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Asymmetric formal synthesis of (−)-pancracine via catalytic enantioselective C–H amination process

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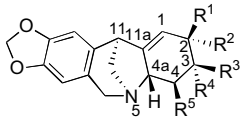
ABSTRACT

The reaction of silyl enol ethers derived from cyclohexanone with [(4-nitrophenylsulfonyl)-imino]phenyliodinane (*p*NsN=IPh) catalyzed by dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TCPTTL)$_4$, provides, after desilylation, *N*-*p*Ns-protected (*S*)-β-aminocyclohexanone in up to 72% ee. This represents the first example of the insertion of nitrene species into an allylic C–H bond of silyl enol ethers. Using this process, a new catalytic asymmetric route to an advanced intermediate in Overman's synthesis of the montanine-type Amaryllidaceae alkaloid (−)-pancracine has been developed. The key steps involve (a) a one-pot Rh_2(*R*-TCPTTL)$_4$-catalyzed sequential 1,4-hydrosilylation/enantioselective C–H amination of 2-cyclohexen-1-one, (b) N-alkylation and subsequent intramolecular Mukaiyama aldol reaction/dehydration, and (c) a regio- and stereocontrolled reductive deoxygenation of bicyclic enone **27** with migration of the double bond to create the C1/C11a double bond and the stereogenic center at C11 of 3-arylhexahydroindole **31**.

1. Introduction

The montanine class of Amaryllidaceae alkaloids,[1] including (−)-montanine (**1**),[2] (−)-coccinine (**2**),[2] (−)-pancracine (**3**),[3] (−)-brunsvigine (**4**),[4] (−)-manthine (**5**),[2] (−)-nangustine (**6**),[5] and (+)-montabuphine (**7**),[6] shares a 5,11-methanomorphanthridine core with a C1/C11a double bond and differ only in the nature and stereochemistry of the oxygen-based substituents at C2 and C3, except for (−)-nangustine (**6**). These alkaloids have been shown to display anxiolytic, antidepressive, anticonvulsive and weak hypotensive activities.[7]



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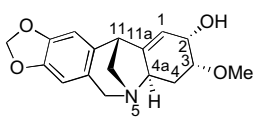

(+)-montabuphine (**7**)

R^1 = H; R^2 = OMe; R^3 = OH; R^4 = H; R^5 = H: (−)-montanine (**1**)
R^1 = OMe; R^2 = H; R^3 = OH; R^4 = H; R^5 = H: (−)-coccinine (**2**)
R^1 = H; R^2 = OH; R^3 = OH; R^4 = H; R^5 = H: (−)-pancracine (**3**)
R^1 = H; R^2 = OH; R^3 = H; R^4 = OH; R^5 = H: (−)-brunsvigine (**4**)
R^1 = H; R^2 = OMe; R^3 = OMe; R^4 = H; R^5 = H: (−)-manthine (**5**)
R^1 = H; R^2 = H; R^3 = H; R^4 = OH; R^5 = OH: (−)-nangustine (**6**)

In the early 1990s, Overman and Shim accomplished the first total synthesis of (±)- and (−)-pancracine employing a tandem aza-Cope rearrangement/Mannich cyclization of **B** and a Pictet–Spengler cyclization of **A** as the pivotal steps (Scheme 1).[8] Hoshino and coworkers described the first total synthesis of (±)-coccinine, (±)-montanine, and (±)-pancracine utilizing an intramolecular reductive cyclization of **D** as the key step to assemble the pentacyclic framework.[9] The same group also developed a radical cyclization strategy (**E**→**C**) for the formal total synthesis of these alkaloids.[10] Since their pioneering studies, this class of alkaloids has been the subject of a considerable amount of innovative synthetic work. Weinreb and Jin reported the enantioselective synthesis of alkaloids **1**–**4** exploiting an intramolecular concerted allenylsilane imino ene cyclization of **F**.[11] Pearson and Lian achieved the enantioselective total synthesis of (+)-coccinine employing an intramolecular cycloaddition of the 2-azaallyl anion derived from **H**.[12] Sha and coworkers developed an anionic cyclization method (**J**→**I**) for the total synthesis of (−)-brunsvigine[13] and (−)-manthine.[13b] Banwell and co-workers developed chemoenzymatic approaches including a radical addition/elimination sequence (**N**→**K**–**M**) for the total synthesis of (+)-brunsvigine,[14] (+)-nangustine,[15] and (+)-montabuphine.[16] In addition, several groups achieved a formal total synthesis of these alkaloids by devising innovative strategies and

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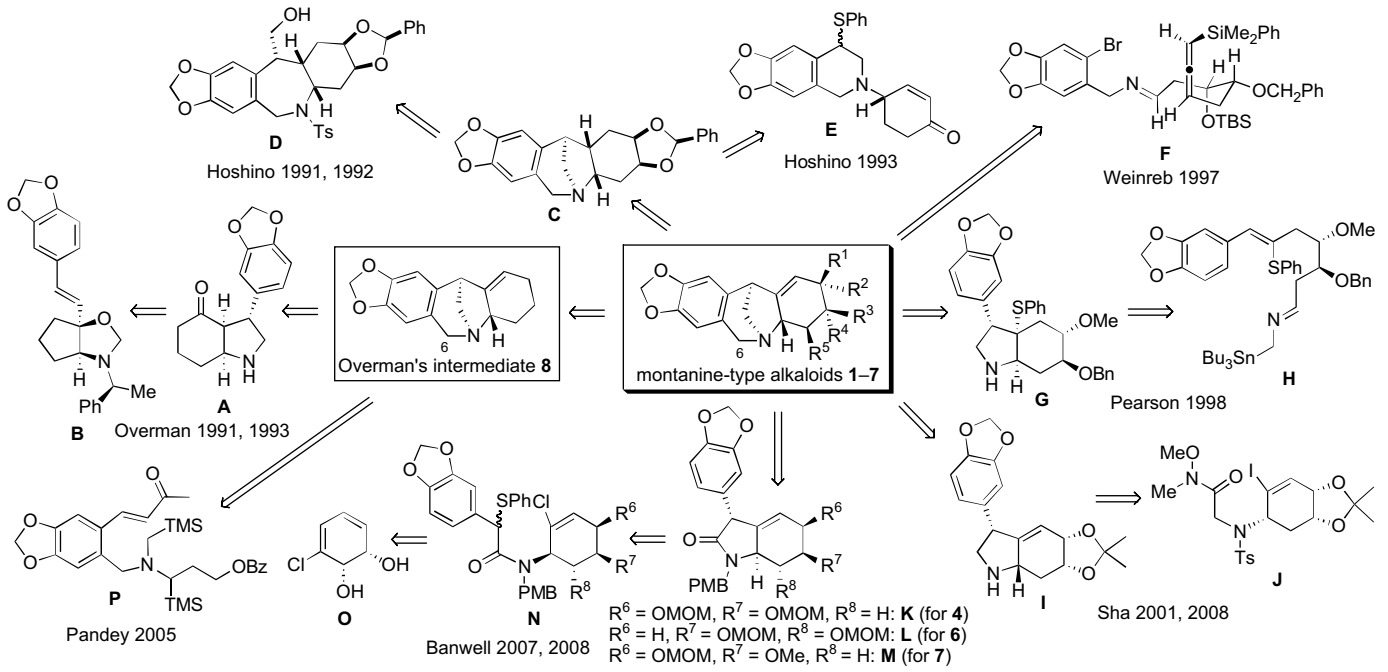
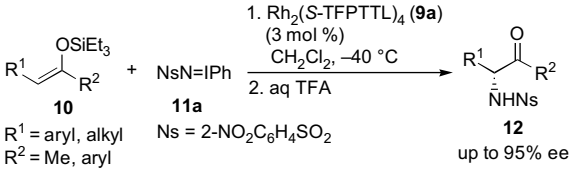


Scheme 1. Representative synthetic strategies toward montanine-type alkaloids **1**–**7**.

tactics, wherein the key features include a 5-*exo*-*trig* radical cyclization of *N*-(2-cyclohexenyl)-α-aryl-α-(phenylthio)acetamide,[17] a Mitsunobu-promoted nucleophilic displacement of an allylic alcohol by a tethered sulfonamide,[18] an intramolecular aldol condensation of ketone prepared from *trans*-(2*S*,4*R*)-4-hydroxyproline,[19] and an intramolecular 1,3-dipolar cycloaddition of nonstabilized azomethine ylide derived from **P**.[20] It is notable that all of the reported synthetic strategies except for those by the Hoshino, Weinreb, and Pandey groups rely on the construction of appropriate 3-arylperhydroindoles and the subjection of such intermediates to a Pictet–Spengler cyclization so as to install the C6 methylene group associated with the target framework as originally established in Overman's synthesis of (±)-pancracine.

