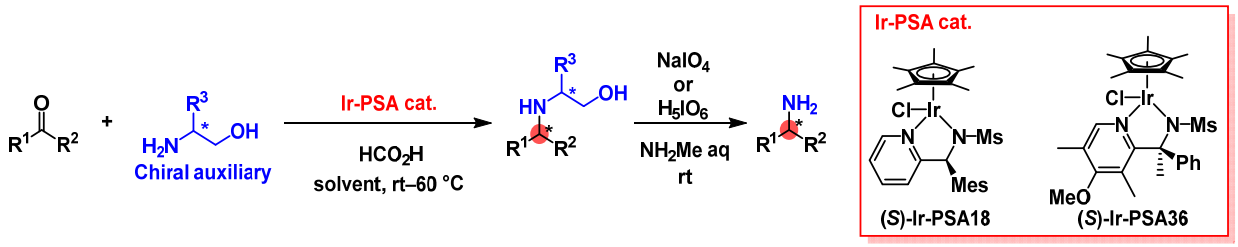
Iridium Catalyst for Chiral Amine Synthesis

～ Efficient synthesis of chiral amines by reductive amination ～

ver.2

Asymmetric synthesis of optically active amine compounds

eg. Synthesis of optically active amine compounds combination with chiral auxiliary



J. Org. Chem. 2022, 87, 8458-463.

Chiral amines are useful compounds used in a wide range of applications such as synthetic intermediates for pharmaceuticals, agrochemicals, and functionalized materials.

We have newly developed asymmetric iridium catalysts for reductive amination of ketones under mild conditions. With the aid of chiral amino alcohols as chiral auxiliary, these catalysts realize practical preparation of various optically active amines which can not be synthesized efficiently by conventional method. Please use them for your product development and research.

High reactivity

High catalytic activity	Reductive amination proceeds at a substrate-to-catalyst molar ratio(S/C) of >5,000.

High stereoselectivity

Asymmetric catalyst＋ Chiral auxiliaries	Combination with easily-available amino alcohols as chiral auxiliaries leads high stereoselectivity.

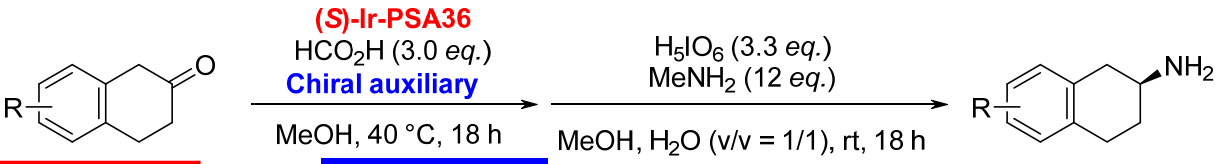
Simple operation

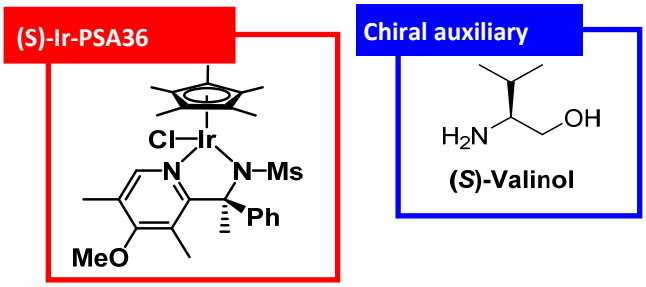
No need of special equipment	No need of H_2 and pressure vessel on both reductive amination and auxiliary cleavage.
Short reaction process	No need of isolation of imine. Enable one-pot synthesis till auxiliary cleavage.
Mild reaction condition	From room temperature to 60 ℃

Kanto Chemical Co., Inc.

