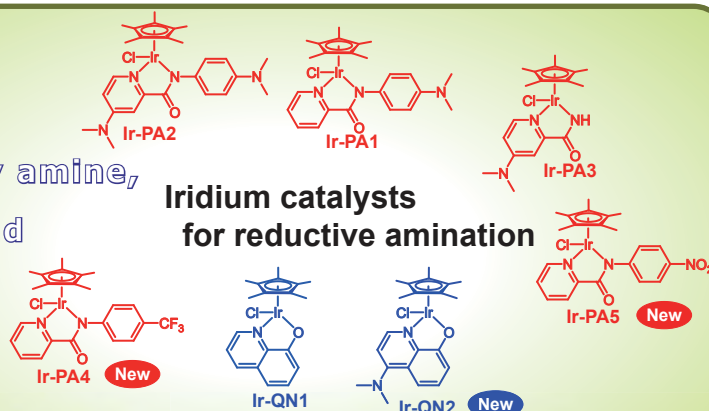


# New Catalysts for Reductive Amination

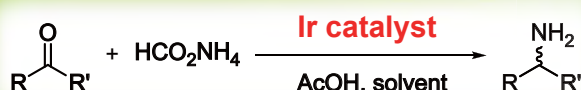
– Ver.4 –



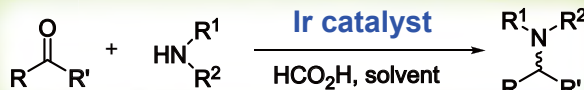
From a carbonyl compound,  
a primary amine, a secondary amine,  
a tertiary amine are easily and  
conveniently synthesized  
in a one-pot synthesis



**primary amines synthesis**



**secondary and tertiary amines synthesis**



Amine compounds are useful compounds used in a wide range of applications such as pharmaceuticals, agricultural materials, functionalized materials, and starting materials for resins. Reductive amination of carbonyl compounds is known as one of the effective synthetic methods for amines. We Kanto Chemical has developed and marketed a reductive amination catalyst (iridium catalyst) excellent in practicality that can synthesize primary amines, secondary amines, and tertiary amines under mild conditions so far, We have received popularity from everyone. We have newly added 3 reductive amination catalysts with different substrate coverage. Please use it for your product development and research.

## High reactivity

**High catalytic activity**

1-Phenylethylamine can be synthesized from acetophenone under the condition of S / C = 10,000.

**Chemoselective reaction**

Primary amines can be synthesized from acetophenone derivatives without impairing functional groups.

**High diastereoselectivity**

Primary amines can be synthesized diastereoselectively from cycloaliphatic ketones with substituents.

## Simple operation

**Not necessary special equipment**

Since ammonium formate or formic acid is used as a hydrogen source, special equipment is not required.

**Mild reaction conditions**

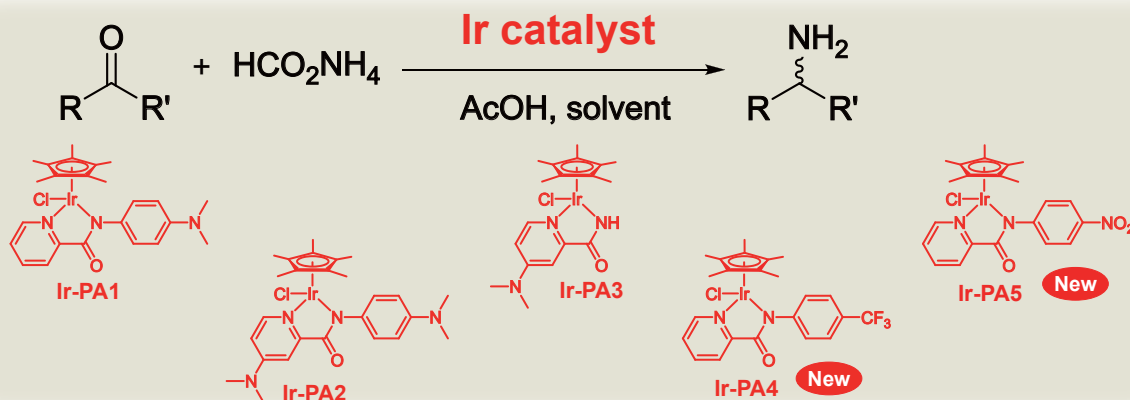
Since this catalyst can be used under reflux conditions from 60 °C, it has high practicality.

