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Iridium-catalyzed aziridination of aliphatic aldehydes, aliphatic amines and ethyl diazoacetate

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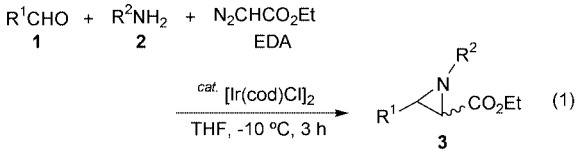
Three-component coupling reactions of aliphatic aldehydes, aliphatic amines and ethyl diazoacetate to the corresponding aziridine derivatives has been achieved by the use of $[Ir(cod)Cl]_2$ as a catalyst under mild conditions; for instance, the reaction of *n*-butyraldehyde, *tert*-butylamine and ethyl diazoacetate in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ in THF at −10 °C gave 1-*tert*-butyl-2-ethoxycarbonyl-3-propylaziridine in 85% yield in high stereoselectivity (*cis* : *trans* = 96 : 4).

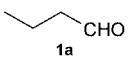
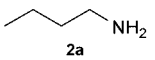
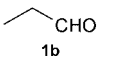
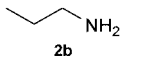
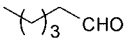
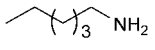
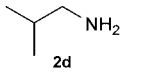
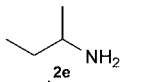
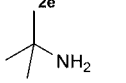
Aziridines are versatile compounds as precursors for the synthesis of various types of nitrogen-containing compounds, which are biologically important, such as amino acids, amino alcohols and β-lactams, *etc.*[1] There are many reports on the synthesis of aziridines, *e.g.* trapping of nitrenes and carbenes by alkenes[2] and imines,[3] respectively, and Lewis acid-catalyzed reaction of imines with ethyl diazoacetate (EDA).[4] These methods are suitable for the synthesis of aziridines derived from aromatic imines and diazo compounds; however, aziridine synthesis from aliphatic imines and EDA has not yet been established. Recently, Nagayama and Kobayashi have reported a three-component coupling reaction of aldehydes, amines and EDA in the presence of $Ln(OTf)_3$, although 5 Å molecular sieves must be added to the reaction system.[5] Now we have found that the three-component coupling reaction of aliphatic aldehydes, aliphatic amines and EDA to aziridine derivatives proceeds smoothly using an iridium complex as a catalyst and without any dehydrating agents [eqn. (1)].



To a solution of $[Ir(cod)Cl]_2$ in THF was added *n*-butyraldehyde **1a** and *n*-butylamine **2a**. After stirring for 10 min, EDA was added and then the mixture was stirred at −10 °C for 3 h (standard conditions).† The reaction produced 1-butyl-2-ethoxycarbonyl-3-propylaziridine **3aa**‡ which consists of a *ca.* 1 : 1 stereoisomeric mixture of *cis*-**3aa** and *trans*-**3aa** in 71% yield (Table 1, run 1). Table 1 summarizes the results for various three-component coupling reactions of aldehydes, amines and EDA under selected reaction conditions. $[Ir(cyclooctene)_2Cl]_2$ also catalyzed the coupling reaction to form **3aa** in 75% yield, while $IrCl_3$ was inert (runs 2 and 3). Various solvents could be employed for this reaction. (runs 4–6).

On the basis of these results, the reaction of aldehydes, amines and EDA was examined in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ in THF under standard conditions. The reaction led to the corresponding aziridines in fair to good yields (runs 7–11). Interestingly, the stereoselectivity of the resulting aziridines was found to be improved by the use of a bulky amine such as *tert*-butylamine **2f**. For instance, the reaction of **1a**, **2e** with EDA afforded 1-*tert*-butyl-2-ethoxycarbonyl-3-propylaziridine **3af** in 83% yield in excellent stereoselectivity (*cis* : *trans* = 96 : 4) (run 11).§ In this reaction, ethanol was also suitable as a solvent, and **3af** was obtained in almost the same yield and stereoselectivity as those in THF (run 12). No aziridine was detected in the reaction of benzaldehyde **1d**, aniline **2g**, and EDA under these reaction conditions (run 13). These results will be discussed later.