Example

Synthesis of optically active 2-aminotetralins

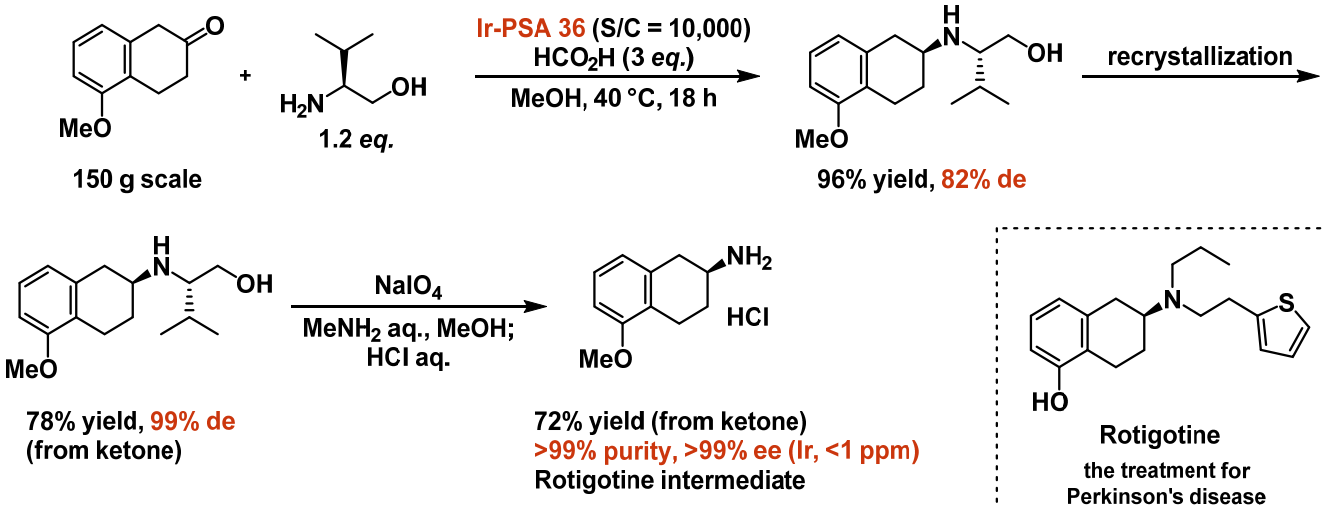




R	S/C	Isolated yield(%)	ee (%)
H	5,000	80	82
6-F	5,000	77	82
6-Cl	1,000	86	84
6-Br	1,000	86	84
6-CN	1,000	93	81
6-OMe	5,000	94	86
7-OMe	5,000	91	84
8-OMe	5,000	87	87

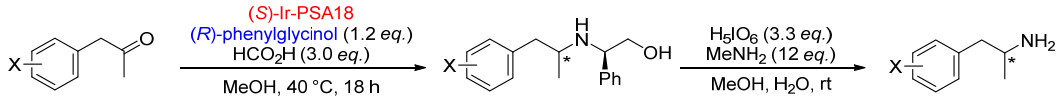
Chiral 2-aminotetralins with high optical purity can be efficiently obtained from β-tetralones substituted with electron-withdrawing (cyano, halogen) or electron-donating (methoxy) groups. The effect of substitution position was almost not observed.

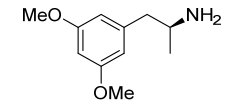
Scale up synthesis for application of pharmaceutical intermediate.

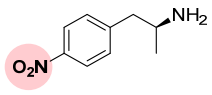


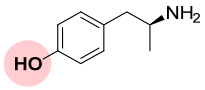
In the scale-up synthesis of (*S*)-2-amino-5-methoxytetralin, the important intermediate of Rotigotine, the reductive amination of 5-methoxy-2-tetralone was completed even at S/C = 10,000. Since the selectivity of this reaction was high enough, the optical purity was easily increased to 99% de by recrystallization. Following cleavage of the auxiliary group afforded 99% ee of 2-amino-5-methoxytetralin hydrochloride in 72% total yield. In addition, the metal component could be almost completely removed by the recrystallization and the residual Ir in the product was less than 1 ppm.

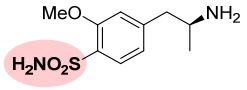
Synthesis of optically active acyclic β-arylamines

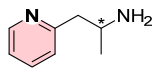


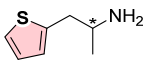

S/C = 5,000
Isolated yield 93%
94% ee

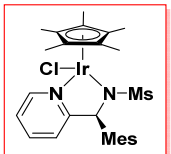

S/C = 5,000
Isolated yield 93%
97% ee

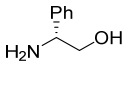

S/C = 5,000
Isolated yield 68%
97% ee


S/C = 5,000
Isolated yield 95%
95% ee


S/C = 5,000
Isolated yield 81%
90% ee


S/C = 3,000
Isolated yield 85%
91% ee


(S)-Ir-PSA18

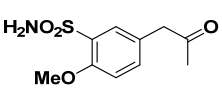
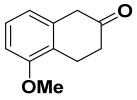
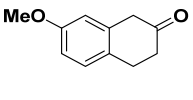
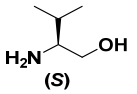
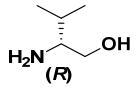
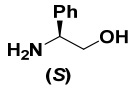
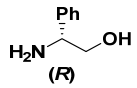

(R)-Phenylglycinol

Various chiral acyclic β-arylamines are also efficiently obtained in the reaction. In the case of ketones having α-arylacetone scaffolds, the combination of Ir-PSA18 and phenylglycinol performs well. The reaction proceeds efficiently even in the presence of nitro groups, phenolic hydroxyl groups or sulfonamides. In addition, this method can be applied to substrates with heterocycle such as pyridine or thiophene.

