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Iridium-Catalyzed Asymmetric Hydrogenation of α-Substituted α,β-Unsaturated Acyclic Ketones: Enantioselective Total Synthesis of (−)-Mesembrine

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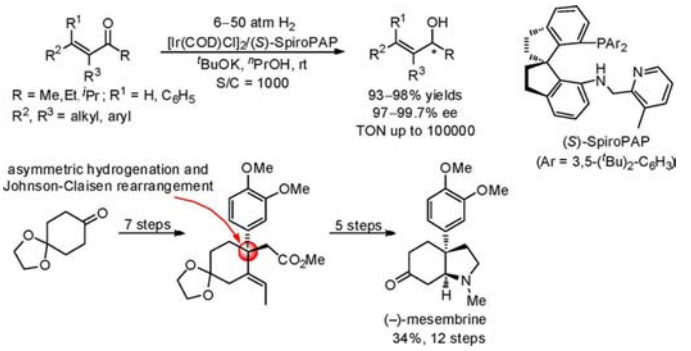
ABSTRACT



A highly efficient asymmetric hydrogenation of α-substituted α,β-unsaturated acyclic ketones catalyzed by chiral spiro iridium complexes for the preparation of chiral 2-substituted allylic alcohols has been developed (ee up to 99.7%). This method provides a concise route to (−)-mesembrine (34% yield, 12 steps).

Chiral allylic alcohols are popular subunits of a variety of chiral natural products and pharmaceuticals. The asymmetric catalysis provides a highly efficient and environmentally benign method for the synthesis of chiral allylic alcohols.[1] Among the catalytic asymmetric preparations of chiral allylic alcohols, the selective reduction of the carbonyl group of α,β-unsaturated ketones by catalytic asymmetric hydrogenations is one of the most direct methods.[2] With chiral ruthenium diphosphine/diamine catalysts, pioneered by Noyori et al.,[3] a series of α,β-unsaturated acyclic and cyclic ketones has been hydrogenated to the corresponding chiral allylic alcohols with high yields and high enantioselectivities.[4] Our recent investigations showed that the chiral iridium complexes of spiro aminophosphine ligands SpiroAP were efficient catalysts for the

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hydrogenation of α-arylmethylene cycloalkanones, a type of *exo*-cyclic α,β-unsaturated ketone, providing chiral cyclic allylic alcohols in up to 97% ee and TONs of as high as 10000.[5] However, the asymmetric catalytic hydrogenation of α,β-unsaturated acyclic ketones is still a challenging task if the substrates have an α-substituent.[6] On the other hand, the products of asymmetric hydrogenation of α-substituted α,β-unsaturated acyclic ketones, the chiral 2-substituted acyclic allylic alcohols are core structures in a number of natural products such as jerangolids A and D,[7] tedanolide,[8] and epothilones A and B[9] (Figure 1).

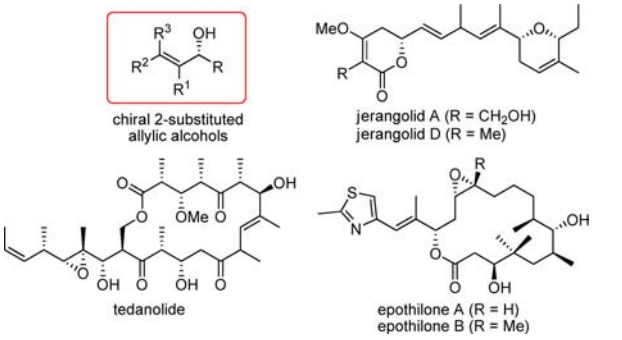
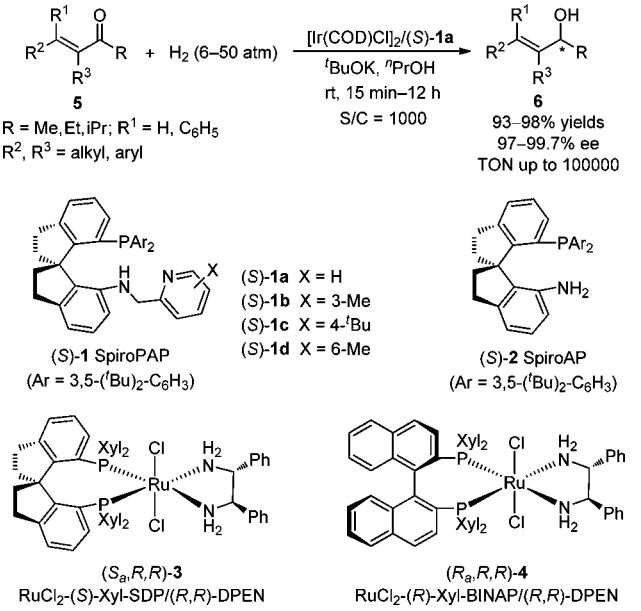