**Air-stable catalysts**

Since this catalyst can be handled stably in the air, it can be weighed with ordinary laboratory equipment

A list of reductive amination catalyst products is posted on the back cover

Primary amine synthesis



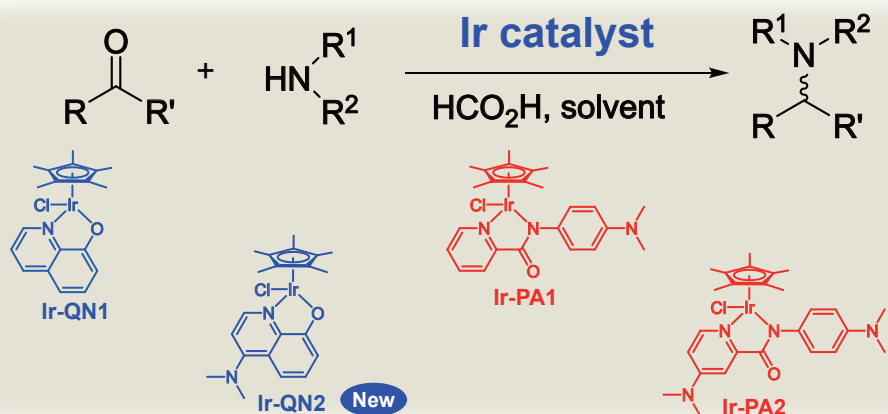
Ir-PA1~Ir-PA5 catalysts which have picolin amide particles are suitable for primary amine synthesis. The feature of each catalyst are described below.

Catalyst	Feature and use application
<b>Ir-PA1</b>	Ir-PA1 shows a wide range of substrate adaptability. We recommend that you consider using this catalyst when you first try.
<b>Ir-PA2</b>	Ir-PA2 has high activity, and it is also applicable to substances with high bulkiness near the carbonyl group. If the by-product of the alcohol is less in the reaction of Ir-PA1 catalyst, Ir-PA2 can be expected to reduce the amount of catalyst.
<b>Ir-PA3</b>	We recommend using Ir-PA3 catalyst together with the Ir - PA 2 catalyst when studying the reaction of a substrate that is sterically bulky near the carbonyl group.
<b>Ir-PA4</b> <b>Ir-PA5</b>	These catalysts are suitable for electron-deficient substrates. In the reaction using the Ir - PA1 catalyst or the Ir - PA2 catalyst, this catalyst may be effective when the by - production of the alcohol is remarkable.

Reaction condition of catalyst

hydrogen source amine source	Ammonium formate are used as hydrogen source in this reaction. 3 to 5 equivalents to the substrate are optimum.
solvent	Ethanol is optimum in terms of solubility and reactivity of ammonium formate. Water can also be used in the case of water-soluble substrates.
temperature	It is suitable to reflux conditions from 60 °C (eg around 80 °C for methanol). Reflux conditions are recommended in terms of reactivity, but when side reactions occur concurrently, side reactions can be suppressed by lowering the reaction temperature.
additive	Add 1 equivalent of acetic acid to the substrate. Increasing the amount of acetic acid added (eg 2 equivalents) to improve reactivity can improve yield.
control of by-product	As the main by-product of the reaction, there are formyl, alcohol(reduced form of ketone) and overalkylated forms(A reductant of an imine formed by a condensation reaction between a primary amine and a ketone substrate) of primary amines which is the target product. Formyl compounds tend to increase with increasing reaction time, so caution is necessary when extending the reaction time beyond necessity. Alcohol may be observed conspicuously depending on the substrate, but as mentioned above, the use of Ir - PA 4 catalyst or Ir - PA 5 catalyst may make it possible to suppress alcohol.
caution	Carbon dioxide is released as this reaction progresses. Avoid reacting in a closed system, for example connect it to a line of inert gas, or connect it to a highly gas-tight gas balloon and carry out the reaction while releasing the generated carbon dioxide outside the system.