We have recently documented the utility of Rh_2(*S*-TFPTTL)$_4$ (**9a**) and Rh_2(*S*-TCPTTL)$_4$ (**9b**),[21] characterized by the substitution of fluorine or chlorine atoms for four hydrogen atoms on the phthalimido group in the parent dirhodium(II) complex, Rh_2(*S*-PTTL)$_4$ (**9c**)[22] (Fig. 1), in the catalysis of enantioselective nitrene transfer reactions such as C–H amination[23,24] and olefin aziridination.[25] More recently, we have reported that Rh_2(*S*-TFPTTL)$_4$-catalyzed enantioselective amination of silyl enol ethers **10** derived from acyclic ketones or enones with [(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN=IPh, **11a**) provides *N*-(2-nitrophenylsulfonyl)-α-amino ketones **12** with enantioselectivities of up to 95% ee (Eq. 1),[26,27] the effectiveness of which has been demonstrated by an asymmetric formal synthesis of (−)-metazocine[26a] and (−)-ritodrine hydrochloride.[26b] In these processes, the use of NsN=IPh (**11a**) as the nitrene precursor is not only crucial for high levels of enantioselection but also synthetically advantageous since the alkylation of resultant *N*-monosubstituted Ns-amides and deprotection proceed under mild conditions as established by the group of Fukuyama.[28]



(1)

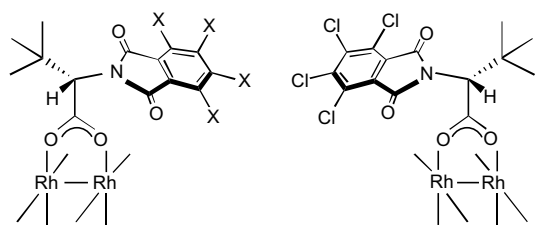
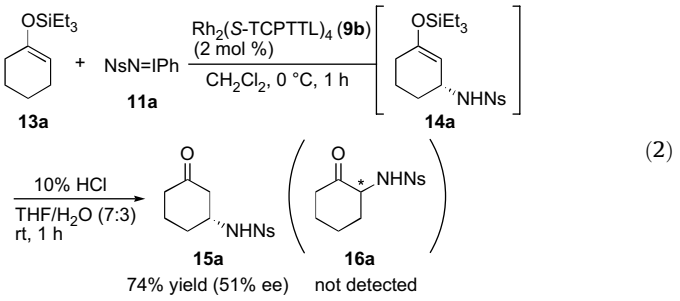


Figure 1. Chiral dirhodium(II) catalysts.

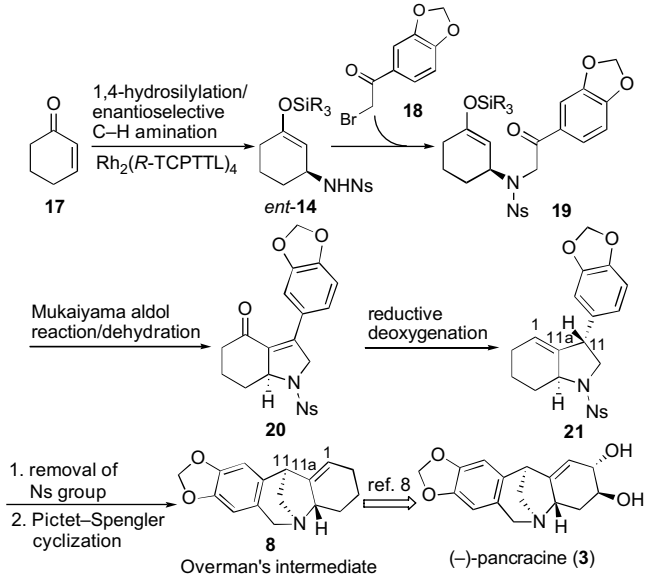
During the course of the above studies, we found that the reaction of 1-triethylsiloxy-1-cyclohexene (**13a**) with NsN=IPh (**11a**) in CH_2Cl_2 at 0 °C in the presence of 2 mol % of Rh_2(*S*-TCPTTL)$_4$ (**9b**) gave, after treatment with 10% HCl, β-amino ketone **15a** derived from allylic C–H insertion by rhodium(II) nitrene species in 74% yield and 51% ee, with no trace of the expected α-amino ketone product **16a** (Eq. 2). The surprising outcome with **13a** adopting *E*-geometry might be related to the fact that only *Z*-isomers of silyl enol ethers **10** are responsible for the formation of α-amino ketones in the foregoing catalytic process, whereas the corresponding *E*-isomers did not react under the same conditions.[26a,27] Although results of several studies on nitrene transfer from a suitable nitrene source to silyl enol ether substrates by means of thermolysis,[29] photolysis,[30] and transition metal catalysts[31,32] have been reported, there have been no examples of the formation of an allylic C–H amination product. It has been shown that nitrene species undergo aziridinations of silyl enol ethers to produce *N*-substituted α-amino

ketones via ring opening of the aziridine intermediates in modest to good yields.



(2)

Attracted by this unprecedented result, we set out to enhance the enantioselectivity in this reaction system. Furthermore, taking full advantage of Fukuyama's Ns-strategy,[28] we hoped to apply a catalytic enantioselective C–H amination of this type to the synthesis of the montanine-type Amaryllidaceae alkaloid (−)-pancracine (**3**) as outlined in Scheme 2. Since a highly efficient conversion of **8** to **3** had already been established by Overman and Shim,[8] we directed our efforts to the asymmetric synthesis of Overman's intermediate **8** via a Pictet–Spengler cyclization at a late stage. We anticipated that the *N*-Ns-protected β-amino silyl enol ether *ent*-**14** obtained by a one-pot Rh_2(*R*-TCPTTL)$_4$-sequential 1,4-hydrosilylation/enantioselective C–H amination of 2-cyclohexen-1-one (**17**) would undergo alkylation and subsequent Mukaiyama aldol reaction/dehydration to produce aza bicyclic enone **20**. The most crucial step in the synthesis is conversion of **20** to 3-arylhexahydroindole **21**, which would require a regio- and stereocontrolled reductive deoxygenation of enone with migration of the double bond to create the C1/C11a double bond and the stereogenic center at C11. Results of these studies are presented in this paper.



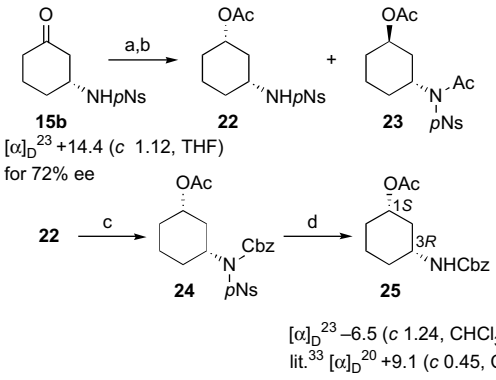
Scheme 2. Synthetic strategy for (−)-pancracine (**3**).

