Iridium-Catalyzed Annulation of Salicylimines with 1,3-Dienes

Yusuke Ebe and Takahiro Nishimura*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
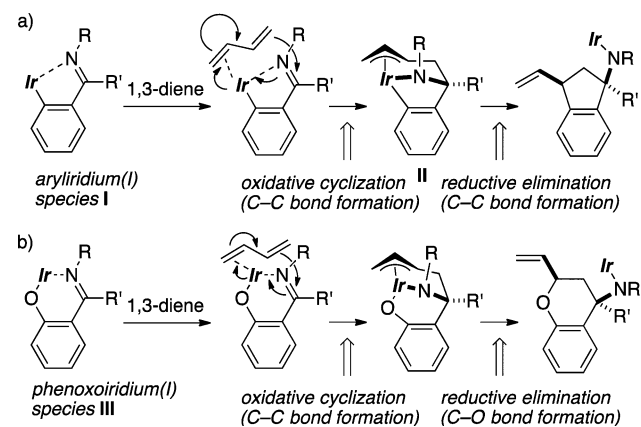
Ⓢ *Supporting Information*

ABSTRACT: Iridium-catalyzed annulation of salicylimines with 1,3-dienes gave high yields of the corresponding 4-aminochromanes with high stereoselectivity. The use of a chiral diene ligand enabled the asymmetric reaction to give 4-aminochromanes with high enantioselectivity.

Transition-metal-catalyzed intermolecular cycloaddition is one of the most powerful methods for the synthesis of carbo- and heterocyclic compounds,[1] and in particular, the development of highly atom-efficient cycloaddition reactions without formation of wastes[2] is a significant objective to realize ideal molecular transformations of carbon resources in synthetic organic chemistry.[3] In this regard, we recently reported the iridium-catalyzed [3 + 2] annulation of cyclic *N*-sulfonyl ketimines with 1,3-dienes giving spiroaminoindane derivatives, where the reaction proceeds via aryliridium(I) species **I** generated by the chelation-assisted ortho C−H activation of the aromatic ring (Scheme 1a).[4] The aryliridium-

Scheme 1. Iridium-Catalyzed Annulation Using 1,3-Dienes

(I) species **I** undergoes the oxidative cyclization[5−7] with the 1,3-diene forming π-allyliridium(III) species **II** and the subsequent reductive elimination gives the aminoindane derivative, and thus, two C−C bond formations occur to create the indane skeleton. We focused on the oxidative cyclization/reductive elimination sequence for the synthesis of oxygen-containing heterocycles as shown in Scheme 1b, where the reaction involves phenoxoiridium(I) species **III**. Here we report an iridium-catalyzed formal [4 + 2] annulation of salicylimines with 1,3-dienes to give 4-aminochromane derivatives. The asymmetric variant of the reaction by use of a chiral diene ligand[8] is also described.
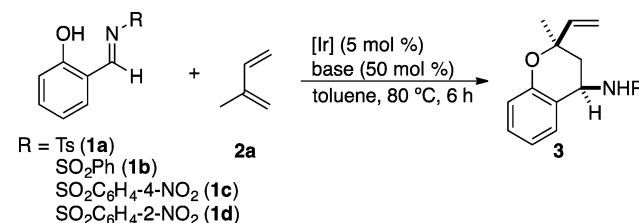
4-Aminochromanes are a structurally important core unit found in many biologically active compounds and natural products,[9] and their synthesis has attracted considerable attention. Salicylimines have been used as good starting materials for the synthesis of 4-aminochromanes in the acid- or base-catalyzed reactions with electron-rich alkenes,[10] azalactones,[11] and allenic esters[12] as well as electron-deficient alkenes and alkynes.[13] Our approach is focused on the use of the *N*-tosylsalicylimines **1** for the formation of the phenoxoiridium(I) species **III** intramolecularly coordinated with the imine nitrogen (Scheme 1b and Table 1). Treatment of *N*-tosylsalicylimine **1a** with isoprene (**2a**) in the presence of [IrCl(cod)]₂ (5 mol % of Ir, cod = 1,5-cyclooctadiene), KOAc (50 mol %) in toluene at 80 °C for 6 h gave the annulation