## Secondary and tertiary amine synthesis



For the synthesis of secondary amines and tertiary amines, an Ir - QN 1, and Ir - QN 2 with a quinolinol ligand are suitable. However, in the synthesis of secondary amines that are not sterically bulky like the reaction of aldehydes with primary amines, tertiary amine as a by-product by overalkylation reaction is a concern. So in this case, secondary amines can be obtained highly selectively by using Ir - PA1 catalyst or Ir - PA2 catalyst with picolinamide ligand. Please see the table below for the characteristics and proper use of each catalyst.

Catalyst	Feature and use application
<b>Ir-QN1</b>	Ir-QN1 shows a wide range of substrate adaptability. We recommend that you consider using this catalyst when you first try.
<b>Ir-QN2</b>	Ir-QN-2 is a catalyst with higher activity than Ir - QN1, and when the reaction result of Ir - QN1 catalyst is good, Ir-QN2 can be expected to reduce the amount of the catalyst.
<b>Ir-PA1</b> <b>Ir-PA2</b>	In the case of synthesis of secondary amines that are not sterically bulky when the by-production of tertiary amines becomes a problem due to an overalkylation, secondary amines can be obtained highly selectively

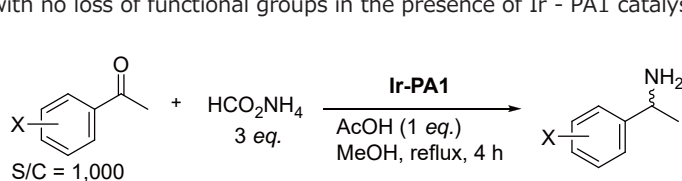
### Reaction condition of catalyst

hydrogen source	Formic acid are used as hydrogen source in this reaction. 3 to 5 equivalents to the substrate are optimum.
solvent	Various solvents can be used in consideration of the solubility and reactivity of the substrate.
temperature	In general it is recommended to perform at 40 °C to 60 °C.
control of by-product	If alcohol is produced as a by-product, yield can be expected to be improved by changing reaction solvent and increasing amine equivalent..
caution	Carbon dioxide is released as this reaction progresses. Avoid reacting in a closed system, for example connect it to a line of inert gas, or connect it to a highly gas-tight gas balloon and carry out the reaction while releasing the generated carbon dioxide outside the system.

## Primary amine synthesis

### Reductive amination of functionalized substrate such as electron attracting group

Acetophenones substituted with nitro, cyano and halogen groups also give the corresponding primary amines in good yield with no loss of functional groups in the presence of Ir - PA1 catalyst.



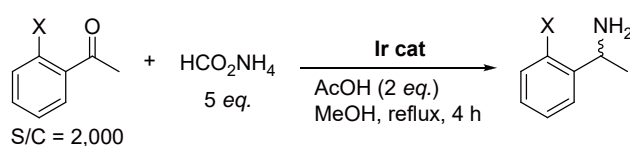
X	yield (%)	X	yield (%)	X	yield (%)
OCH <sub>3</sub>	97	OCH <sub>3</sub>	98	OCH <sub>3</sub>	92
Br <sup>a</sup>	99	Cl	99	CH <sub>3</sub>	35
NO <sub>2</sub> <sup>a</sup>	94	NO <sub>2</sub>	98	F	96
CN <sup>a</sup>	96			Cl	41
				Br	21

<sup>a</sup> Conditions: 60 °C

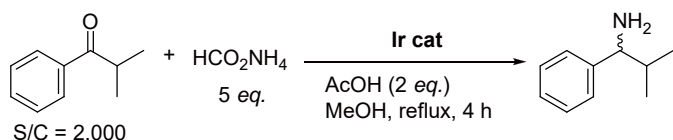
### Reductive amination of bulky substrate

In the reaction of a substrate having a substituent at the ortho position as described above, the yield tends to decrease due to steric hindrance. In that case, the yield can be expected to be improved by using Ir - PA 2 catalyst or Ir - PA 3 catalyst.