2. Results and discussion

2.1. Enantioselective C–H amination of silyl enol ethers

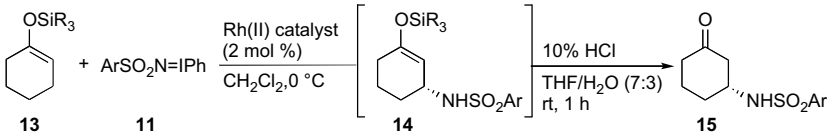
At the outset of this work, we explored the optimization of the C–H amination of 1-triethylsiloxy-1-cyclohexene (**13a**), the enantioselectivity of which was assayed by chiral HPLC (Table 1). Our initial studies began with an evaluation of the performance of two other chiral dirhodium(II) complexes, Rh_2(*S*-TFPTTL)$_4$ (**9a**) and Rh_2(*S*-PTTL)$_4$ (**9c**).[21] The reaction of **13a** with NsN=IPh (**11a**) in CH_2Cl_2 at 0 °C in the presence of 2 mol % of the catalyst **9a** or **9c** afforded, after desilylation, β-amino ketone **15a** in 57% and 52% yields with 41% and 19% ee, respectively (entries 2 and 3). From this comparison, Rh_2(*S*-TCPTTL)$_4$ proved to be the catalyst of choice in terms of both product yield and enantioselectivity (74% yield and 51% ee, entry 1). Using Rh_2(*S*-TCPTTL)$_4$, we next evaluated the effect of two other nitrene precursors, [(4-nitrophenylsulfonyl)imino]phenyliodinane (*p*NsN=IPh, **11b**) and [(2,4-dinitrophenylsulfonyl)imino]phenyliodinane (DNsN=IPh, **11c**), on enantioselection and yield. This screening revealed that *p*NsN=IPh (**11b**) was the optimal nitrene precursor for this transformation (79% yield and 72% ee, entries 4 vs 1 and 5), although the reason for the advantage of **11b** is not clear at this time. It is noteworthy that no signs of the corresponding α-amino ketone products could be detected in the crude reaction mixture, regardless of the nature of the nitrene precursors. A survey of solvents revealed that the use of CH_2Cl_2 was the superior choice in terms of enantioselectivity (entries 4 vs 6 and 7), although the product **15b** was also formed with similar yields in toluene and α,α,α-trifluorotoluene. Using the optimal combination of Rh_2(*S*-TCPTTL)$_4$ as the catalyst, *p*NsN=IPh as the nitrene precursor, and CH_2Cl_2 as the solvent, we also examined the effect of the silicon substituents of silyl enol ethers **13a**–**d**. The use of trimethylsilyl enol ether **13b** exhibited nearly the same enantioselectivity as that found with **13a** but led to a marked decrease in product yield probably because of the instability of **13b** under these reaction conditions (47% yield and 67% ee, entry 8). The use of **13c**,**d** with larger silicon substituents relative to the triethylsilyl group resulted in lower product yields and enantioselectivities (entries 9 and 10). Thus, the triethylsilyl functionality was found to be optimal for this process, 72% ee being the highest achievement.

The preferred absolute configuration of the *N*-*p*Ns-protected β-aminocyclohexanone **15b** with 72% ee {$[\alpha]_D^{20}$ +14.4 (*c* 1.12, THF)} was determined by its transformation to the known 1-acetoxy-3-(benzyloxycarbonylamino)cyclohexane (**25**)[33] (Scheme 3). Reduction of **15b** with $NaBH_4$ in EtOH followed by acetylation gave a 7:1 mixture of *cis*-acetate **22** and *N*-acetyl-protected *trans*-acetate **23** in 96% combined yield. Treatment of **22** with CbzCl followed by removal of the *p*Ns group under standard Fukuyama conditions afforded **25** {$[\alpha]_D^{23}$ −6.5 (*c* 1.24, $CHCl_3$); lit.[33] $[\alpha]_D^{20}$ +9.1 (*c* 0.45, $CHCl_3$) for (1*R*,3*S*)-enantiomer} in 53% yield. Thus, the preferred absolute configuration of **15b** was established as *R*.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C, 10 min; (b) Ac_2O, pyridine, CH_2Cl_2, 0 °C, 1 h, 96% (**22**/**23**=7:1, two steps); (c) NaH, CbzCl, CH_2Cl_2, 0 °C, 1 h, 58%; (d) PhSH, K_2CO_3, DMF, rt, 30 min, 91%.

Table 1
Enantioselective C–H amination of silyl enol ethers **13** with [*N*-(arylsulfonyl)imino]phenyliodinanes **11** catalyzed by chiral dirhodium(II) carboxylates[a]



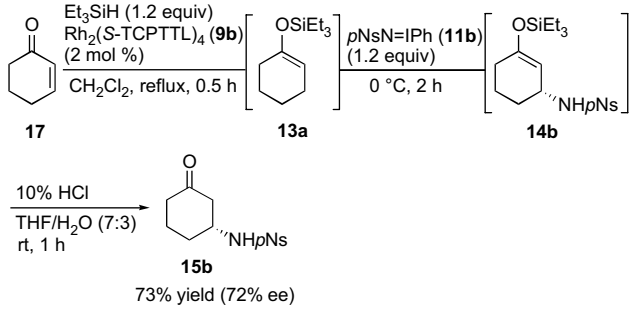
13 11 14 15

Entry	Silyl enol ether **13**		Iminoiodinane **11**		Rh(II) catalyst	Solvent	Time, h	β-Amino ketone **15**		
		R_3Si		Ar					Yield,[b] %	ee, %
1	**13a**	Et_3Si	**11a**	2-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	CH_2Cl_2	1.5	**15a**	74	51[c]
2	**13a**	Et_3Si	**11a**	2-$NO_2C_6H_4$	Rh_2(*S*-TFPTTL)$_4$ (**9a**)	CH_2Cl_2	1	**15a**	57	41[c]
3	**13a**	Et_3Si	**11a**	2-$NO_2C_6H_4$	Rh_2(*S*-PTTL)$_4$ (**9c**)	CH_2Cl_2	3	**15a**	52	19[c]
4	**13a**	Et_3Si	**11b**	4-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	CH_2Cl_2	1	**15b**	79	72[d]
5	**13a**	Et_3Si	**11c**	2,4-$(NO_2)_2C_6H_3$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	CH_2Cl_2	2.5	**15c**	53	46[c]
6	**13a**	Et_3Si	**11b**	4-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	Toluene	3	**15b**	65	45[d]
7	**13a**	Et_3Si	**11b**	4-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	$CF_3C_6H_5$	3	**15b**	73	52[d]
8	**13b**	Me_3Si	**11b**	4-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	CH_2Cl_2	1.5	**15b**	47	67[d]
9	**13c**	*t*-$BuMe_2Si$	**11b**	4-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	CH_2Cl_2	2	**15b**	55	60[d]
10	**13d**	*i*-Pr_3Si	**11b**	4-$NO_2C_6H_4$	Rh_2(*S*-TCPTTL)$_4$ (**9b**)	CH_2Cl_2	2	**15b**	51	59[d]

[a] All reactions were performed on a 0.2 mmol scale (0.1 M) with 1.2 equiv of **11**.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralpak AD-H).
[d] Determined by HPLC (Daicel Chiralpak IA).

2.2. One-pot sequential 1,4-hydrosilylation/enantioselective C–H amination

We previously reported that dirhodium(II) carboxylates are effective catalysts for 1,4-hydrosilylation of α,β-unsaturated ketones and aldehydes.[34] Based on this work, we recently developed a one-pot Rh_2(*S*-TFPTTL)$_4$-catalyzed sequential 1,4-hydrosilylation/amination procedure for the enantioselective synthesis of *N*-Ns-protected α-amino ketones from α,β-enones.[26a] In order to improve the operation efficiency, we became interested in the possibility of applying the one-pot methodology in the present system. Upon completion of the 1,4-hydrosilylation reaction of 2-cyclohexen-1-one (**17**) with triethylsilane (1.2 equiv) in the presence of 2 mol % of Rh_2(*S*-TCPTTL)$_4$ (performed in CH_2Cl_2 under reflux for 0.5 h), the reaction mixture was treated with *p*NsN═IPh (**11b**) (1.2 equiv) at 0 °C for 2 h in the same reaction vessel. After the usual workup, the desired β-amino ketone **15b** was obtained in 73% overall yield with 72% ee, comparable to that obtained in the amination of **13a** (Scheme 4 vs Table 1, entry 4). While the mechanistic profile of the dirhodium(II) carboxylate-catalyzed 1,4-hydrosilylation is unclear at present, the result with this system again suggested that the integrity of the ligands on the dirhodium framework was not compromised during the 1,4-hydrosilylation process.