Table 1. Iridium-Catalyzed Annulation of Salicylimines 1 with 2a[a]

entry	Ir catalyst	base		yield of 3 (%)[b]
1	[IrCl(cod)]₂	KOAc	**3aa**	26
2	[IrCl(cod)]₂	KHCO₃	**3aa**	13
3	[IrCl(cod)]₂	K₂CO₃	**3aa**	3
4	[IrCl(cod)]₂	K₃PO₄	**3aa**	0
5	[IrCl(cod)]₂	KOt-Bu	**3aa**	0
6	[IrCl(cod)]₂	NaOAc	**3aa**	45
7	[IrCl(cod)]₂	LiOAc·2H₂O	**3aa**	6
8	[IrCl(coe)₂]₂	NaOAc	**3aa**	92
9[c]	[IrCl(coe)₂]₂	NaOAc	**3aa**	98[d]
10	[RhCl(coe)₂]₂	NaOAc	**3aa**	30
11	[IrCl(coe)₂]₂	NaOAc	**3ba**	80
12	[IrCl(coe)₂]₂	NaOAc	**3ca**	58
13[e]	[IrCl(coe)₂]₂	NaOAc	**3ca**	76[d]
14[e]	[IrCl(coe)₂]₂	NaOAc	**3da**	74[d]

[a] Reaction conditions: salicylimine **1** (0.10 mmol), **2a** (0.15 mmol), [Ir] (5 mol % of Ir), base (50 mol %) in toluene (0.4 mL) at 80 °C for 6 h. [b] Determined by ¹H NMR analysis using 1,4-dimethoxybenzene as an internal standard. [c] Salicylimine **1a** (0.20 mmol), **2a** (0.30 mmol), [IrCl(coe)₂]₂ (2 mol % of Ir), NaOAc (50 mol %) in toluene (0.8 mL) at 80 °C for 12 h. [d] Isolated yield. [e] For 36 h.

product **3aa** in 26% yield (Table 1, entry 1), where very high regio- and stereoselectivity of the annulation was observed: a more substituted alkene moiety of isoprene participates in the reaction to give **3aa** with the 2,4-cis relative stereochemistry. The reactions with other bases, such as KHCO₃ and K₂CO₃, gave much lower yields of **3aa** than that with KOAc (entries 2 and 3), and the use of K₃PO₄ and KOt-Bu resulted in no formation of the annulation product (entries 4 and 5). The use of NaOAc gave a higher yield of **3aa** than that obtained with KOAc or LiOAc (entry 6 vs entries 1 and 7). The catalytic activity was dramatically increased by use of [IrCl(coe)₂]₂ (5 mol % of Ir, coe = cyclooctene) instead of [IrCl(cod)]₂ as a catalyst precursor, giving a 92% yield of **3aa** (entry 8). This result indicates that the iridium species coordinated with the 1,3-diene as a ligand formed by an exchange of two cyclooctenes on [IrCl(coe)₂] displays high catalytic activity. The reaction with a reduced amount of the iridium catalyst (2 mol % of Ir) also proceeded well, giving a 98% yield of the annulation product (entry 9). A Rh catalyst [RhCl(coe)₂]₂ can also catalyze the present reaction, although its catalytic activity was much lower than that of the Ir catalyst (entry 10). The reactions of *N*-benzenesulfonylimine **1b** and *N*-nitrobenzene-sulfonylimines **1c** and **1d** proceeded to give the corresponding annulation products **3ba**, **3ca**, and **3da**, respectively (entries 11−14), where the relatively electron-deficient substituents on the imine nitrogen lowered the reactivity.

The results obtained for the iridium-catalyzed annulation of salicylimine **1a** with various types of 1,3-dienes are summarized in Table 2. In a similar vein as isoprene (**2a**), myrcene (**2b**) and 2-phenylbutadiene (**2c**) underwent the annulation of **1a** to give the corresponding annulation products **3ab** and **3ac** in yields of 86% and 83%, respectively (entries 1−3). The reaction of 2-siloxybutadiene **2d** gave **3ad** in 86% yield with very high regio- and stereoselectivity (entry 4). In the reaction of 2-siloxy-methylbutadiene **2e**, a more substituted alkene moiety participated in the reaction to give **3ae** accompanied by a small amount of its regioisomer **4ae** (**3ae**/**4ae** = 97:3, entry 5). 2,3-Disubstituted butadienes are also good substrates for the present annulation (entries 6−8). The reaction of 2,3-dimethyl-1,3-butadiene (**2f**) gave **3af** in 85% yield (entry 6). On the other hand, it should be noted that the reactions of unsymmetrically 2,3-disubstituted butadienes **2g** and **2h** also displayed high regioselectivity to give annulation products **3ag** and **3ah** as the major products, respectively (entries 7 and 8), where less bulky alkene parts preferentially participated in the reaction. Diene **2i** based on a dihydropyrrole group gave benzobicyclic compound **3ai** in 53% yield (entry 9).