Figure 1. Examples of natural products containing a chiral 2-substituted allylic alcohol structure.

Encouraged by our recent successes in the asymmetric hydrogenation of ketones catalyzed by chiral iridium catalysts of spiro pyridine−aminophosphine ligands (**1**, SpiroPAP)[10] and the asymmetric hydrogenation of α-arylmethylene cycloalkanones catalyzed by iridium catalysts of spiro aminophosphine ligands (**2**, SpiroAP),[5] we attempted the asymmetric hydrogenation of α-substituted α,β-unsaturated acyclic ketones **5** toward the enantioselective preparation of chiral 2-substituted acyclic allylic alcohols. The catalyst iridium−SpiroPAP (Ir−(*S*)-**1a**) offered the corresponding chiral 2-substituted acyclic allylic alcohols **6** in excellent enantioselectivities (up to 99.7% ee) and TONs of as high as 100000 (Scheme 1). We herein report the details of the asymmetric hydrogenation of α-substituted α,β-unsaturated acyclic ketones **5** with catalysts Ir−(*S*)-**1** and its application in the asymmetric total synthesis of (−)-mesembrine, a natural alkaloid containing a chiral arylated quaternary carbon center.[11]

Scheme 1. Asymmetric Hydrogenation of α-Substituted α,β-Unsaturated Acyclic Ketones **5**



Initially, (*E*)-3,4-diphenylbut-3-en-2-one (**5a**) was selected as a standard substrate, and the hydrogenation was performed in ^{n}PrOH under 6 atm of H_2 at room temperature in the presence of KO^{t}Bu as a base. When the catalyst Ir−(*S*)-**1a** was used, the product (*R*)-**6a** was obtained in 98% yield and 99.4% ee within 15 min (Table 1, entry 1). The catalyst Ir−(*S*)-**2** also gave high enantioselectivity (95% ee), albeit requiring a longer reaction time (entry 2). The chiral ruthenium−diphosphine/diamine catalysts such as (S_a,*R*,*R*)-**3** and (R_a,*R*,*R*)-**4**, which have been demonstrated to be highly efficient for the hydrogenation of α,β-unsaturated acyclic ketones without α-substituent,[2a] were also evaluated, and only moderate enantioselectivities (69 and 60% ee, respectively) were obtained after a very long reaction time (ca. 15 h) under 50 atm of H_2, although the yields are also high (entries 3 and 4). The solvent experiments showed MeOH and EtOH were suitable solvents (entries 6 and 7 vs 1), but ^{i}PrOH and toluene were inferior, giving low conversions (entries 5 and 8). Base also plays an important role in the reaction, with KO^{t}Bu being

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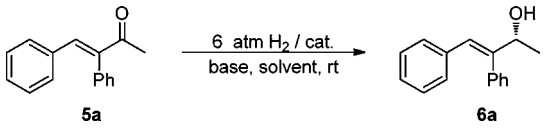
the choice of base. KOH also offered the desired product (*R*)-**6a** in 98% yield with 97% ee, although the reaction became slow (15 h, entry 9). When K_2CO_3 was used, the conversion of the reaction dropped to 50% (entry 10). The organic base NEt_3 was inert for this reaction (entry 11). Subsequently, we screened the chiral SpiroPAP ligands ((*S*)-**1**) and found that the substituent on the pyridine group of the catalyst has almost no effect on the reactions (entries 1 and 12−14). In addition, when the catalyst loading was lowered to 0.001 mol % (S/C = 100000) the reaction still performed very well under 50 atm of H_2 in excellent enantioselectivity (99.7% ee) with 100% conversion (entry 15).

