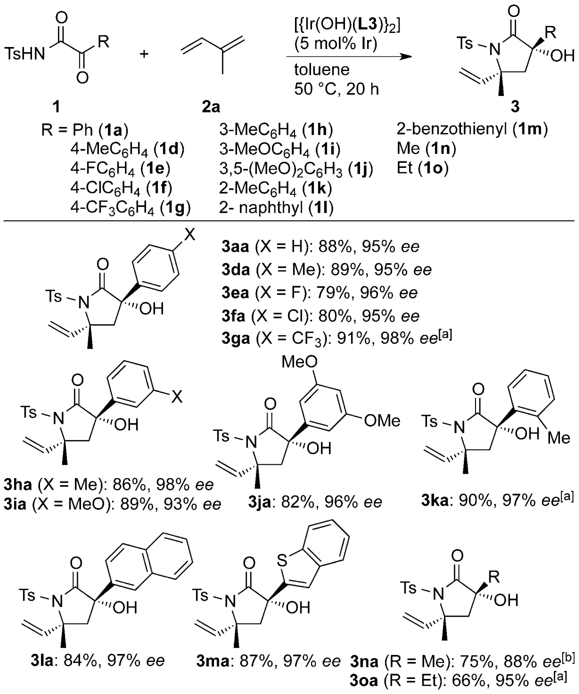


1a: X = Ts, **1b**: X = Ms, **1c**: X = H

Entry	Catalyst	**1**	Yield [%][b]	*ee* [%][c]
1	[{Ir(OH)(cod)}$_2$]	**1a**	96	–
2[d]	[{IrCl(cod)}$_2$]/K$_2$CO$_3$	**1a**	8	–
3[e]	[{IrCl(cod)}$_2$]/KOH$_{aq}$	**1a**	23	–
4	[{Rh(OH)(cod)}$_2$]	**1a**	0	–
5	[{Ir(OH)(cod)}$_2$]	**1b**	74	–
6	[{Ir(OH)(cod)}$_2$]	**1c**	0	–
7[e,f]	[{IrCl(coe)$_2$}$_2$]/(*R*)-binap/KOH$_{aq}$	**1a**	0	–
8	[{Ir(OH)((*S*,*S*)-Me-tfb*)}$_2$]	**1a**	12	74
9	[{Ir(OH)((*S*,*S*)-Fc-tfb*)}$_2$]	**1a**	26	71
10	[{Ir(OH)((*S*,*S*)-Ph-tfb*)}$_2$]	**1a**	14	15
11	[{Ir(OH)((*S*,*S*)-**L1**)}$_2$]	**1a**	48	94
12	[{Ir(OH)((*S*,*S*)-**L2**)}$_2$]	**1a**	68	97
13	[{Ir(OH)((*S*,*S*)-**L3**)}$_2$]	**1a**	87	95
14	[{Ir(OH)((*S*,*S*)-**L4**)}$_2$]	**1a**	0	–
15	[{Ir(OH)((*S*,*S*)-**L5**)}$_2$]	**1a**	4	–[g]

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.30 mmol), catalyst (5 mol% of Ir) in toluene (0.4 mL) at 50°C for 3 h. For entries 8–15, the corresponding hydroxoiridium complexes were generated by pretreatment of the IrCl(diene) complexes with KOH$_{aq}$, and the reaction was conducted for 24 h; see the Supporting Information for details. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Performed with K$_2$CO$_3$ (10 mol%). [e] Performed with 1 M KOH$_{aq}$ (10 mol%). [f] Performed with (*R*)-binap (10 mol%). [g] Not determined. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; cod = 1,5-cyclooctadiene; coe = cyclooctene.