Even in relatively bulky substrates such as isopropyl phenyl ketone, the Ir - PA 2 catalyst and Ir - PA 3 catalyst show higher reactivity than the Ir - PA 1 catalyst, giving the corresponding primary amines in high yield.



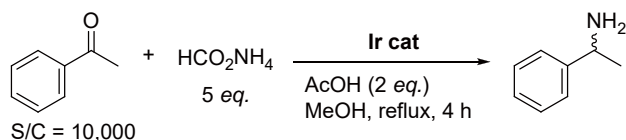
entry	X	Ir cat	yield (%)
1	Cl	<b>Ir-PA1</b>	45
2	Cl	<b>Ir-PA2</b>	90
3	Cl	<b>Ir-PA3</b>	86
-----			
4	Br	<b>Ir-PA1</b>	18
5	Br	<b>Ir-PA2</b>	69
6	Br	<b>Ir-PA3</b>	85



Ir cat	yield (%)
<b>Ir-PA1</b>	53
<b>Ir-PA2</b>	97
<b>Ir-PA3</b>	97

### Reduction of use of catalyst

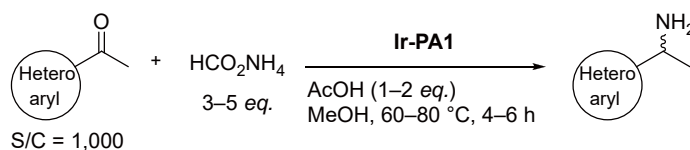
In the reaction of acetophenone, Ir-PA2 catalyst shows the highest reactivity when comparing the catalytic performances of Ir-PA1, Ir-PA2, and Ir-PA3 catalyst under the condition of S / C (substrate / catalyst molar ratio) = 10,000 (Entry 2).



entry	Ir cat	yield (%)
1	<b>Ir-PA1</b>	55
2	<b>Ir-PA2</b>	90
3	<b>Ir-PA3</b>	31

### Reductive amination of heteroaromatic ring compound.

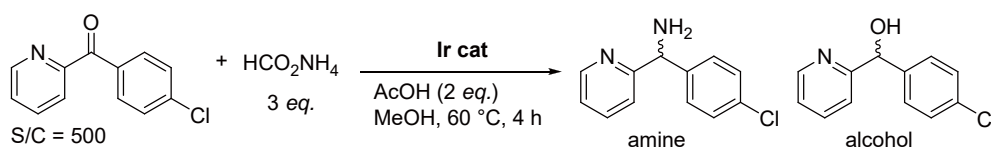
Amines containing heteroaromatic rings are important compounds contained in pharmaceuticals, agricultural materials, and functionalized materials. In the presence of the Ir - PA1 catalyst, the reaction of the furan ring, the thiophene ring, and the ketones having a pyrrole ring progresses smoothly, giving the corresponding primary amines in good yield.



Hetero aryl:	yield (%)
	72
	92
	93
	96
	89
	>99
	94

### Reaction control of a substrate on which an alcohol is easily by-produced

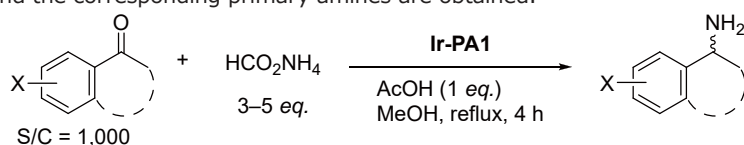
In the reaction of 2-(4-chlorobenzoyl) pyridine having a heteroaromatic ring in the molecule, use of Ir-PA 2 catalyst or Ir-PA 1 catalyst with high catalytic activity produces a negligible amount of alcohol form (Entries 1 and 2), Ir-PA4 catalyst or Ir-PA5 catalyst with controlled reducing power can greatly reduce alcohol by-product (Entries 3 and 4). Ir-PA4 catalyst and Ir-PA5 catalyst may work effectively in reaction of electron-deficient substrate.