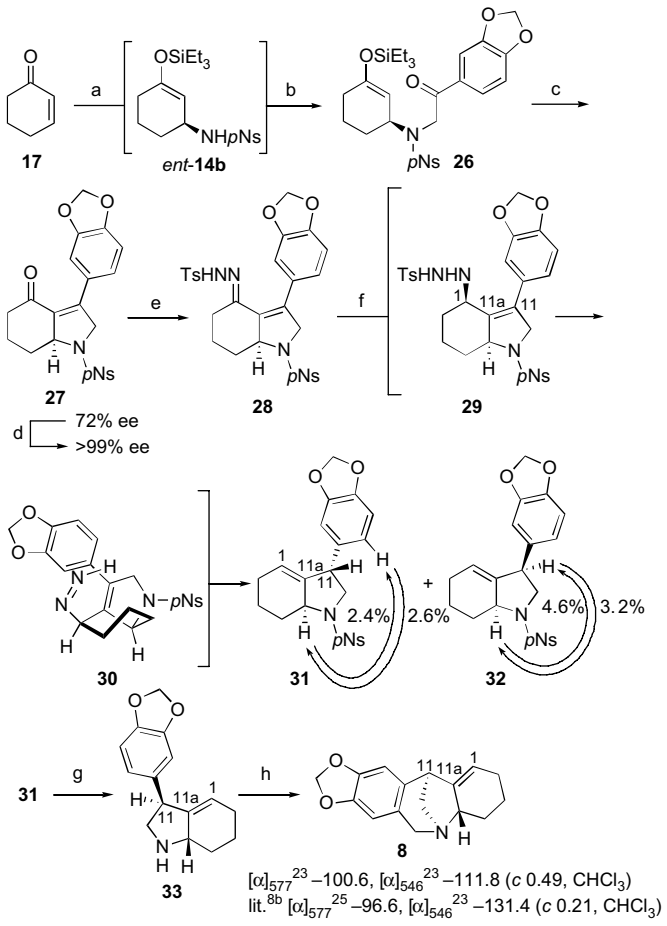
17 13a 14b 15b
73% yield (72% ee)

Scheme 4. One-pot sequential 1,4-hydrosilylation/enantioselective C–H amination.

2.3. Asymmetric formal synthesis of (−)-pancracine

With the process of 2-cyclohexen-1-one into the *N*-*p*Ns-protected β-aminocyclohexanone optimized, we then proceeded to the elaboration of an advanced intermediate in Overman's synthesis of (−)-pancracine (Scheme 5). The one-pot 1,4-hydrosilylation/C–H amination of 2-cyclohexen-1-one (**17**) with *p*NsN═IPh (**11b**) using 2 mol % of Rh_2(*R*-TCPTTL)$_4$ (**9d**) led to the formation of the *N*-*p*Ns-protected β-amino silyl enol ether *ent*-**14b**. Since silyl enol ether *ent*-**14b** was relatively unstable and could not be obtained in pure form by column chromatography on Wakogel C-200, the crude product of this process was used for the next step. N-Alkylation of *ent*-**14b** with 1-(bromoacetyl)-3,4-methylenedioxybenzene (**18**)[35] in the presence of K_2CO_3 was uneventfully followed by column chromatography on Wakogel C-200 to give the *N*,*N*-disubstituted β-amino silyl enol ether **26** in 58% yield in three steps from **17**. Intramolecular Mukaiyama aldol reaction of **26** and subsequent dehydration were effected with the aid of $BF_3{\cdot}OEt_2$, providing bicyclic enone **27** in 81% yield. At this point, the enantiomeric excess of **27** was confirmed to be 72% by HPLC analysis (Daicel Chiralpak IA). Fortunately, two recrystallizations of **27** from EtOAc/hexane produced optically pure material, mp 146.0–147.0 °C, $[\alpha]_D^{23}$ −81.7 (*c* 1.06, $CHCl_3$) in 53% yield.

The stage was now set for the reductive deoxygenation of enone **27** (>99% ee) with migration of the double bond to create the C1/C11a double bond and the stereogenic center at C11 of 3-arylhexahydroindole **31**. After some experimentation,[36] we were gratified to find that this goal could be readily achieved by employing Hutchins' tosylhydrazone reduction protocol.[36a] Thus, the α,β-unsaturated tosylhydrazone **28** prepared from the *cisoid* enone **27** was reduced with $NaBH_3CN$ in acidic DMF/sulfolane at 100 °C to produce the desired alkene **31** in 64% yield, along with 6% of its C11 epimer **32**. Stereochemical assignments of **31** and **32** were obtained from ^1H NOE experiments. The stereochemical outcome of this process can be rationalized from the mechanism of reduction of unsaturated hydrazones.[36] Because of the steric hindrance of the 3,4-methylenedioxyphenyl group oriented perpendicularly to the plane of the C11/C11a double bond, hydride attack at C1 of the protonated tosylhydrazone occurs predominantly from the α-side of the molecule to give the 1β-tosylhydrazine intermediate **29**, which subsequently decomposes to the desired alkene **31** via a suprafacial 1,5-sigmatropic rearrangement of the diazene intermediate **30** with loss of dinitrogen.[37] Removal of the *p*Ns group in **31** under standard Fukuyama conditions[28] followed by the Pictet–Spengler cyclization of 3-arylhexahydroindole **33** under Banwell conditions[18] furnished Overman's intermediate



Scheme 5. Reagents and conditions: (a) Et_3SiH (1.2 equiv), Rh_2(*R*-TCPTTL)$_4$ (**9d**) (2 mol %), CH_2Cl_2, 40 °C, 0.5 h, then *p*NsN=IPh (**11b**) (1.2 equiv), 0 °C, 2 h; (b) 1-(bromoacetyl)-3,4-methylenedioxybenzene (**18**) (1.5 equiv), K_2CO_3, DMF, rt, 0.5 h, 58% (three steps); (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to rt, 2 h, 81%; (d) recrystallization from EtOAc/hexane, 53%; (e) $TsNHNH_2$, TsOH, EtOH, reflux, 1.5 h; (f) $NaBH_3CN$, concd HCl, DMF/sulfolane (1:1), 100 °C, 10 h, 64% of **31** and 6% of **32** from **27**; (g) PhSH, $LiOH{\cdot}H_2O$, DMF, rt, 0.5 h, 86%; (h) paraformaldehyde, HCO_2H, reflux, 1.5 h, 72%.

8[8b] in 72% yield. The spectroscopic data of our synthetic **8** were identical to those reported by Overman and Shim (IR, ^{1}H NMR, ^{13}C NMR, HRMS). The optical rotation {$[\alpha]_{577}^{23}$ −100.6, $[\alpha]_{546}^{23}$ −111.8 (*c* 0.49, $CHCl_3$)} of our synthetic material was in good agreement with that reported {$[\alpha]_{577}^{25}$ –96.6, $[\alpha]_{546}^{23}$ −131.4 (*c* 0.21, $CHCl_3$)}.[8b] Therefore, we have completed a catalytic, asymmetric formal synthesis of (−)-pancracine.

3. Conclusion

We have developed an enantioselective C–H amination of silyl enol ethers derived from cyclohexanone with *p*Ns=IPh using Rh_2(*S*-TCPTTL)$_4$ as a catalyst, which provides, after desilylation, *N*-*p*Ns-protected (*S*)-β-aminocyclohexanone as the sole product in up to 72% ee. To the best of our knowledge, this is the first example of allylic C–H amination of silyl enol ethers by nitrene transfer reactions.[38] However, we were greatly disappointed to find that the protocol was successful only with silyl enol ethers from cyclohexanone as those from cyclopentanone and cycloheptanone gave a mixture of α- and β-amino ketones in modest yield, together with a complex mixture of products.[39]

Using this process, we have developed a new, concise, and catalytic asymmetric route to the 5,11-methanomorphanthridine Amaryllidaceae (−)-pancracine from 2-cyclohexen-1-one. The key features of the synthetic strategy include (a) a one-pot Rh_2(*R*-TCPTTL)$_4$-catalyzed sequential 1,4-hydrosilylation/enantioselective C–H amination of 2-cyclohexen-1-one, (b) N-alkylation of the *N*-*p*Ns-protected β-amino silyl enol ether, and subsequent Mukaiyama aldol reaction/dehydration to construct aza bicyclic enone **27**, and (c) a regio- and stereocontrolled reductive deoxygenation of enone **27** employing Hutchins' method to create the C1/C11a double bond and the stereogenic center at C11 of 3-arylhexahydroindole **31**. Further extension of this and related methodology to other natural products is currently in progress.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1030 digital polarimeter with a sodium or a mercury lamp. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^{1}H NMR spectra were recorded on JEOL EX 270 (270 MHz) spectrometer, JEOL JNM-ECX 400P (400 MHz) spectrometer, or JNM-ECA 500 (500 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00, $CDCl_3$ at δ_H 7.26, or C_6D_6 δ_H 7.20). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad), coupling constant, integration, and assignment. ^{13}C NMR spectra were recorded on JEOL JNM-ECX 400P (100 MHz) spectrometer or JEOL JNM-ECA 500 (125 MHz) spectrometer. The following internal references were used ($CDCl_3$ at δ 77.0, C_6D_6 at δ 128.0, CD_2Cl_2 at δ 53.8, or acetone-d_6 at δ 30.3). EIMS spectra were obtained on a JEOL JMS-FABmate spectrometer, operating with ionization energy of 70 eV. FABMS spectra were obtained on a JEOL JMS-HX 110 spectrometer. Column chromatography was carried out on Kanto silica gel 60 N (63–210 mesh), Wakogel® C-200 (75–200 μm), or Fuji Silysia Chromatorex® NH (100–200 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with UV light, anisaldehyde stain solution, or phosphomolybdic acid stain solution followed by heating. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/VIS detector. Detection was performed at 254 nm. Chiralpak AD-H and IA columns (0.46 cm×25 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with JASCO–Borwin analysis system.