Table 1. Optimization of the Hydrogenation Conditions[a]



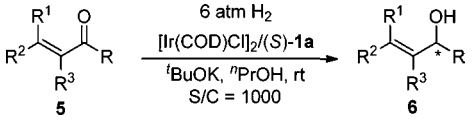
5a **6a**

entry	cat.	base	solvent	time	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	Ir-(*S*)-**1a**	^{t}BuOK	^{n}PrOH	15 min	100	98	99.4 (*R*)
2	Ir-(*S*)-**2**	^{t}BuOK	^{n}PrOH	3 h	100	95	95 (*R*)
3[e]	(S_a,*R*,*R*)-**3**	^{t}BuOK	^{i}PrOH	15 h	100	98	69 (*S*)
4[e]	(R_a,*R*,*R*)-**4**	^{t}BuOK	^{i}PrOH	15 h	100	97	60 (*S*)
5	Ir-(*S*)-**1a**	^{t}BuOK	^{i}PrOH	15 h	44	42	97 (*R*)
6	Ir-(*S*)-**1a**	^{t}BuOK	MeOH	20 min	100	98	99 (*R*)
7	Ir-(*S*)-**1a**	^{t}BuOK	EtOH	20 min	100	98	99.2 (*R*)
8	Ir-(*S*)-**1a**	^{t}BuOK	Toluene	15 h	30	25	96 (*R*)
9	Ir-(*S*)-**1a**	KOH	^{n}PrOH	15 h	100	98	97 (*R*)
10	Ir-(*S*)-**1a**	K_2CO_3	^{n}PrOH	15 h	50	48	99.2 (*R*)
11	Ir-(*S*)-**1a**	NEt_3	^{n}PrOH	15 h	3	2	12 (*R*)
12	Ir-(*S*)-**1b**	^{t}BuOK	^{n}PrOH	15 min	100	98	99.4 (*R*)
13	Ir-(*S*)-**1c**	^{t}BuOK	^{n}PrOH	15 min	100	97	99.5 (*R*)
14	Ir-(*S*)-**1d**	^{t}BuOK	^{n}PrOH	15 min	100	97	99.1 (*R*)
15[f]	Ir-(*S*)-**1a**	^{t}BuOK	EtOH	10 h	100	98	99.7 (*R*)

[a] Reaction conditions: 1.5 mmol scale, [substrate] = 2.1 M, 0.15 mmol % of catalyst, [KO^{t}Bu] = 0.04 M, solvent (2.0 mL), 6 atm of H_2, rt (25−30 °C). [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] Determined by HPLC. [e] 50 atm of H_2, 4 mL of ^{i}PrOH, [KO^{t}Bu] = 0.05 M. [f] 50 atm of H_2, S/C = 100000.

Under the optimized reaction conditions, a series of α-substituted α,β-unsaturated ketones **5** were hydrogenated to chiral allylic alcohols **6** in high yields (90−99%) and excellent enantioselectivities (97−99.7% ee) with catalyst Ir−(*S*)-**1a** at S/C = 1000 (Table 2). Either the electron-withdrawing group or the electron-donating group on the phenyl ring of the substrates (**5a**−**m**) has little effect on the reactivity and enantioselectivity of the reaction; the reactions were completed within 15 min and yielded the corresponding products (**6a**−**m**) in excellent yields and enantioselectivities (97−99.7% ee, entries 1−13). When the α-substituent R^3 in the substrates **5** was changed from phenyl to alkyl groups such as methyl and ethyl the hydrogenation reactions also showed excellent enantioselectivities (99% ee, entries 14−16). The cycloalkenyl ketone **5q** could be hydrogenated to allylic alcohol **6q** in 99% ee by catalyst Ir−(*S*)-**1a**, although a longer reaction time was required (12 h, entry 17). It is worthy of mention that the spiro iridium catalyst Ir−(*S*)-**1a** was also efficient for the hydrogenation of tetrasubstituted α,β-unsaturated acyclic ketones such as **5r** and **5s**, giving the corresponding chiral tetrasubstituted allylic alcohols **6r** and **6s** in excellent yields with 98 and 97% ee, respectively (entries 18 and 19).