entry	Ir cat	yield (%)	
		amine	alcohol
1	<b>Ir-PA2</b>	34	54
2	<b>Ir-PA1</b>	73	15
3	<b>Ir-PA4</b>	81	9
4	<b>Ir-PA5</b>	82	8

### Reductive amination of cycloaromatic ketone

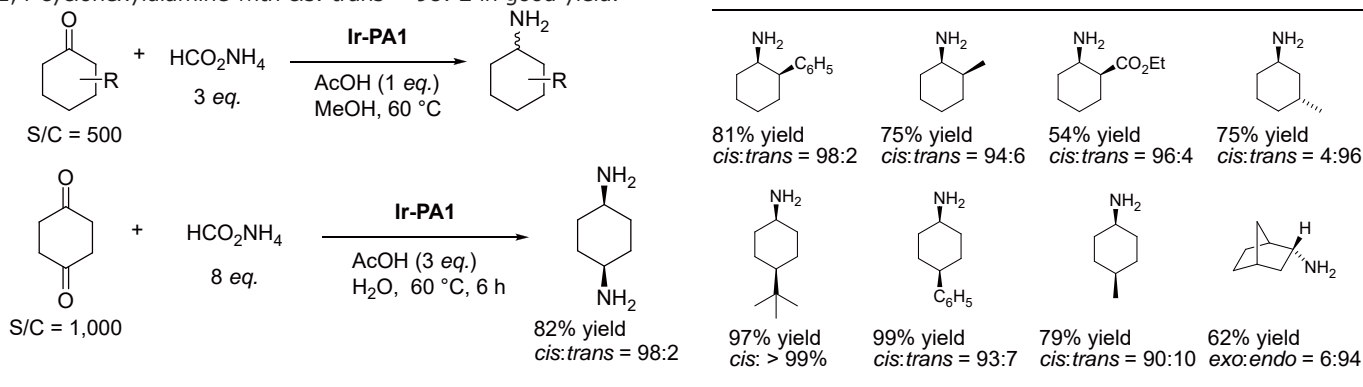
Amines derived from indanone, tetralone, and chromanone are important compounds contained in the basic skeleton of pharmaceuticals. The reaction of such aromatic cyclic ketones also proceeds smoothly in the presence of the Ir - PA1 catalyst and the corresponding primary amines are obtained.



yield (%)	80	73	94	90

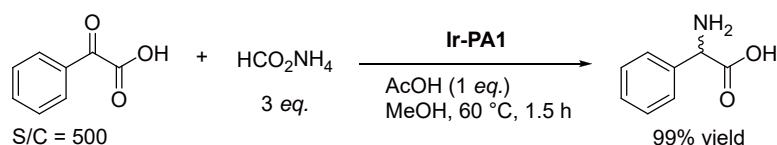
### High diastereoselective and reductive amination of cycloaliphatic ketones

In the case of cycloaliphatic ketones with substituents, the reaction proceeds higher diastereoselectively than known synthetic methods, giving the corresponding primary amines. In the reaction of 1,4-cyclohexanedione and ammonium formate, the reaction proceeds smoothly in the presence of Ir-PA1 catalyst by using water as a reaction solvent, giving 1,4-cyclohexyldiamine with *cis:trans* = 98:2 in good yield.