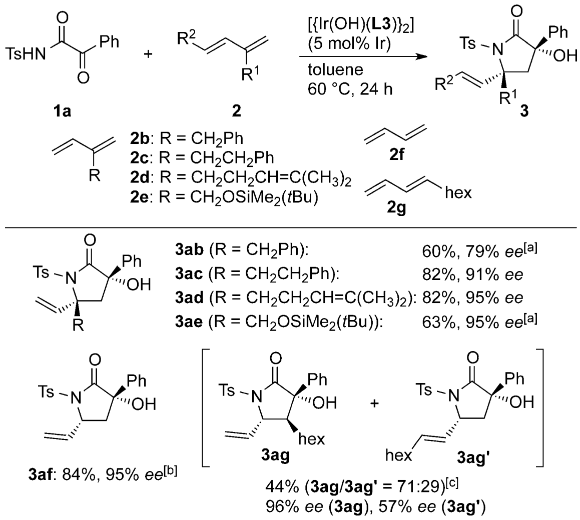


Scheme 2. Iridium-catalyzed asymmetric annulation of α-oxocarboxamides **1** with isoprene (**2a**). Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), and [{Ir(OH)((*S*,*S*)-**L3**)}$_2$] (5 mol%, generated by pretreatment of the [{IrCl(**L3**)}$_2$] complex with KOH$_{aq}$) in toluene (0.8 mL) at 50°C for 20 h. See the Supporting Information for details. Yields of isolated products are shown. *ee* was determined by HPLC analysis on a chiral stationary phase. [a] For 48 h. [b] At 60°C for 48 h.

effective in the present annulation to give **3aa** in low yields with low to moderate enantioselectivities (entries 8–10). The high enantioselectivity was achieved by use of new unsymmetrically substituted tfb ligands **L1**–**L3**, which have a methyl group and an amide moiety (entries 11–13). In particular, a hydroxoiridium complex with ligand **L3** bearing an *N-tert*-butylamide displayed a high catalytic activity and enantioselectivity to give **3aa** in 87% yield with 95% *ee* (entry 13).[13] An *N*,*N*-dimethylamide group of ligand **L4** deactivated the iridium catalyst (entry 14). It should be noted that the use of bicyclo[2.2.2]octadiene **L5**, which is substituted with the same functional groups at the diene moiety as **L3**, gave **3aa** in only 4% yield (entry 15), probably because of the lower coordination ability of **L5** toward the iridium compared to that of the rigid tfb ligand **L3**.[12b]

The results obtained for the enantioselective annulation of several α-oxocarboxamides with isoprene (**2a**) catalyzed by the Ir/**L3** complex are summarized in Scheme 2. The reaction of α-oxocarboxamides bearing *para*- (**1d**–**g**), *meta*- (**1h**–**j**), and *ortho*-substituted phenyl (**1k**) proceeded well to give the corresponding lactams **3da**–**3ka** in high yields with 93–98% *ee*. α-Oxocarboxamides substituted with 2-naphthyl (**1l**) and 2-benzothienyl (**1m**) are also good substrates to give the corresponding lactams **3la** and **3ma**, respectively, with 97% *ee*. Alkyl-substituted α-oxocarboxamides **1n** and **1o** also underwent the annulation with isoprene to give **3na** and **3oa** in 75 and 66% yield, respectively. The absolute configuration of **3la** was determined to be 3*S*,5*R* by X-ray crystallographic analysis.

