ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

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

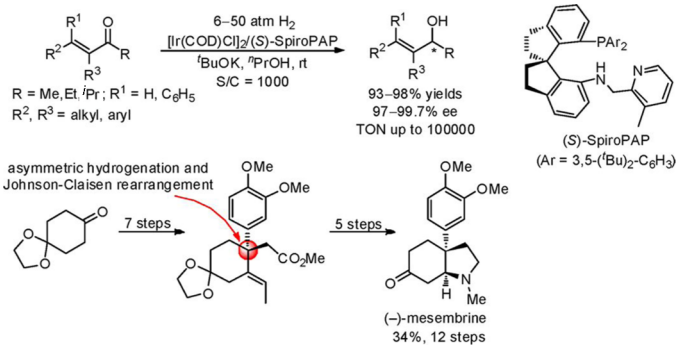
Qian-Qian Zhang, Jian-Hua Xie,* Xiao-Hui Yang, Jian-Bo Xie, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

jhxie@nankai.edu.cn; qlzhou@nankai.edu.cn

Received October 16, 2012

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

(1) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 6A. (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 621. (c) Tsuji, J. *Palladium Reagents and Catalysis*; VCH: Chichester, 1997; Chapter 4.

(2) (a) Ohkuma, T.; Noyori, R. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; p 1106. (b) Noyori, R.; Okuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (c) Xie, J.-H.; Zhou, Q.-L. *Acta Chim. Sinica* **2012**, *70*, 1427.

(3) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675.

(4) For selected recent papers, see: (a) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508. (b) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (c) Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. *Chem.—Eur. J.* **2003**, *9*, 2963. (d) Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681. (e) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muñz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288. (f) Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1770. (g) Arai, N.; Azuma, K.; Nii, N.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7475. (h) Li, W.; Sun, X.; Zhou, L.; Hou, G.; Yu, S.; Zhang, X. *J. Org. Chem.* **2009**, *74*, 1397.

10.1021/ol302842h

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).

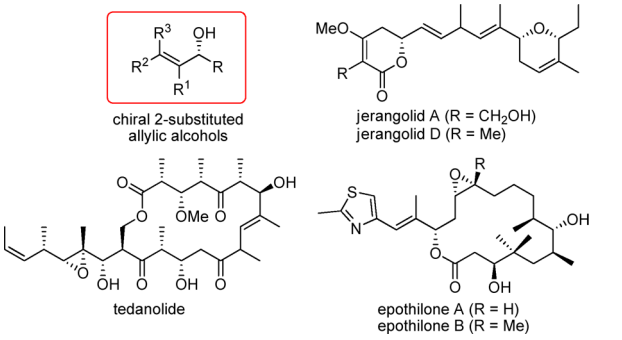
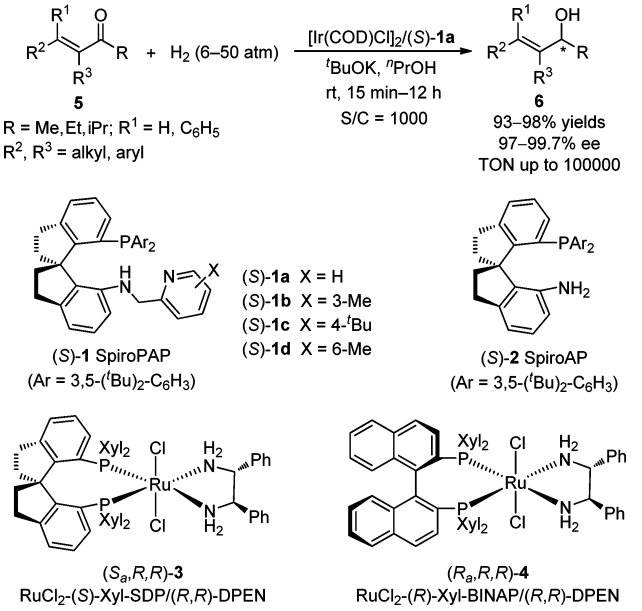


Figure 1. Examples of natural products containing a chiral 2-substituted allylic alcohol structure.

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

(5) Xie, J.-B; Xie, J.-H; Liu, X.-Y; Kong, W.-L; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4538.

(6) For selected papers of asymmetric reduction of α-substituted α,β-unsaturated acyclic ketones, see: (a) Nolin, K. A.; Ahn, R. W.; Kobayashi, Y.; Kennedy-Smith, J. J.; Toste, F. D. *Chem.—Eur. J.* **2010**, *16*, 9555. (b) Moser, R.; Boškovic, Z. V.; Crowe, C. S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 7852. (c) Yokoyama, R.; Matsumoto, S.; Nomura, S.; Higaki, T.; Yokoyama, T.; Kiyooka, S.-i. *Tetrahedron* **2009**, *65*, 5181. For selected papers of asymmetric hydrogenation of α-substituted α,β-unsaturated cyclic ketones, see: (d) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529. (e) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173. (f) Junge, K.; Wendt, B.; Addis, D.; Zhou, S.-L.; Das, S.; Fleischer, S.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 101.