Table 3 summarizes the results obtained for the reaction of several salicylimines **1** with 1,3-diene **2a**. The reactions of salicylimines substituted at the 5-position with electron-donating groups, Me (**1e**) and MeO (**1f**), and electron-withdrawing groups, F (**1g**), Cl (**1h**), and Br (**1i**), are all good substrates to give high yields of the annulation products **3ea**–**3ia** (entries 1−5). The reactions of salicylimines **1j** and **1k**, which are substituted with a methyl group at meta and ortho to the hydroxy group, gave the annulation products **3ja** and **3ka**, respectively, in good yields (entries 6 and 7). Salicylimines **1l** and **1m** substituted at the 6-position are also applicable to the present annulation to give high yields of the corresponding 4-aminochromanes (entries 8 and 9). The annulation of naphthol derivative **1n** gave **3na** in 80% yield (entry 10).

These annulation reactions presumably go through a catalytic cycle illustrated in Scheme 2. The reaction of salicylimine **1a**

Table 2. Scope of 1,3-Dienes 2[a]

entry	diene 2	product	yield (%)[b]
1	**2a**	**3aa**: R = Me	98
2	**2b**	**3ab**: R = CH₂CH₂CH=CMe₂	86
3	**2c**	**3ac**: R = Ph	83
4	**2d**	**3ad**: R = OSiMe₂Ph	86
5	**2e**	**3ae**: R = CH₂OSiMe₂t-Bu	86 (**3ae**/**4ae** = 97:3)
6	**2f**	**3af**	85
7	**2g**	**3ag**: X = NHTs	90 (**3ag**/**4ag** = 97:3)
8	**2h**	**3ah**: X = OSiMe₂t-Bu	96 (**3ah**/**4ah** = 92:8)
9[c]	**2i**	**3ai**	53

[a]Reaction conditions: salicylimine **1a** (0.20 mmol), **2** (0.30 mmol), [IrCl(coe)₂]₂ (2 mol % of Ir), NaOAc (50 mol %) in toluene (0.8 mL) at 80 °C for 12 h. [b]Isolated yields. [c]Performed with [IrCl(coe)₂]₂ (5 mol % of Ir).

with a chloroiridium complex, which is coordinated with a 1,3-diene, in the presence of NaOAc forms phenoxoiridium(I) species **A** intramolecularly coordinated with the imine nitrogen. The species **A** undergoes oxidative cyclization with the 1,3-diene via 18-electron species **B** forming π-allyliridium(III) species **C**. The intermediate **C** undergoes reductive elimination forming a carbon−oxygen bond to give species **D**, and subsequent protonolysis gives **3aa** and regenerates the phenoxoiridium **A**.

Because iridium/diene complexes can catalyze the present reaction,[14] the use of chiral diene ligands is promising for the development of the asymmetric variant. On the other hand, the high catalytic activity of the iridium complex coordinated with the substrate 1,3-diene observed above indicates a requirement of the use of a chiral diene ligand that has a stronger coordination ability than the substrate diene to avoid the nonenantioselective background reaction. After a screening of

Table 3. Scope of Salicylimines 1[a]

entry	1		product	isolated yield (%)
1	**1e**: X = Me		**3ea**	94
2	**1f**: X = MeO		**3fa**	97
3	**1g**: X = F		**3ga**	96
4	**1h**: X = Cl		**3ha**	97
5	**1i**: X = Br		**3ia**	99
6	**1j**		**3ja**	93
7[b,c]	**1k**		**3ka**	86
8[b]	**1l**: X = Cl		**3la**	92[d]
9[b]	**1m**: X = Me		**3ma**	78[e]
10[b,c,f]	**1n**		**3na**	80

[a]Reaction conditions: salicylimine **1** (0.20 mmol), **2a** (0.30 mmol), [IrCl(coe)$_2$]$_2$ (2 mol % of Ir), NaOAc (50 mol %) in toluene (0.8 mL) at 80 °C for 12 h. [b]Performed with [IrCl(coe)$_2$]$_2$ (5 mol % of Ir). [c]For 24 h. [d]The isolated product includes a 3% of the isomer. [e]Isomers were also formed (ca. 3%). [f]KOAc (50 mol %) was used instead of NaOAc.