All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Benzene was distilled from sodium benzophenone ketyl. Chiral dirhodium(II) carboxylates **9a**–**d**,[21,23a,40] arylsulfonyliminoiodinanes **11a**–**c**,[41] silyl enol ethers **13a**,[34] **13b**,[42] **13c**,[43] and **13d**,[44] and 1-(bromoacetyl)-3,4-methylenedioxybenzene (**18**)[35] were prepared according to the literature procedures.

4.2. Representative procedure for the amination reaction of silyl enol ether (Table 1, entry 4): (*R*)-3-[(4-nitrophenylsulfonyl)amino]cyclohexan-1-one (15b)

*p*NsN=IPh (**11b**) (97.0 mg, 0.24 mmol) was added in one portion to a solution of silyl enol ether **13a** (42.5 mg, 0.2 mmol) and Rh_2(*S*-TCPTTL)$_4{\cdot}$2EtOAc (**9b**) (7.8 mg, 0.004 mmol) in CH_2Cl_2 (2 mL, 0.1 M) at 0 °C. After stirring at this temperature for 1 h, the reaction mixture was evaporated in vacuo. The residue was dissolved in THF/H_2O (7:3, 1 mL) and then 10% aqueous HCl (0.1 mL) was added at room temperature. After stirring for 1 h, the mixture was partitioned between EtOAc (2 mL) and pH 7.0 phosphate buffer (3 mL), and the whole was extracted with EtOAc (15 mL). The organic layer

was washed with H_2O (2×3 mL) and brine (2×3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 2:1 hexane/EtOAc) gave **15b** (47.1 mg, 79%) as a white solid: R_f=0.31 (1:1 hexane/EtOAc); mp 154.5–156.0 °C; $[\alpha]_D^{23}$ +14.4 (*c* 1.12, THF) for 72% ee; IR (KBr) 3240, 1708, 1527, 1350, 1313, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.69–1.75 (m, 2H, H-5), 1.95–2.02 (m, 2H, H-4), 2.24–2.39 (m, 3H, H-2a, H-6), 2.56 (dd, *J*=4.6, 13.9 Hz, 1H, H-2b), 3.70 (m, 1H, NC*H*), 5.41 (d, *J*=7.5 Hz, 1H, N*H*), 8.08 (dt, *J*=9.2, 2.0 Hz, 2H, *Ar*), 8.38 (dt, *J*=9.2, 2.0 Hz, 2H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (CH_2), 31.7 (CH_2), 40.5 (CH_2), 48.3 (CH_2), 52.8 (CH), 124.5 (CH), 128.2 (CH), 146.5 (C), 150.1 (C), 207.8 (C=O); HRMS (EI) calcd for $C_{12}H_{14}N_2O_5S$ $(M)^+$ 298.0623, found 298.0611. Anal. Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.31; H, 4.73; N, 9.39; S, 10.75. Found: C, 48.22; H, 4.66; N, 9.29; S, 10.75. The enantiomeric excess of **15b** was determined to be 72% by HPLC with a Chiralpak IA column (1:1 hexane/THF, 1.0 mL/min): t_R (major)=5.9 min for (*R*)-**15b**; t_R (minor)=9.1 min for (*S*)-**15b**. The preferred absolute configuration of **15b** was determined to be *R* by chemical correlation (vide infra).

4.3. (*R*)-3-[(2-Nitrophenylsulfonyl)amino]cyclohexan-1-one (15a)

The β-amino ketone was prepared according to the representative procedure for amination reaction (2.0 mL of CH_2Cl_2, 1.5 h at 0 °C) employing the silyl enol ether **13a** (42.5 mg, 0.2 mmol), Rh_2(*S*-TCPTTL)$_4$·2EtOAc (**9b**) (7.8 mg, 0.004 mmol), and NsN=IPh (**11a**) (97.0 mg, 0.24 mmol) to provide **15a** (44.4 mg, 74%) as a white solid after column chromatography (silica gel, 2:1 hexane/EtOAc); R_f=0.33 (1:1 hexane/EtOAc); mp 142.0–144.0 °C; $[\alpha]_D^{23}$ +16.8 (*c* 1.03, THF) for 51% ee; IR (KBr) 3356, 1709, 1536, 1362, 1342, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59–1.77 (m, 2H, H-5), 2.03 (m, 1H, H-4a), 2.11 (m, 1H, H-4b), 2.23–2.38 (m, 3H, H-2a, H-6), 2.56 (ddt, *J*=4.5, 14.1, 1.8 Hz, 1H, H-2b), 3.75 (m, 1H, NC*H*), 5.43 (d, *J*=7.7 Hz, 1H, N*H*), 7.74–7.80 (m, 2H, *Ar*), 7.90 (m, 1H, *Ar*), 8.16 (m, 1H, *Ar*); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 22.0 (CH_2), 32.2 (CH_2), 40.7 (CH_2), 48.8 (CH_2), 53.6 (CH), 125.8 (CH), 131.0 (CH), 133.5 (CH), 134.3 (CH), 134.4 (C), 148.1 (C), 207.5 (C=O); HRMS (EI) calcd for $C_{12}H_{14}N_2O_5S$ $(M)^+$ 298.0623, found 298.0618. Anal. Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.31; H, 4.73; N, 9.39; S, 10.75. Found: C, 48.20; H, 4.67; N, 9.35; S, 10.66. The enantiomeric excess of **15a** was determined to be 51% by HPLC with a Chiralpak AD-H (3:1 hexane/*i*-PrOH, 1.0 mL/min): t_R=14.7 min for major enantiomer; t_R=20.0 min for minor enantiomer. The preferred absolute configuration of **15a** was not determined.

4.4. (*R*)-3-[(2,4-Dinitrophenylsulfonyl)amino]cyclohexan-1-one (15c)

The β-amino ketone was prepared according to the representative procedure for amination reaction (2.0 mL of CH_2Cl_2, 2.5 h at 0 °C) employing the silyl enol ether **13a** (42.5 mg, 0.2 mmol), Rh_2(*S*-TCPTTL)$_4$·2EtOAc (**9b**) (7.8 mg, 0.004 mmol), and DNsN=IPh (**11c**) (107.8 mg, 0.24 mmol) to provide **15c** (36.4 mg, 53%) as a white solid after column chromatography (silica gel, 2:1 hexane/EtOAc); R_f=0.36 (1:1 hexane/EtOAc); mp 167.0–170.0 °C; $[\alpha]_D^{22}$ +13.7 (*c* 1.04, EtOAc) for 46% ee; IR (KBr) 3333, 1710, 1548, 1540, 1351, 1333, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.66–1.79 (m, 2H, H-5), 1.99–2.13 (m, 2H, H-4), 2.23–2.40 (m, 3H, H-2a, H-6), 2.58 (m, 1H), 3.84 (m, 1H, NC*H*), 5.46 (d, *J*=7.5 Hz, 1H, N*H*), 8.39 (d, *J*=8.6 Hz, 1H, *Ar*), 8.58 (dd, *J*=2.3, 8.6 Hz, 1H, *Ar*), 8.70 (d, *J*=2.3 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, acetone-d_6) δ 22.7 (CH_2), 33.0 (CH_2), 41.2 (CH_2), 49.4 (CH_2), 54.4 (CH), 121.7 (CH), 128.6 (CH), 133.5 (CH), 140.5 (C), 149.4 (C), 151.6 (C), 207.5 (C=O); HRMS (FAB) calcd for $C_{12}H_{13}N_3O_7S$ $(M)^+$ 343.0474, found 343.0484. Anal. Calcd for $C_{12}H_{13}N_3O_7S$: C, 41.98; H, 3.82; N, 12.24; S, 9.34. Found: C, 41.77; H, 3.82; N, 12.00; S, 9.37. The enantiomeric excess of **15c** was determined to be 46% by HPLC with a Chiralpak AD-H column (1:1 hexane/*i*-PrOH, 1.0 mL/min): t_R=9.7 min for major enantiomer; t_R=13.3 min for minor enantiomer. The preferred absolute configuration of **15c** was not determined.