(7) Gerth, K.; Washausen, P.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71.

(8) Schmitz, F. J. S.; Gunasekera, P.; Yalamanchili, G.; Hossain, M. B.; Vanderhelm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

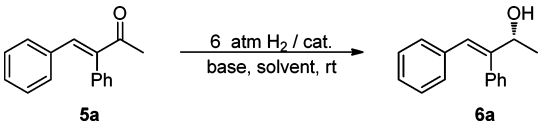
(9) (a) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560. (b) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567.

(10) (a) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329. (b) Xie, J.-H.; Liu, X.-Y.; Yang, X.-H.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 201.

(11) (a) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind.* **1961**, 402.

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]

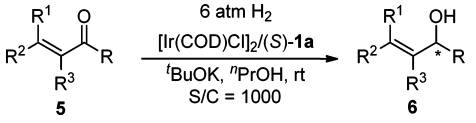


entry	cat.	base	solvent	time	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	Ir-(*S*)-**1a**	^{t}BuOK	^{n}PrOH	15 min	100	98	99.4 (*R*)
2	Ir-(*S*)-**2**	^{t}BuOK	^{n}PrOH	3 h	100	95	95 (*R*)
3[e]	(S_a,*R*,*R*)-**3**	^{t}BuOK	^{i}PrOH	15 h	100	98	69 (*S*)
4[e]	(R_a,*R*,*R*)-**4**	^{t}BuOK	^{i}PrOH	15 h	100	97	60 (*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]



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.

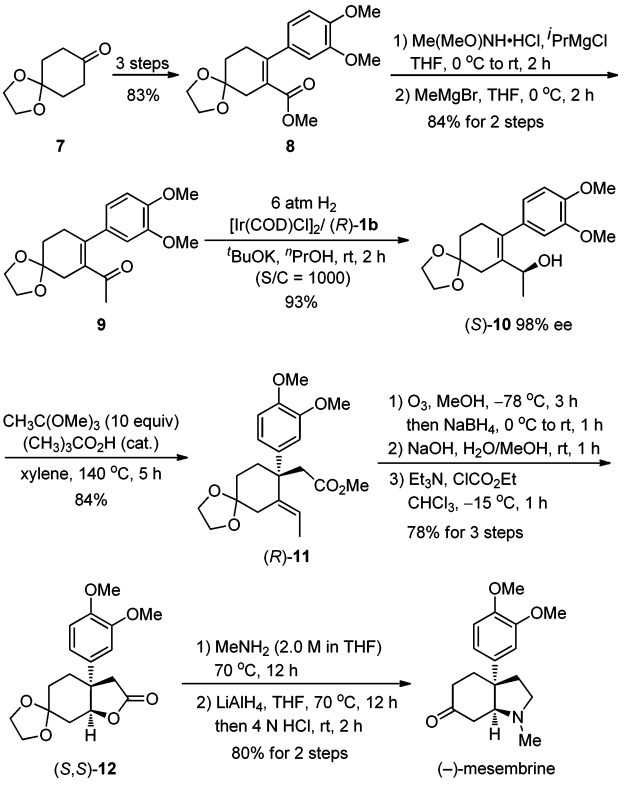
Starting with commercially available 1,4-dioxaspiro-[4.5]decan-8-one (**7**), the unsaturated ester **8** was prepared

(12) Gericke, N. P.; Van Wyk, B.-E. PCT Int. Appl. WO 9746234.

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



Acknowledgment. We thank the National Natural Science Foundation of China, the National Basic Research Program of China (973 Program) (2012CB821600), and the "111" project (B06005) of the Ministry of Education of China for financial support.

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.

(13) For a review, see: (a) Zhao, Y.-H.; Zhou, Y.-Y; Du, F.-X.; Liang, L.-L; Zhang, H.-B. *Chin. J. Org. Chem.* **2010**, *30*, 47. For selected papers of enantioselective synthesis of (−)-mesembrine or its enantiomer, see: (b) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. (c) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007. (d) Saito, M.; Matsuo, J.-i.; Ishibashi, H. *Tetrahedron* **2007**, *63*, 4865. (e) Ilardi, E. A.; Isaacman, M. J.; Qin, Y.-C.; Shelly, S. A.; Zakarian, A. *Tetrahedron* **2009**, *65*, 3261. (f) Tuan, L. A.; Kim, G. *Tetrahedron Lett.* **2010**, *51*, 2354. (g) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785. (h) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135. (i) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (j) Yamada, O.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 7747. (k) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711. (l) Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519.

(14) Su, J.; Tang, H.-Q.; Mckittrick, B. A. *Tetrahedron Lett.* **2011**, *52*, 3382.

(15) Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.-i.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chem.—Eur. J.* **2006**, *12*, 63.

(16) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) For a review, see: Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(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.