Combination of catalyst and chiral auxiliary group

The combination of the catalyst and the chiral auxiliary group is very important in our catalyst system. Please consider the appropriate combination according to the substrate structure.

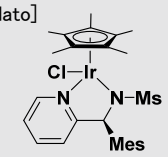
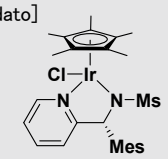
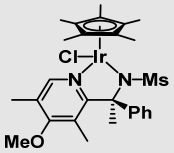
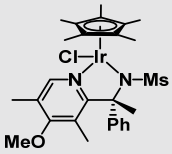
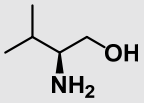
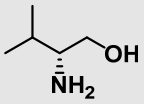
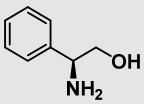
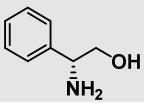
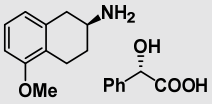
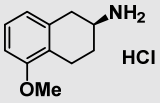
If the product is an enantiomer of the desired compound, it can be synthesized by setting both of the catalyst and chiral auxiliary group the opposite senses.

Substrate, Catalyst / Chiral Auxiliary				
	(S)-Ir-PSA18	(S)-Ir-PSA36	(S)-Ir-PSA18	(S)-Ir-PSA36
 (S)	57% 50% ee (R) mismatch	69% 97% ee (R) match	90% 65% ee (S) match	96% 83% ee (S) match
 (R)	72% 92% ee (S) match	15% 52% ee (S) mismatch	90% 39% ee (R) mismatch	81% 11% ee (R) mismatch
 (S)	94% 52% ee (R) mismatch	94% 95% ee (R) match	97% 65% ee (S) match	99% 61% ee (S) match
 (R)	95% 95% ee (S) match	84% 46% ee (S) mismatch	99% 32% ee (R) mismatch	87% 9% ee (R) mismatch

Contract synthesis / Contract development

We can find a suitable catalyst for your preferred substrate. We will also search for appropriate chiral auxiliary groups and reaction conditions. We are also available for custom synthesis, so please contact us.

Product List

Product	Product No.	Package
Chloro[(*S*)-*N*-[pyridin-2-yl(2,4,6-trimethylphenyl)methyl]methanesulfonamidato](pentamethylcyclopentadienyl)iridium(III) Abbreviation: (*S*)-Ir-PSA18 CAS RN® : – 	07060-68	100 mg
Chloro[(*R*)-*N*-[pyridin-2-yl(2,4,6-trimethylphenyl)methyl]methanesulfonamidato](pentamethylcyclopentadienyl)iridium(III) Abbreviation: (*R*)-Ir-PSA18 CAS RN® : – 	07071-68	100 mg
Chloro[(*S*)-*N*-(1-(4-methoxy-3,5-dimethylpyridin-2-yl)-1-phenylethyl)methanesulfonamidato](pentamethylcyclopentadienyl)iridium(III) Abbreviation: (*S*)-Ir-PSA36 CAS RN® : – 	07658-68	100 mg
Chloro[(*R*)-*N*-(1-(4-methoxy-3,5-dimethylpyridin-2-yl)-1-phenylethyl)methanesulfonamidato](pentamethylcyclopentadienyl)iridium(III) Abbreviation: (*R*)-Ir-PSA36 CAS RN® : – 	07035-68	100 mg
L-Valinol [(*S*)-(-)-2-Amino-3-methyl-1-butanol] CAS RN® : 2026-48-4 	44078-52 44078-32	5 g 25 g
D-Valinol [(*R*)-(-)-2-Amino-3-methyl-1-butanol] CAS RN® : 4276-09-9 	42247-2A 42247-3A	5 g 25 g
(*S*)-(+)-2-Phenylglycinol CAS RN® : 20989-17-7 	30757-1A 30757-2A	1 g 25 g
(*R*)-(-)-2-Phenylglycinol [D(-)-α-Phenylglycinol] CAS RN® : 56613-80-0 	18382-1A 18382-2A	5 g 25 g
(*S*)-2-Amino-5-methoxytetralin (*S*)-mandelate CAS RN® : 439133-67-2 	01769-55	5 g
(*S*)-2-Amino-5-methoxytetralin hydrochloride CAS RN® : 58349-17-0 	01770-55	5 g

- Please use the products listed in the catalog as reagents (chemicals used for testing or research purpose).
- Product information is subject to change without notice. For the latest information, please have a look at our website "Cica-Web".

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