Table 2. Asymmetric Hydrogenation of α-Substituted α,β-Unsaturated Acyclic Ketones **5** with Ir-(*S*)-**1a**[a]



5 **6**

entry	R	R^1	R^2	R^3	**6**	time (min)	yield[b] (%)	ee[c] (%)
1	Me	H	C_6H_5	C_6H_5	**6a**	15	98	99.4 (*R*)
2	Me	H	2-ClC_6H_4	C_6H_5	**6b**	15	98	99.5
3	Me	H	3-MeC_6H_4	C_6H_5	**6c**	15	98	99.6
4	Me	H	4-MeC_6H_4	C_6H_5	**6d**	15	97	98
5	Me	H	4-MeOC_6H_4	C_6H_5	**6e**	15	99	99
6	Me	H	4-ClC_6H_4	C_6H_5	**6f**	15	98	99
7	Me	H	C_6H_5	2-ClC_6H_4	**6g**	15	97	99.6
8	Me	H	C_6H_5	3-MeC_6H_4	**6h**	15	98	97
9	Me	H	C_6H_5	4-MeC_6H_4	**6i**	15	99	99.1
10	Me	H	C_6H_5	4-MeOC_6H_4	**6j**	15	98	99.4
11	Me	H	C_6H_5	4-ClC_6H_4	**6k**	15	98	97
12	Et	H	C_6H_5	C_6H_5	**6l**	15	98	99.7
13	^{i}Pr	H	C_6H_5	C_6H_5	**6m**	15	98	98
14	Me	H	C_6H_5	Me	**6n**	15	99	99.1(*R*)
15	Me	H	C_6H_5	Et	**6o**	15	99	99 (*R*)
16[d]	Me	H	Me	Me	**6p**	30	90	99
17	Me	H	$-(CH_2)_4-$		**6q**	12 h	98	99 (*R*)
18	Me	Me	C_6H_5	Me	**6r**	15	97	98
19[d]	Me	C_6H_5	$-(CH_2)_4-$		**6s**	60	96	97

[a] Reaction conditions: 1.5 mmol scale, [substrate] = 2.1 M, 0.15 mmol % of catalyst, [KO^{t}Bu] = 0.04 M, solvent (2.0 mL), 6 atm of H_2, rt (25−30 °C). [b] Isolated yield. [c] Determined by HPLC or SFC with chiral column. [d] Using ligand (*R*)-**1b**.

To demonstrate the utility of this highly efficient asymmetric hydrogenation, a *Sceletium* alkaloid (−)-mesembrine[11] bearing a quaternary carbon center was synthesized. (−)-Mesembrine has been found to have potent serotonin reuptake inhibitor activity[12] and has received extensive synthetic studies over the past decades.[13] The challenge of synthesis of (−)-mesembrine is the construction of the unique congested chiral arylated quaternary carbon center. Among the total syntheses of (−)-mesembrine or its enantiomer, a few successful examples used asymmetric catalysis.[13g−l] Our synthetic strategy is outlined in Scheme 2, employing iridium-catalyzed asymmetric hydrogenation and Johnson−Claisen rearrangement to install the chiral arylated quaternary carbon center.