4.5. (1*S*,3*R*)-1-Acetoxy-3-[(4-nitrophenylsulfonyl)amino]-cyclohexane (22) and (1*S*,3*S*)-1-acetoxy-3-[acetyl-(4-nitrophenylsulfonyl)amino]cyclohexane (23)

A solution of sulfonamide **15b** (68.2 mg, 0.17 mmol) in EtOH (0.5 mL) was added to a suspension of $NaBH_4$ (6.3 mg, 0.17 mmol) in EtOH (1 mL) under argon atmosphere at 0 °C. After stirring at this temperature for 10 min, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the whole was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave the crude amino alcohol product, which was dissolved in pyridine (0.5 mL). Ac_2O (24.6 mg, 0.242 mmol) was added to the mixture at 0 °C. After stirring at this temperature for 1 h, the reaction was quenched with crushed ice. The reaction mixture was partitioned between EtOAc (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the whole was extracted with EtOAc (10 mL). The organic layer was washed with 10% aqueous HCl (2×3 mL) and brine (2×3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 5:1→3:1 hexane/EtOAc) provided **22** (48.9 mg, 84%) as a colorless oil and **23** (7.2 mg, 12%) as a colorless oil. *Compound* ***22***: R_f=0.55 (1:1 hexane/EtOAc); $[\alpha]_D^{24}$ +8.4 (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 3382, 1732, 1534, 1365, 1350, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09–1.28 (m, 4H), 1.64–1.72 (m, 2H), 1.80 (m, 1H), 1.94 (s, 3H, COC*H*$_3$), 2.00 (m, 1H), 3.22 (m, 1H, NC*H*), 4.58 (m, 1H, OC*H*), 5.52 (d, *J*=8.9 Hz, 1H, N*H*), 8.01 (d, *J*=8.6 Hz, 2H, *Ar*), 8.30 (d, *J*=8.6 Hz, 2H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6 (CH_2), 21.1 (CH_3), 30.1 (CH_2), 32.5 (CH_2), 38.4 (CH_2), 51.0 (CH), 70.5 (CH), 124.4 (CH), 128.0 (CH), 146.9 (C), 149.8 (C), 170.2 (C=O); HRMS (FAB) calcd for $C_{14}H_{19}N_2O_6S$ $(M+H)^+$ 343.0964, found 343.0963. *Compound* ***23***: R_f=0.63 (1:1 hexane/EtOAc); $[\alpha]_D^{24}$ −3.5 (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 3020, 1731, 1718, 1536, 1365, 1351, 1173 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20–1.40 (m, 4H), 1.75 (m, 1H, CH*H*), 1.85–2.01 (m, 3H), 2.03 (s, 3H, COC*H*$_3$), 2.33 (s, 3H, COC*H*$_3$), 2.44 (q, *J*=11.2 Hz, 1H, H-2a), 4.09 (m, 1H, NC*H*), 4.66 (m, 1H, OC*H*), 8.10 (dt, *J*=8.6, 2.3 Hz, 2H, *Ar*), 8.42 (dt, *J*=8.6, 2.3 Hz, 2H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2 (CH_3), 22.4 (CH_2), 26.4 (CH_3), 29.3 (CH_2), 30.4 (CH_2), 35.6 (CH_2), 58.7 (CH), 71.7 (CH), 124.5 (CH), 128.8 (CH), 145.5 (C), 150.5 (C), 170.2 (C=O), 170.3 (C=O); HRMS (FAB) calcd for $C_{16}H_{20}N_2NaO_7S$ $(M+Na)^+$ 407.0889, found 407.0889.

4.6. (1*S*,3*R*)-1-Acetoxy-3-[benzyloxycarbonyl-(4-nitrobenzenesulfonyl)amino]cyclohexane (24)

A solution of **22** (42.4 mg, 0.124 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of NaH (7.4 mg, 0.186 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After stirring at this temperature for 0.5 h, CbzCl (30.6 mg, 0.186 mmol) was added and stirred for 1 h and then the reaction was quenched with crushed ice. The reaction mixture was partitioned between EtOAc (3 mL) and saturated aqueous $NaHCO_3$ (3 mL), and the whole was extracted with EtOAc (15 mL). The organic layer was washed with brine (2×3 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 3:1 hexane/EtOAc) gave **24** (34.0 mg, 58%) as a white solid; R_f=0.53 (2:1 hexane/EtOAc); mp 130.5–134.0 °C; $[\alpha]_D^{24}$ −13.6 (*c* 1.34, $CHCl_3$); IR ($CHCl_3$) 3434, 1747, 1734, 1532, 1381, 1353, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 1H), 1.42 (m, 1H), 1.84–2.01 (m, 3H), 2.04 (s, 3H, COC*H*$_3$), 2.08–2.22 (m, 2H), 2.33 (q, *J*=11.3 Hz, 1H, H-2a), 4.48 (tt, *J*=3.6, 12.7 Hz, 1H, H-3), 4.77 (tt, *J*=4.1, 11.3 Hz, 1H, H-1), 5.06 (s, 2H, PhC*H*$_2$), 7.16 (m, 2H, *Ar*), 7.31–7.38 (m, 3H, *Ar*), 7.86 (d, *J*=9.1 Hz, 2H, *Ar*), 8.09 (d, *J*=9.1 Hz, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 22.0

(CH_2), 29.6 (CH_2), 30.4 (CH_2), 35.9 (CH_2), 56.8 (CH), 69.5 (CH_2), 71.6 (CH), 123.7 (CH), 128.6 (CH), 128.8 (CH), 129.01 (CH), 129.03 (CH), 133.6 (C), 145.4 (C), 150.0 (C), 151.2 (C=O), 170.3 (C=O); HRMS (FAB) calcd for $C_{22}H_{25}N_2O_8S$ $(M+H)^+$ 477.1332, found 477.1343.

4.7. (1*S*,3*R*)-1-Acetoxy-3-(benzyloxycarbonylamino)-cyclohexane (25)

K_2CO_3 (19.8 mg, 0.142 mmol) was added to a solution of **24** (34.0 mg, 0.072 mmol) and PhSH (9.5 μL, 0.092 mmol) in DMF (0.3 mL) at room temperature. After stirring at this temperature for 30 min, the reaction mixture was partitioned between EtOAc (2 mL) and 10% aqueous NaOH (2 mL), and the whole was extracted with EtOAc (10 mL). The organic layer was washed with H_2O (2×3 mL) and brine (2×3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 2:1 hexane/EtOAc) provided **25** (19.0 mg, 91%) as a white solid; R_f=0.53 (1:1 hexane/EtOAc); mp 101.5–104.0 °C; $[\alpha]_D^{23}$ −6.5 (*c* 1.24, $CHCl_3$) [lit.[33] $[\alpha]_D^{20}$ +9.1 (*c* 0.45, $CHCl_3$) for (1*R*,3*S*)-**25**]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.05–1.50 (m, 5H), 1.85–1.90 (m, 3H), 2.03 (s, 3H, COC*H*$_3$), 2.22 (m, 1H), 3.63 (m, 1H, NC*H*), 4.79 (m, 1H, OC*H*), 5.09 (s, 2H, PhC*H*$_2$), 7.31–7.35 (m, 5H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_2), 21.3 (CH_3), 30.6 (CH_2), 32.0 (CH_2), 38.0 (CH_2), 48.0 (CH), 66.5 (CH_2), 71.0 (CH), 128.07 (CH), 128.10 (CH), 128.5 (CH), 136.4 (C), 155.3 (C=O), 170.1 (C=O).

4.8. One-pot 1,4-hydrosilylation/enantioselective C–H amination of 2-cyclohexen-1-one catalyzed by 9b: (*R*)-3-[(4-nitrophenylsulfonyl)amino]cyclohexanone (15b) from 2-cyclohexen-1-one (17)

A mixture of triethylsilane (27.9 mg, 0.24 mmol), 2-cyclohexen-1-one (**17**) (19.2 mg, 0.2 mmol), and Rh_2(*S*-TCPTTL)$_4$·2EtOAc (**9b**) (7.8 mg, 0.004 mmol, 2 mol %) in CH_2Cl_2 (0.2 mL) was heated at reflux for 0.5 h. The mixture was diluted with CH_2Cl_2 (2 mL) at room temperature and then cooled to 0 °C. *p*NsN=IPh (**11b**) (97.0 mg, 0.24 mmol) was added in one portion to the mixture. After stirring at this temperature for 2 h, the reaction mixture was evaporated in vacuo. The residue was dissolved in THF/H_2O (7:3, 1 mL) and then 10% aqueous HCl (0.1 mL) was added at room temperature. After stirring for 1 h, the mixture was partitioned between EtOAc (2 mL) and pH 7.0 phosphate buffer (3 mL), and the whole was extracted with EtOAc (15 mL). The organic layer was washed with water (2×3 mL) and brine (2×3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 2:1 hexane/EtOAc) provided **15b** (43.6 mg, 73%) as a white solid; mp=155.0–157.0 °C; $[\alpha]_D^{20}$ +14.2 (*c* 1.07, THF) for 72% ee. The enantiomeric excess of **15b** was determined to be 72% by HPLC with a Chiralpak IA (1:1 hexane/THF, 1.0 mL/min).