### Synthesis of $\alpha$ -amino acid from $\alpha$ -keto acid

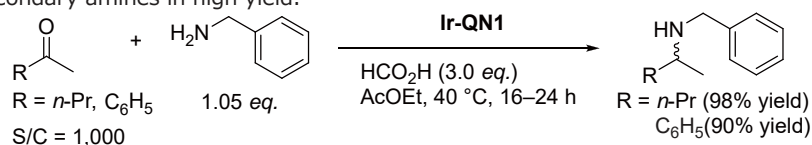
$\alpha$ -Amino acids are major compounds as pharmaceutical raw materials. In the reaction of  $\alpha$ -keto acid with ammonium formate in the presence of Ir-PA 1 catalyst, giving the corresponding  $\alpha$ -amino acid in high yield.



## Secondary and tertiary amine synthesis

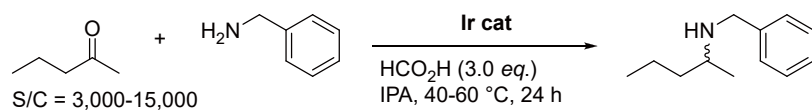
### Synthesis of secondary amines from ketones and primary amines

In the presence of Ir-QN1 catalyst, the reaction of ketones with primary amines proceeds smoothly, giving the corresponding secondary amines in high yield.



### Reduction of use of catalyst

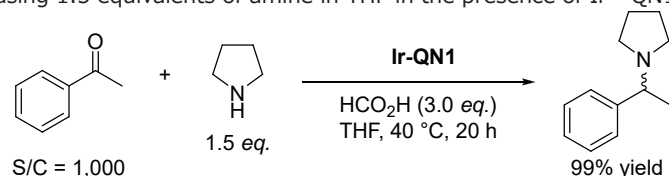
Comparing the catalytic performances of the Ir - QN1 catalyst and the Ir - QN2 catalyst in the reaction of 2 - pentanone with benzylamine, the Ir - QN2 catalyst shows high reactivity (Entries 1 and 2). Furthermore, by optimizing the equivalence of amine and the reaction temperature in the presence of the Ir - QN 2 catalyst, The reaction can be proceeded quantitatively even under the condition of S / C = 15,000 (entry 3). The reaction progresses quantitatively (entry 3).



entry	Ir cat	S/C	Benzyl amine (eq.)	temp. (°C)	yield (%)
1	Ir-QN1	3,000	1.05	40	63
2	Ir-QN2	3,000	1.05	40	97
3	Ir-QN2	15,000	1.2	60	99

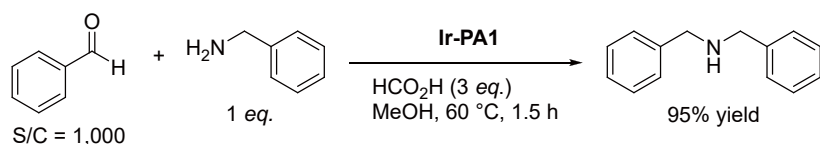
### Synthesis of tertiary amines from ketones and secondary amines

Synthesis of tertiary amines by reaction of ketones with secondary amines is a reaction that is likely to cause reductive reactions of ketones due to the difficulty of forming imines. To control side reactions, selection of reaction solvent and amount of amine used are important. In the reaction between acetophenone and pyrrolidine, the corresponding tertiary amine is given quantitatively by using 1.5 equivalents of amine in THF in the presence of Ir - QN1 catalyst.

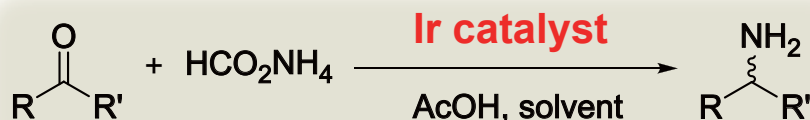


### Synthesis of secondary amines in high yield from aldehydes and primary amines

In the reaction of aldehydes with primary amines, the preparation of tertiary amines by overalkylation reaction can be suppressed by using the Ir-PA1 catalyst, and the corresponding secondary amines can be obtained in high yield.