Table 1 Three-component coupling reaction of aldehyde **1**, amine **2** and EDA[a]

Run	Aldehyde	Amine	Adirizine	Yield (%)[b]	
1	 **1a**	 **2a**	**3aa**	71	(63/37)
2[c]	**1a**	**2a**	**3aa**	75	(52/48)
3[d]	**1a**	**2a**	**3aa**	No reaction	
4[e]	**1a**	**2a**	**3aa**	68	(46/54)
5[f]	**1a**	**2a**	**3aa**	74	(53/47)
6[g]	**1a**	**2a**	**3aa**	79	(63/37)
7	 **1b**	 **2b**	**3bb**	52	(57/43)
8	 **1c**	 **2c**	**3cc**	54	(51/49)
9	**1a**	 **2d**	**3ad**	76	(63/37)
10	**1a**	 **2e**	**3ae**	83	(83/14)
11	**1a**	 **2f**	**3af**	83	(96/ 4)
12[g]	**1a**	**2f**	**3af**	82	(96/ 4)
13	Ph—CHO **1d**	Ph—NH_2 **2g**	**3dg**	No reaction	

[a] Aldehyde (1 mmol), amine (1 mmol) and EDA (2 mmol) were allowed to react in the presence of $[Ir(cod)Cl]_2$ (0.05 mmol) in THF (1 mL) at −10 °C for 3 h under Ar atmosphere. [b] Parentheses indicate *cis*/*trans* ratio. [c] $[Ir(cyclooctene)_2Cl]_2$ (0.05 mmol) used as catalyst. [d] $IrCl_3$ (0.05 mmol) used as catalyst. [e] Dichloromethane (1 mL) used as solvent. [f] *n*-Hexane (1 mL) used as solvent. [g] Ethanol (1 mL) used as solvent.

The present Ir-catalyzed three-component coupling reaction seems to proceed *via* the formation of imine which then reacts with EDA. Indeed, *N*-butylidene-*n*-butylamine **4aa** prepared independently from **1a** and **2a** was allowed to react with EDA under standard conditions to form **3aa** (73%) as expected [eqn. (2)]. Although the $La(OTf)_3$-catalyzed three-component coupling reaction requires the presence of 5 Å molecular sieves,[5] the present three-component coupling reaction was performed without any dehydrating agents. It is noteworthy that the Ir-

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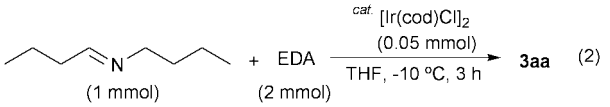
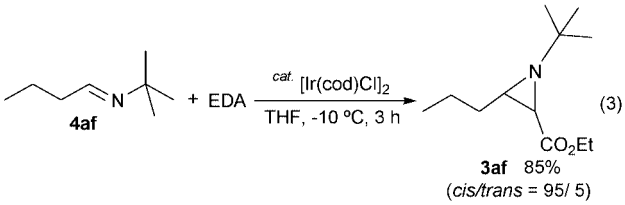
catalyzed aziridination was not affected by water in the reaction system. When the reaction of imine **4aa** with EDA was carried out in the presence of a small amount of water, **3aa** was obtained in almost the same yield as the reaction in the absence of water [(eqn. (2)].



Additive	Yield (%)
–	73
H_2O (1 mmol)	69

Furthermore, the reaction of *N*-butylidene-*tert*-butylamine **4af** with EDA took place in high stereoselectivity, giving **3af** in 85% yield (*cis*:*trans* = 95:5) [(eqn. (3)]. For the reaction of *N*-benzylideneaniline **4dg** with EDA, however, diethyl maleate **5** and diethyl fumarate **6** were formed in 46% yield, and **4dg** was recovered unchanged.



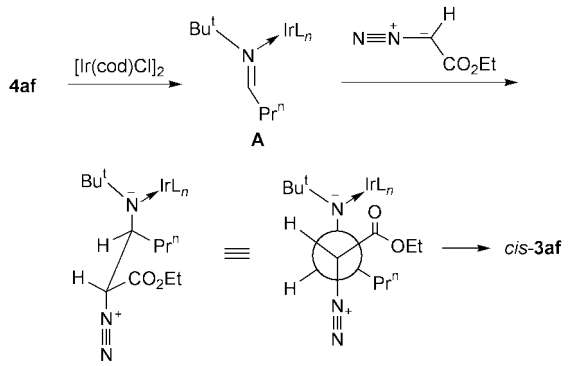
Addtionally, the reaction of a ketimine such as *N*-(1-ethylpropylidene)-*n*-butylamine with EDA led to 1-butyl-3,3-diethyl-2-ethoxycarbonylaziridine in 54% yield.