4.9. (*S*)-*N*-(2-Benzo[1,3]dioxol-5-yl-2-oxoethyl)-4-nitro-*N*-(3-triethylsiloxycyclohex-2-enyl)benzenesulfonamide (26)

A mixture of triethylsilane (463.2 μL, 2.9 mmol), 2-cyclohexen-1-one (**17**) (232.0 mg, 2.4 mmol), and Rh_2(*R*-TCPTTL)$_4$·2EtOAc (**9d**) (90.4 mg, 0.048 mmol, 2 mol %) in CH_2Cl_2 (2 mL) was heated at reflux for 0.5 h. The mixture was diluted with CH_2Cl_2 (12 mL) at room temperature and then cooled to 0 °C. *p*NsN=IPh (**11b**) (1.17 g, 2.9 mmol) was added in one portion to the mixture. After stirring at this temperature for 2 h, the reaction mixture was filtered through a Celite®. The filtrate was evaporated in vacuo and diluted with DMF (10 mL). 1-(Bromoacetyl)-3,4-methylenedioxybenzene (**18**)[35] (875.0 mg, 3.6 mmol) and K_2CO_3 (663.4 mg, 4.8 mmol) were added to the solution at room temperature. After stirring at this temperature for 0.5 h, the mixture was partitioned between EtOAc (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and the whole was extracted with EtOAc (30 mL). The organic layer was washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (Wakogel® C-200, 5:1 hexane/EtOAc) provided **26** (803.1 mg, 58%) as a pale yellow oil; R_f=0.34 (3:1 hexane/EtOAc); $[\alpha]_D^{23}$ −34.5 (*c* 1.05, $CHCl_3$) for 72% ee; IR (film) 1697, 1657, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (q, *J*=7.7 Hz, 6H, SiC*H*$_2$), 0.87 (t, *J*=7.7 Hz, 9H, SiCH$_2$C*H*$_3$), 1.21–1.30 (m, 2H), 1.65 (m, 1H), 1.81–2.00 (m, 3H), 4.51 (br s, 1H, H-2), 4.53 (m, 1H, NC*H*), 4.66 (d, *J*=18.1 Hz, 1H, NCH*H*), 4.72 (d, *J*=18.1 Hz, 1H, NCH*H*), 6.06 (s, 2H, OC*H*$_2$O), 6.87 (d, *J*=8.3 Hz, 1H, OCH$_2$OCC*H*CH), 7.38 (d, *J*=1.5 Hz, 1H, OCH$_2$OCC*H*C), 7.51 (dd, *J*=1.5, 8.3 Hz, 1H, OCH$_2$OCCHC*H*), 8.22 (d, *J*=8.6 Hz, 2H, *Ar*), 8.38 (d, *J*=8.6 Hz, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8 (CH_2), 6.5 (CH_3), 20.6 (CH_2), 28.0 (CH_2), 29.1 (CH_2), 48.7 (CH_2), 55.3 (CH), 101.9 (CH_2), 102.2 (CH), 107.4 (CH), 107.9 (CH), 123.7 (CH), 123.9 (CH), 128.8 (CH), 129.2 (C), 146.6 (C), 148.1 (C), 149.6 (C), 152.1 (C), 156.5 (C), 192.0 (C); HRMS (FAB) calcd for $C_{27}H_{34}N_2NaO_8SSi$ $(M+Na)^+$ 597.1703, found 597.1688.

4.10. (*S*)-3-(1,3-Benzodioxol-5-yl)-*N*-(4-nitrophenylsulfonyl)-1,2,5,6,7,7a-hexahydroindol-4-one (27)

BF_3·OEt_2 (0.38 mL, 3.0 mmol) was added to a solution of silyl enol ether **26** (574.7 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After stirring at this temperature for 0.5 h, the reaction mixture was allowed to warm to room temperature over 1 h and stirred for an additional 1 h. The mixture was partitioned between EtOAc (2 mL) and pH 7.0 phosphate buffer (5 mL), and the whole was extracted with EtOAc (25 mL). The organic layer was washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 5:1 hexane/EtOAc) provided **27** (357.5 mg, 81%) as a pale yellow solid; R_f=0.54 (1:1 hexane/EtOAc); mp 136.5–139.0 °C; $[\alpha]_D^{24}$ −56.5 (*c* 1.00, $CHCl_3$) for 72% ee; IR (KBr) 1683, 1530, 1352, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74–1.96 (m, 2H, H-6a, H-7a), 2.12 (m, 1H, H-6b), 2.31 (ddd, *J*=6.6, 12.9, 16.3 Hz, 1H, H-5a), 2.56 (m, 1H, H-5b), 2.75 (m, 1H, H-7b), 4.34 (dd, *J*=3.2, 15.0 Hz, 1H, NCH*H*), 4.55 (m, 1H, NC*H*), 4.70 (dd, *J*=5.4, 15.0 Hz, 1H, NCH*H*), 5.97 (s, 2H, OC*H*$_2$O), 6.76 (d, *J*=8.2 Hz, 1H, OCC*H*CH), 6.99 (dd, *J*=1.8, 8.2 Hz, 1H, OCCHC*H*), 7.08 (d, *J*=1.8 Hz, 1H, OCC*H*C), 8.06 (dt, *J*=9.1, 2.2 Hz, 2H, *Ar*), 8.41 (dt, *J*=9.1, 2.2 Hz, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_2), 34.1 (CH_2), 42.1 (CH_2), 57.9 (CH_2), 69.8 (CH), 101.4 (CH_2), 107.9 (CH), 108.9 (CH), 122.9 (CH), 124.5 (C), 124.6 (CH), 128.7 (CH), 131.3 (C), 138.0 (C), 142.3 (C), 147.4 (C), 149.0 (C), 150.3 (C), 198.1 (C); HRMS (EI) calcd for $C_{21}H_{18}N_2O_7S$ $(M)^+$ 442.0835, found 442.0837. Compound **27** (300.0 mg, 72% ee) was recrystallized twice from hexane/EtOAc (1:1) to afford optically pure material (155.6 mg, 53% yield, >99% ee) as pale yellow needles; mp 146.0–147.0 °C; $[\alpha]_D^{23}$ −81.7 (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{21}H_{18}N_2O_7S$: C, 57.01; H, 4.10; N, 6.33; S, 7.25. Found; C, 57.18; H, 4.22; N, 6.18; S, 7.18. The homochirality of **27** was established by comparison of retention time in HPLC (Chiralpak IA, 1:1 hexane/THF, 1.0 mL/min) with a racemic sample: t_R (major)=4.29 min for (*S*)-**27** and t_R (minor)=5.00 min for (*R*)-**27**.