**Standard procedure for primary amine synthesis**



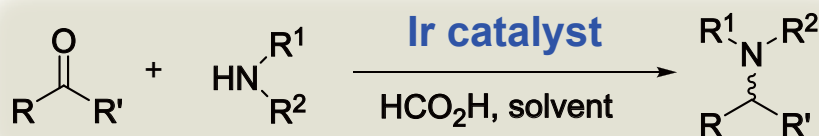
**Reaction**

Glass round-bottom flask (dry)  
 ↓  
 ← HCO<sub>2</sub>NH<sub>4</sub>  
 Degas and recharge with an inert gas (Ar or N<sub>2</sub>)  
 ↓  
 ← MeOH\*<sup>1</sup>, ketone substrate, acetic acid, Ir catalyst\*<sup>2</sup>  
 Stir until a reaction is finished\*<sup>3</sup>)  
 ↓  
 Cool to room temperature  
 ↓

**Purification**

↓  
 Remove MeOH under vacuum  
 ↓  
 ← aqueous KOH or aqueous NaOH\*<sup>4</sup>  
 Extract with CH<sub>2</sub>Cl<sub>2</sub>  
 ↓  
 Remove CH<sub>2</sub>Cl<sub>2</sub> under vacuum  
 ↓  
 The amine can be obtained through the prescribed refining method\*<sup>5</sup>

**Standard procedure for secondary and tertiary amine synthesis**



**Reaction**

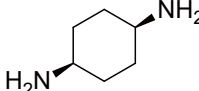
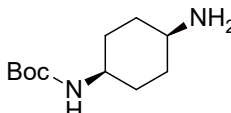
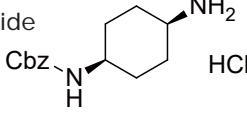
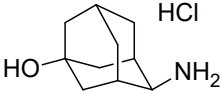
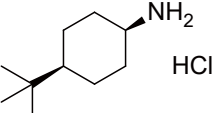
Glass round-bottom flask (dry)  
 ↓  
 Degas and recharge with an inert gas (Ar or N<sub>2</sub>)  
 ↓  
 ← solvent\*<sup>1</sup>, ketone substrate, amine  
 Cool below 10°C in ice bath  
 ↓  
 ← HCO<sub>2</sub>H  
 Warm to room temperature  
 ↓  
 ← Ir catalyst\*<sup>2</sup>  
 Stir until a reaction is finished\*<sup>3</sup>)  
 ↓  
 Cool to room temperature  
 ↓

**Purification**

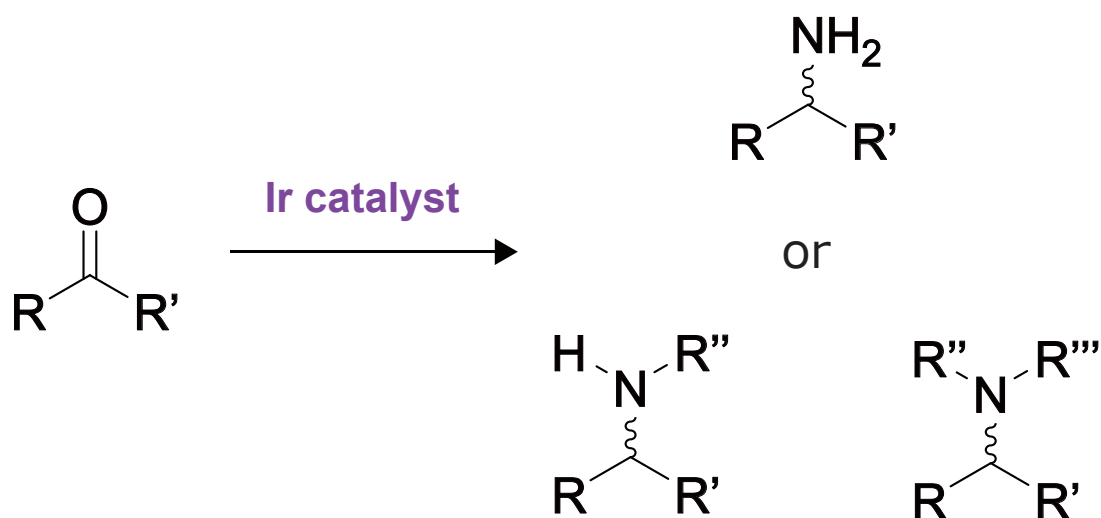
↓  
 Remove solvent under vacuum  
 ↓  
 ← aqueous KOH or aqueous NaOH\*<sup>4</sup>  
 Extract with CH<sub>2</sub>Cl<sub>2</sub>  
 ↓  
 Remove CH<sub>2</sub>Cl<sub>2</sub> under vacuum  
 ↓  
 The amine can be obtained through the prescribed refining method\*<sup>5</sup>