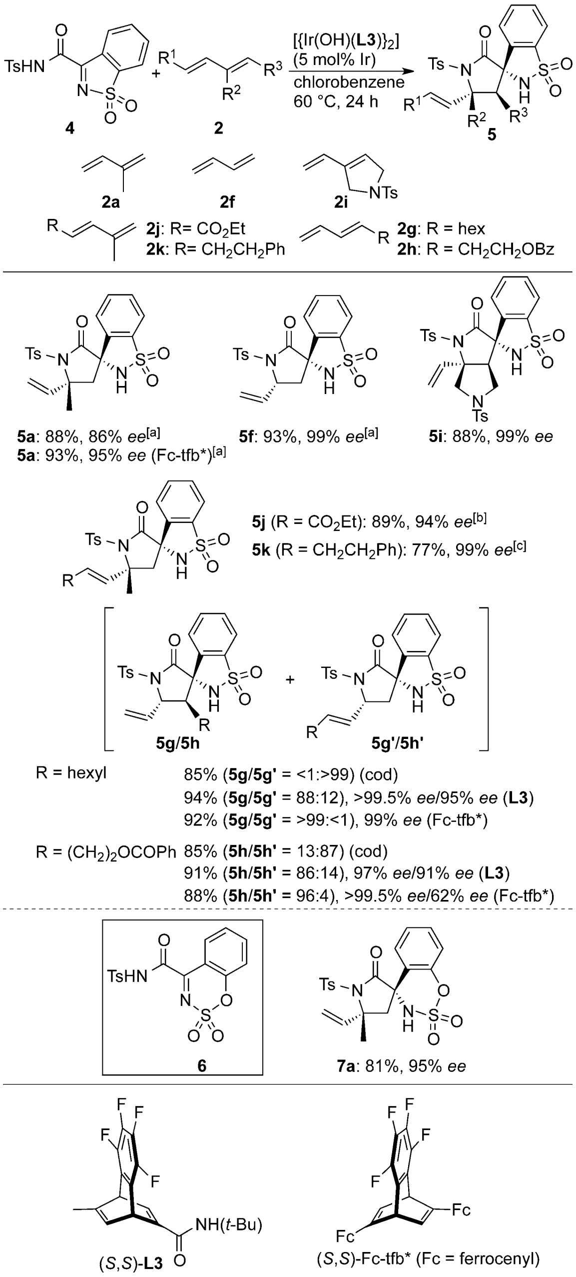
Scheme 3 summarizes the results obtained for the reaction of α-oxocarboxamide **1a** with several 1,3-dienes. The reaction of 2-benzylbutadiene **2b**, 2-(2-phenylethyl)butadiene **2c**, myrcene (**2d**), and 2-siloxymethylbutadiene **2e** proceeded in a similar vein as isoprene to give the corresponding lactams **3ab**–**3ae** in 79–95% *ee*. 1,3-Butadiene (**2f**) also reacted with **1a** to give **3af** in 84% yield with 95% *ee*. In the reaction of 1,3-decadiene (**2g**), the internal alkene moiety preferentially participated in the reaction to give **3ag** as a major isomer accompanied by the formation of its regioisomer **3ag′** (**3ag**/**3ag′** = 71:29). On the other hand, alkenes such as styrene, butyl vinyl ether, and 1-vinyl-2-pyrrolidinone did not undergo the annulation, implying that the formation of the π-allyliridium(III) intermediate as shown in Scheme 1b is important for the present annulation. The reaction of **1a**



Scheme 3. Iridium-catalyzed asymmetric annulation of **1a** with 1,3-dienes **2**. Reaction conditions: **1a** (0.20 mmol), **2** (0.60 mmol), and [{Ir(OH)((*S*,*S*)-**L3**)}$_2$] (5 mol% Ir) in toluene (0.8 mL) at 60 °C for 24 h. Yields of isolated products are shown. *ee* was determined by HPLC analysis on a chiral stationary phase. [a] At 80 °C for 48 h. [b] Performed with **2f** (5.0 equiv) at 50 °C for 24 h. [c] For 48 h.

with a conjugated enyne, 1-(*tert*-butyldimethylsilyl)-but-3-en-1-yne, gave a complex mixture of products.