4.11. (3*R*,7a*S*)-3-(1,3-Benzodioxol-5-yl)-*N*-(4-nitrophenylsulfonyl)-2,3,5,6,7,7a-hexahydro-*1H*-indole (31) and (3*R*,7a*R*)-3-(1,3-benzodioxol-5-yl)-*N*-(4-nitrophenylsulfonyl)-2,3,5,6,7,7a-hexahydro-*1H*-indole (32)

$TsNHNH_2$ (22.3 mg, 0.12 mmol) was added to a solution of **27** (50.0 mg, 0.11 mmol) and TsOH·H_2O (2.1 mg, 0.011 mmol) in EtOH (1 mL) and the resulting mixture was heated at reflux for 1.5 h. The solvent was evaporated in vacuo, and the reaction mixture was partitioned between EtOAc (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The whole was extracted with EtOAc (20 mL), and the

organic layer was washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude tosylhydrazone product, which was dissolved in DMF/sulfolane (1:1, 2 mL). $NaBH_3CN$ (25.8 mg, 0.46 mmol) and small amount of Methyl Yellow were added to the solution at room temperature. The mixture was heated at 100 °C in a preheated oil bath and then a few drops of concd hydrochloric acid (ca. 50 μL) were added cautiously until the pH was <2.9 as indicated by a color change from yellow to red. After stirring at 100 °C for 5 h, a few drops of concd hydrochloric acid (ca. 50 μL) were added to maintain the pH below 2.9 and heating was continued for 5 h. The reaction mixture was partitioned between EtOAc (3 mL) and H_2O (3 mL), and the whole was extracted with EtOAc (20 mL). The organic layer was washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 4:1 hexane/EtOAc) gave **31** (30.2 mg, 64%) as a yellow oil and **32** (2.8 mg, 6%) as a yellow oil. *Compound **31***: R_f=0.29 (4:1 hexane/EtOAc); $[\alpha]_D^{21}$ −24.3 (*c* 1.13, $CHCl_3$); IR (film) 1526, 1348, 1163 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.26–1.47 (m, 2H), 1.58 (m, 1H), 1.70–1.75 (m, 2H), 2.76 (m, 1H), 3.14 (d, *J*=6.3 Hz, 1H, H-3), 3.31 (dd, *J*=1.8, 11.3 Hz, 1H, H-2a), 3.51 (dd, *J*=6.3, 11.3 Hz, 1H, H-2b), 3.67 (m, 1H, NC*H*), 5.25 (m, 1H, H-4), 5.30 (d, *J*=1.4 Hz, 1H, OC*H*HO), 5.33 (d, *J*=1.4 Hz, 1H, OC*H*HO), 5.85 (d, *J*=1.8 Hz, 1H, OCC*H*C), 6.00 (m, 1H, OCCHC*H*), 6.27 (d, *J*=8.2 Hz, 1H, OCCHC*H*), 7.33 (dt, *J*=9.1, 2.3 Hz, 2H, *Ar*), 7.56 (dt, *J*=9.1, 2.3 Hz, 2H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (CH_2), 24.4 (CH_2), 30.3 (CH_2), 47.0 (CH), 56.1 (CH_2), 58.9 (CH), 101.2 (CH_2), 106.8 (CH), 108.1 (CH), 120.1 (CH), 123.7 (CH), 125.5 (CH), 128.2 (CH), 135.2 (C), 138.2 (C), 143.0 (C), 146.2 (C), 147.4 (C), 149.6 (C); HRMS (EI) calcd for $C_{21}H_{20}N_2O_6S$ (M^+) 428.1042, found 428.1046. *Compound **32***: R_f=0.34 (4:1 hexane/EtOAc); $[\alpha]_D^{23}$ +19.7 (*c* 0.76, $CHCl_3$); IR (film) 1527, 1347, 1219 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.24–1.40 (m, 2H), 1.56 (m, 1H), 1.63–1.66 (m, 2H), 2.67 (m, 1H), 2.99 (m, 1H, H-3), 3.18 (dd, *J*=1.8, 11.3 Hz, 1H, H-2a), 3.64 (dd, *J*=6.3, 11.3 Hz, 1H, H-2b), 3.75 (m, 1H, NC*H*), 4.94 (m, 1H, H-4), 5.34 (d, *J*=1.4 Hz, 1H, OC*H*HO), 6.30 (m, 1H, OCCHC*H*), 6.49 (d, *J*=8.2 Hz, 1H, OCC*H*), 6.63 (d, *J*=8.0 Hz, 1H, OC*H*CH), 7.53 (dt, *J*=9.1, 2.3 Hz, 2H, *Ar*), 7.66 (dt, *J*=9.1, 2.3 Hz, 2H, *Ar*); ^{13}C NMR (125 MHz, C_6D_6) δ 20.2 (CH_2), 24.1 (CH_2), 30.2 (CH_2), 47.2 (CH), 54.8 (CH_2), 59.8 (CH), 101.1 (CH_2), 108.5 (CH), 108.9 (CH), 122.2 (CH), 122.3 (CH), 124.1 (CH), 128.3 (CH), 131.6 (C), 141.5 (C), 144.1 (C), 147.4 (C), 148.4 (C), 149.8 (C); HRMS (EI) calcd for $C_{21}H_{20}N_2O_6S$ $(M)^+$ 428.1042, found 428.1056.

4.12. (3*R*,7a*S*)-3-(1,3-Benzodioxol-5-yl)-2,3,5,6,7,7a-hexahydro-*1H*-indole (33)

PhSH (72 μL, 0.70 mmol) was added to a suspension of **31** (51.0 mg, 0.12 mmol) and $LiOH·H_2O$ (40.4 mg, 0.96 mmol) in DMF (0.5 mL) at room temperature. After stirring at this temperature for 30 min, the mixture was partitioned between EtOAc (2 mL) and 10% aqueous NaOH (2 mL), and the whole was extracted with EtOAc (2×10 mL). The combined organic layers were washed with H_2O (2×3 mL) and brine (2×3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (Chromatorex NH, 9:1→4:1 hexane/EtOAc) provided **33** (25.2 mg, 86%) as a yellow oil; R_f=0.46 (4:1 $CHCl_3$/MeOH); $[\alpha]_D^{23}$ −52.9 (*c* 1.01, $CHCl_3$); IR (film) 3250, 2929, 1608, 1103, 1039, 936, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.55 (m, 1H), 1.88 (m, 1H), 2.02–2.14 (m, 2H), 2.27 (m, 1H), 2.86 (dd, *J*=8.6, 10.4 Hz, 1H, H-2a), 3.27 (br s, 1H, N*H*), 3.54 (m, 1H), 3.58 (dd, *J*=8.6, 10.4 Hz, 1H, H-2b), 3.78 (t, *J*=8.6 Hz, 1H, H-3), 5.51 (m, 1H, H-4), 5.93 (s, 2H, OCH_2O), 6.67–6.75 (m, 3H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7 (CH_2), 25.1 (CH_2), 28.4 (CH_2), 48.4 (CH), 54.1 (CH_2), 59.5 (CH), 100.9 (CH_2), 107.7 (CH), 108.2 (CH), 120.5 (CH), 121.6 (CH), 137.5 (C), 143.8 (C), 146.0 (C), 147.8 (C); HRMS (EI) calcd for $C_{15}H_{17}NO_2$ $(M)^+$ 243.1259, found 243.1260.

4.13. (4a*S*,11*R*)-8,9-Methylenedioxy-$\Delta^{1(11a)}$-5,11-methanomorphanthridine (8)

Paraformaldehyde (16.2 mg, 0.54 mmol) was added to the solution of **33** (22.0 mg, 0.09 mmol) in formic acid (1 mL). The reaction mixture was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature and then partitioned between EtOAc (15 mL) and 10% aqueous NaOH (3 mL). The organic layer was washed with brine (2×3 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (Chromatorex NH, 9:1 hexane/EtOAc) provided **8** (16.6 mg, 72%) as a white solid; R_f=0.50 (9:1 $CHCl_3$/MeOH); mp 100.5–102.0 °C; $[\alpha]_{577}^{23}$ −100.6, $[\alpha]_{546}^{23}$ −111.8 (*c* 0.49, $CHCl_3$) [lit.[8b] $[\alpha]_{577}^{25}$ −96.6, $[\alpha]_{546}^{25}$ −131.4 (*c* 0.21, $CHCl_3$)]; IR (KBr) 2925, 1501, 1477, 1234, 1223, 1037, 935 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (m, 1H), 1.51 (m, 1H), 1.84 (m, 1H), 2.02–2.12 (m, 3H), 2.99 (br s, 2H, H-12), 3.15 (ddd, *J*=2.5, 4.6, 11.5 Hz, 1H, C4a-H), 3.24 (br s, 1H, H-11), 3.82 (d, *J*=16.6 Hz, 1H, H-5a), 4.34 (d, *J*=16.6 Hz, 1H, H-5b), 5.50 (q, *J*=2.8 Hz, 1H, H-1), 5.86 (d, *J*=1.4 Hz, 1H, OC*H*HO), 5.89 (d, *J*=1.4 Hz, 1H, OC*H*HO), 6.49 (s, 1H, H-7), 6.56 (s, 1H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1 (CH_2), 24.3 (CH_2), 28.3 (CH_2), 45.9 (CH), 55.2 (CH_2), 60.9 (CH_2), 63.5 (CH), 100.7 (CH_2), 106.8 (CH), 107.2 (CH), 115.1 (CH), 124.6 (C), 133.1 (C), 145.9 (C), 146.5 (C), 150.0 (C); HRMS (EI) calcd for $C_{16}H_{17}NO_2$ $(M)^+$ 255.1259, found 255.1278.

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