- \* 1 : Anhydrous and degassed solvent is not necessarily needed.
- \* 2 : Ir cat can be handled in an open air.
- \* 3 : Do not conduct the reaction in a closed system, since carbon dioxide will be released. For example, insert an inert gas line or attach an airtight balloon.
- \* 4 : For water soluble amines, the use of conc. KOH solution is more effective to extract amine compounds from aqueous layer.
- \* 5 : The residual catalyst can be removed by filtering the organic layer through a short column of silica gel.

 Related products

Product	Product No.	Package
<i>cis</i> -1,4-Cyclohexanediamine CAS : 15827-56-2	 07986-35	25 g
<i>N</i> -Boc- <i>cis</i> -1,4-Cyclohexyldiamine CAS : 247570-27-4	 05532-65	1 g
	05532-55	5 g
<i>N</i> -Cbz- <i>cis</i> -1,4-Cyclohexyldiamine hydrochloride CAS : -	 07426-65	1 g
	07426-55	5 g
<i>trans</i> -4-Aminoadamantan-1-ol hydrochloride CAS : 62075-23-4	 01639-45	10 g
<i>cis</i> -4- <i>tert</i> -Butylcyclohexylamine hydrochloride CAS : 61886-14-4	 04928-35	25 g

# contract synthesis / contract development



# List of products

Product	Product No.	Package
Chloro[ <i>N</i> -[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) abbreviation : Cp*IrCl(Dap-picolinamidato) ( <b>Ir-PA1</b> ) CAS : 1364328-83-5 FW : 603.18	07127-68	100 mg
	07127-95	500 mg
Chloro[4-(dimethylamino)- <i>N</i> -(dimethylamino)pheny-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) abbreviation : Cp*IrCl(Dap-Da-picolinamidato) ( <b>Ir-PA2</b> ) CAS : - FW : 646.25	07429-68	100 mg
	07429-95	500 mg
Chloro[4-(dimethylamino)-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) abbreviation : Cp*IrCl(Da-picolinamidato) ( <b>Ir-PA3</b> ) CAS : - FW : 527.09	07430-68	100 mg
	07430-95	500 mg
Chloro(pentamethylcyclopentadienyl)(4-dimethylamino-8-quinolinolato)iridium(III) abbreviation : Cp*IrCl(CF <sub>3</sub> -picolinamidato) ( <b>Ir-PA4</b> ) CAS : - FW : 628.11	07964-68	100 mg
	07964-95	500 mg
Chloro[ <i>N</i> -(4-nitrophenyl)-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) abbreviation : Cp*IrCl(NO <sub>2</sub> -picolinamidato) ( <b>Ir-PA5</b> ) CAS : 1887154-21-3 FW : 605.11	07965-68	100 mg
	07965-95	500 mg
Chloro(pentamethylcyclopentadienyl)(8-quinolinolato)iridium(III) abbreviation : Cp*IrCl(quinolinolato)( <b>Ir-QN1</b> ) CAS : 1217487-22-3 FW : 507.05	07128-68	100 mg
	07128-95	500 mg
Chloro(pentamethylcyclopentadienyl)(4-dimethylamino-8-quinolinolato)iridium(III) abbreviation : Cp*IrCl(Da-8-quinolinolato) ( <b>Ir-QN2</b> ) CAS : - FW : 550.12	07966-68	100 mg
	07966-95	500 mg



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