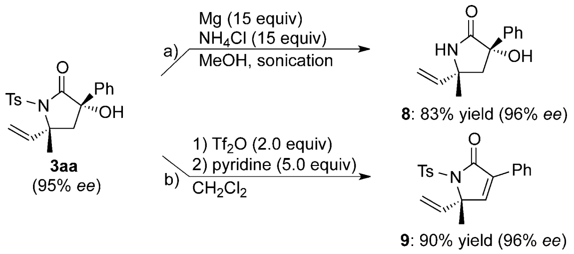
As shown in Scheme 3, the scope of 1,3-dienes is limited to 1,3-butadiene and monosubstituted dienes in the reaction of α-oxocarboxamide **1a**. On the other hand, the same type of the annulation was found to proceed between α-iminocarboxamide **4** and a variety of 1,3-dienes with high regio- and enantioselectivity (Scheme 4). The reaction of α-iminocarboxamide **4** with isoprene smoothly proceeded to give the α-amino-γ-lactam **5a** in 88% yield with 86% *ee*. A much higher enantioselectivity of **5a** (95% *ee*) was obtained by using a ferrocenyl-substituted tfb ligand (Fc-tfb*) instead of **L3**. The reaction with 1,3-butadiene gave a 99% *ee* of **5f**. 1,2-Disubstituted butadiene **2i**, which has a cyclic structure, reacted with **4** giving **5i** in 88% yield with 99% *ee*. The 1,3-disubstituted 1,3-butadienes **2j** and **2k** were also applicable to the reaction with **4** to give the corresponding lactams **5j** and **5k** with 94 and 99% *ee*, respectively. In the reaction with terminally substituted 1,3-butadienes, the regioselectivity of the reacted diene was controlled by the steric effect of the ligand. The reaction of **4** with 1,3-decadiene (**2g**) in the presence of [{Ir(OH)(cod)}$_2$] gave an 85% yield of **5g′**, which is formed by the reaction of the terminal alkene of **2g**. On the other hand, the use of **L3** gave **5g** as a major product, where the internal alkene moiety reacted preferentially. A bulkier ligand Fc-tfb* completely switched the regioselectivity to give **5g** in 92% yield with 99% *ee*. The regioselectivity observed by use of Fc-tfb* is probably due to the coordination of the terminal alkene moiety to the iridium against the steric repulsion of the ligand, resulting in the participation of the internal alkene in the annulation as depicted in Scheme 1b. The similar selectivity was also observed in the reaction of functionalized 1,3-diene **2h**. α-Iminocarboxamide **6** having a six-membered cyclic imine moiety was also applicable to the present annulation to give **7a** in 81% yield with 95% *ee*.



Scheme 4. Iridium-catalyzed asymmetric annulation of α-iminocarboxamides with 1,3-dienes. Reaction conditions: **4** or **6** (0.10 mmol), **2** (0.30 mmol), [{Ir(OH)(**L3**)}$_2$] or [{Ir(OH)((*S*,*S*)-Fc-tfb*)}$_2$] (5 mol% of Ir) in chlorobenzene (0.4 mL) at 60 °C for 24 h. Yields of isolated products are shown. *ee* was determined by HPLC analysis on a chiral stationary phase. The absolute configuration of the products was assigned by analogy with **3**. The absolute configuration of the products obtained with (*S*,*S*)-Fc-tfb* instead of (*S*,*S*)-**L3** is opposite to the one shown above. [a] At 50 °C for 20 h. [b] At 80 °C. [c] Performed with **4** (0.12 mmol) and **2k** (0.10 mmol).

A tosyl group on the α-hydroxy-γ-lactam **3aa** was removed without loss of its enantiomeric purity by treatment with Mg and NH_4Cl in methanol giving **8** in 83% yield (Scheme 5a).[14] On the other hand, a dehydration of **3aa** gave 90% yield of **9** (Scheme 5b).[15]

In summary, we have developed a highly regio- and enantioselective asymmetric annulation of α-oxocarbox-



Scheme 5. Transformations of **3aa**.

amides and an α-iminocarboxamide with 1,3-dienes catalyzed by hydroxoiridium/chiral diene complexes.

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Keywords: [3+2] annulation · asymmetric synthesis · carboxamides · chiral diene · iridium

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