From the mechanistic point of view, it is of note that the selectivity of aziridine is affected by the order of the addition of substrates to the catalyst solution. When 1.0 mmol of imine **4aa** was added to a THF solution containing $[Ir(cod)Cl]_2$ (0.05 mmol) at −10 °C, the solution changed immediately from orange–red to light yellow, and EDA (2 mmol) was added to this solution to form aziridine **3aa** (73%). However, the addition of EDA (2.0 mmol) to a THF solution of $[Ir(cod)Cl]_2$ resulted in a change from orange–red to dark purple, and then **4aa** (1.0 mmol) was added to produce **3aa** in lower yield (59%) along with a homocoupling product of EDA, **5** and **6** (13%), the formation of which may be explained by *in situ* generation of carbene from EDA by the action of an Ir complex. Hence, it is probable that the present Ir-catalyzed aziridine synthesis proceeds *via* the formation of an Ir–imine complex rather than an Ir–carbene complex.

In addition, when imine **4dg** was added to a THF solution of $[Ir(cod)Cl]_2$, no color change was observed, and the aziridine expected was not obtained and instead, dimers of EDA, **5** and **6** as shown above. Therefore, it is reasonable to presume that the reaction of **4dg** with EDA is difficult to occur owing to the difficulty of the complexation of **4dg** with the Ir-complex.

The high stereoselectivity of the reaction of **1a**, **2f** and EDA (Table 1, run 11) may be explained by assuming a similar reaction path suggested in the $Yb(OTf)_3$-catalyzed reaction of *N*-benzylidene-*tert*-butylamine with EDA (Scheme 1).[4f] It is probable that the Ir complex $[Ir(cod)Cl]_2$ coordinates to imine **4af** to lead to a complex **A**.¶ The nucleophilic attack of EDA to the resulting complex **A** would take place from the direction to reduce the steric repulsion between the ester moiety of the incoming EDA and the *tert*-butyl group of the imine to form *cis*-**3af**.

In summary, various types of aziridine derivatives, which are difficult to prepare by the conventional methods, have been prepared by the three-component coupling reaction of aliphatic aldehydes, aliphatic amines and EDA, catalyzed by $[Ir(cod)Cl]_2$. High stereoselectivity was attained by the reaction of aldehyde, tertiary amine and EDA.



Scheme 1 A possible reaction pathway for reaction of **4af** with EDA.

Notes and references

† *Typical reaction procedure*: to a THF solution (1.0 mL) of dichlorobis(cycloocta-1,5-diene)diirdium {$[Ir(cod)Cl]_2$} (0.05 mmol) was added aldehyde (1.0 mmol) and amine (1.0 mmol) at −10 °C under Ar. After stirring for 10 min, EDA (2.0 mmol) was added, and then the reaction mixture was stirred at −10 °C for 3 h. The reaction was quenched with wet diethyl ether, and products were isolated by column chromatography [(230–400 mesh silica gel, ethyl acetate–hexane (1:12) eluent].

‡ *Spectral data* for **3aa**: ^{1}H NMR δ 4.25–4.15 (m, 2H), 2.42–2.06 (m, 2H), 2.09 (d, *J* 6.6 Hz, 1H), 1.72–1.69 (m, 1H), 1.60–1.30 (m, 6H), 1.31 (q, *J* 7.3 Hz, 2H), 1.27 (t, *J* 7.3 Hz, 3H), 0.92 (t, *J* 7.3 Hz, 3H), 0.90 (t, *J* 7.3 Hz, 3H); ^{13}C NMR δ 170.0, 60.8, 60.7, 46.6, 42.6, 31.4, 29.7, 20.6, 20.3, 14.3, 13.9, 13.7; IR (neat) 2959, 1747, 1183 cm^{-1}; MS, *m/z* = 213 (M^+), 198, 140, 84; Anal. Calc. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.25, H, 10.52; N, 6.62%.

§ The stereochemistry of **3af** was determined by comparison of the coupling constant obtained from ^{1}H NMR spectral data for **3af** with that of 2-ethoxylcarbonyl-1,3-diphenylaziridine reported in the literature.[4a,f]

¶ NMR observation showed the formation of the complex **A** from $[Ir(cod)Cl]_2$ and imine; *i.e.* when $[Ir(cod)Cl]_2$ was added to 1.0 equiv. of **4af** in a NMR tube, the ^{13}C NMR signals at δ 164.5 (–CH=N–) and 61.0 (=NCH_2–) of **4af** were shifted to δ 171.6 and 63.6, respectively.

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