Starting with commercially available 1,4-dioxaspiro-[4.5]decan-8-one (**7**), the unsaturated ester **8** was prepared

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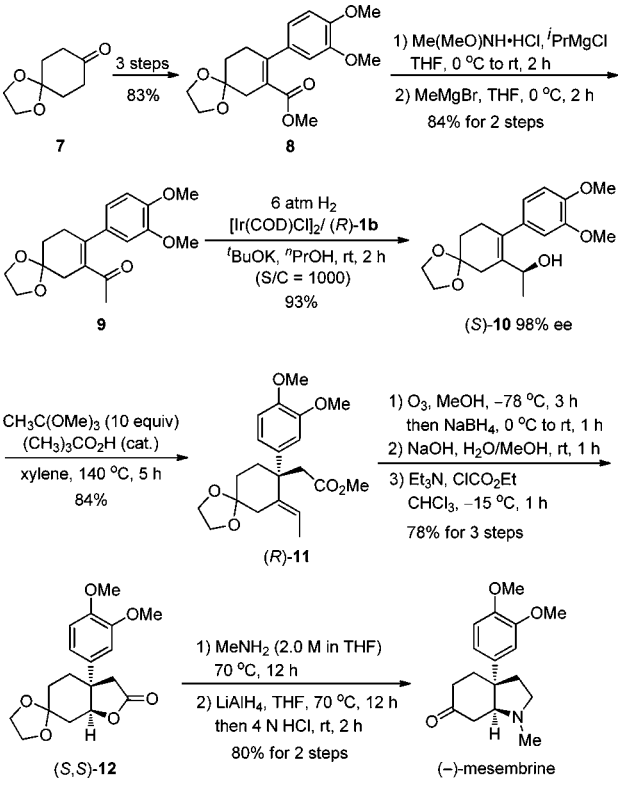
in 83% yield via three steps according to literature method.[14] The ester **8** was converted to α,β-unsaturated methyl ketone **9** in 84% yield (two steps) via a Weinreb amide and subsequent treatment with methylmagnesium bromide.[15] With catalyst Ir−(*R*)-**1b**, the methyl ketone **9** was hydrogenated to chiral tetrasubstituted allylic alcohol (*S*)-**10** in 93% yield with 98% ee under 6 atm of H_2. Subsequently, chiral allylic alcohol (*S*)-**10** was subjected to a Johnson−Claisen rearrangement[16] to generate (*R*)-**11** with a chiral arylated quaternary carbon center in 84% yield. The treatment of compound (*R*)-**11** with an ozonylsis/reduction procedure to cleave the carbon−carbon double bond, base-promoted ester hydrolysis and lactonization with ethyl chloroformate and subsequent triethylamine-assisted addition−elimination yielded lactone (*S*,*S*)-**12** in 78% yield (three steps).[17] Amination of (*S*,*S*)-**12** with methylamine at 70 °C in THF for 12 h and subsequent reduction with $LiAlH_4$ at the same temperature for another 12 h and deprotection of the carbonyl group with aqueous HCl at room temperature for 2 h offered (−)-mesembrine in 80% yield (two steps). The NMR spectroscopic data and the optical rotation ($[\alpha]^{20}_D$ −61.6 (*c* 0.25, MeOH); lit.[13e] $[\alpha]^{20}_D$ −61.6 (*c* 0.20, MeOH); lit.[13l] $[\alpha]^{20}_D$ −61.0 (*c* 0.20, MeOH)) of our synthetic (−)-mesembrine are identical to those reported in a previous synthesis.

In conclusion, a highly efficient asymmetric hydrogenation of α-substituted α,β-unsaturated acyclic ketones catalyzed by chiral iridium complexes of spiro pyridine−aminophosphine ligands has been developed for the preparation of chiral 2-substituted allylic alcohols in excellent enantioselectivities. A highly efficient catalytic enantioselective total synthesis of the *Sceletium* alkaloid (−)-mesembrine was achieved in 34% overall yield over 12 steps from commercially available material by using this asymmetric hydrogenation as a key step.

Scheme 2. Catalytic Enantioselective Synthesis of (−)-Mesembrine



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Supporting Information Available. Experimental procedures, characterization data, and HPLC and SFC spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(17) After the ozonylsis−reduction, the formed hydroxy ester product was very reluctant to cyclize to lactone (*S*,*S*)-**12** via an intramolecular transesterification, and the subsequent ester hydrolysis and activation of the carboxylic acid for the formation of the lactone were required.