Scheme 2. Proposed Catalytic Cycle
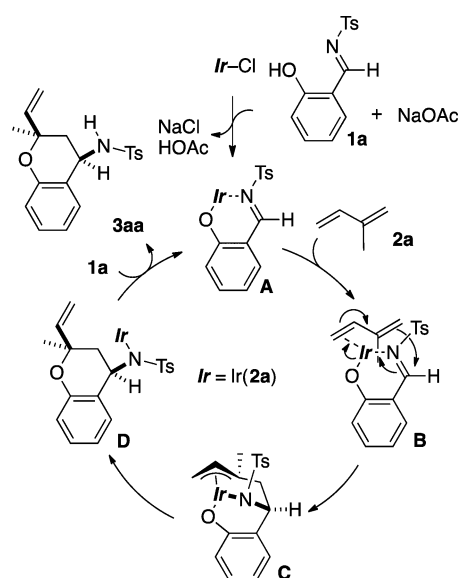
the reaction conditions using recently developed chiral diene ligands based on a tetrafluorobenzobarrelene framework in our group,[15] it was found that an enantioselective annulation of

salicylimines **1** with isoprene (**2a**) or myrcene (**2b**) proceeds in the presence of a chiral Ir/diene catalyst. Thus, treatment of salicylimine **1a** (1.2 equiv) with **2a** in the presence of [IrCl((*S*,*S*)-Fc-tfb*)]$_2$ (5 mol % of Ir), NaBAr$^F_4$ [Ar^F = 3,5-(CF$_3$)$_2$C$_6$H$_3$], and 1,4-diazabicyclo[2.2.2]octane (DABCO) (10 mol %) in dichloromethane at 20 °C for 48 h gave the annulation product **3aa** in 89% yield with 99% ee (Table 4,

Table 4. Asymmetric Annulation of 1 with 2[a]

entry	1		product	isolated yield (%)	ee (%)
1	**1a**: X = H		**3aa**	89	99
2	**1e**: X = Me		**3ea**	92	99
3	**1g**: X = F		**3ga**	92	99
4	**1h**: X = Cl		**3ha**	97	99
5	**1i**: X = Br		**3ia**	97	99
6[b]	**1j**		**3ja**	78	98
7[b]	**1k**		**3ka**	54	98
8	**1a**		**3ab**	65	99

(*S*,*S*)-Fc-tfb*   Fc: ferrocenyl

[a]Reaction conditions: salicylimine **1** (0.24 mmol), **2** (0.20 mmol), [IrCl((*S*,*S*)-Fc-tfb*)]$_2$ (5 mol % of Ir), NaBAr$^F_4$ (10 mol %), DABCO (10 mol %) in CH$_2$Cl$_2$ (0.8 mL) at 20 °C for 48 h. [b]For 72 h.

entry 1).[16] The very high enantioselectivity was also observed in the reactions of salicylimines **1e** and **1g**−**1i** substituted at the 5-position (entries 2−5). The reactions of salicylimines **1j** and **1k** having a methyl group at the 4- and 3-position were slow to give the corresponding products **3ja** and **3ka** in yields of 78% and 54%, respectively, for 72 h (entries 6 and 7). Myrcene (**2b**) can also be applied to the annulation of **1a** to give **3ab** in 65% yield with 99% ee (entry 8). The relative and absolute configurations of **3ha** obtained with (*S*,*S*)-Fc-tfb* were determined to be (2*R*,4*R*) by X-ray crystallographic analysis.

In summary, we have developed a new type of annulation reaction of salicylimines with 1,3-dienes using an Ir catalyst that gives 4-aminochromane derivatives with high regio- and stereoselectivity. The asymmetric annulation with high regio- and enantioselectivity has also been realized by use of an Ir/chiral diene catalyst.

ASSOCIATED CONTENT

S **Supporting Information**

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

tnishi@kuchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

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