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Enantioselective construction of nitrogen-substituted quaternary carbon centers adjacent to the carbonyl group in the cyclohexane ring: first asymmetric synthesis of anesthetic (*S*)-ketamine with high selectivity

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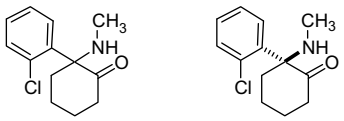
ABSTRACT

Enantioselective construction of nitrogen-substituted quaternary carbon centers adjacent to the carbonyl group in the cyclohexane ring was performed with respect to the asymmetric synthesis of anesthetic (*S*)-ketamine **1**. Diastereoselective nucleophilic 1,2-addition reaction of phenyllithium to α-ketoxime-ether acetal **9** bearing chiral auxiliary on the α-carbonyl function gave benzyloxyamine **11 major** in 83% yield with 82% de, which was converted to the corresponding amino ketone **12**. However, the reaction of 2-chlorophenyllithium did not work in which this route was unavailable for the synthesis of **1**. Then, an alternative strategy directed toward **1**, starting with a compound having 2-chlorophenyl groups in advance, was designed in which the chiral quaternary carbon center bearing a nitrogen atom in the ring is created by the enantioselective reduction of the atropisomeric intermediate ketone **18**, and the sequential allyl cyanate-to-isocyanate rearrangement with complete 1,3-chirality transfer. The first asymmetric synthesis of **1** with excellent selectivity (>99% ee) was accomplished by a short path according to the strategy.

1. Introduction

Ketamine **1**, 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, has been widely used as an anesthetic and analgesic in human and veterinary medicine under the trade name Ketalar since 1963.[1] The racemic ketamine **1** was prepared by Stevens through thermal isomerization of 1-[(2-chlorophenyl) (methylimino)methyl]-cyclopentanol.[2–5] The commercially available ketamine is a racemic mixture of two enantiomers (Chart 1). The (*S*)-enantiomer is shown to be more potent with an approximately 3–4 fold anesthetic potency compared to (*R*)-one: this correlates to the higher binding affinity for the PCP-site of the NMDA-receptor and only (*R*)-**1** is responsible for agitation, hallucination, and restlessness in contrast to (*S*)-**1**.[6] The more active (*S*)-**1** has been increasing in commercially available preparations. However, the enantiopure compound is only obtained via optical resolution of the tartaric acid salt,[7] leaving the undesired (*R*)-**1** as a by-product. Therefore, development of an asymmetric synthesis for the (*S*)-enantiomer is highly desirable. Recently, Brunner challenged an asymmetric rearrangement of 1-[(2-chlorophenyl) (methylimino)methyl]-cyclopentanol to optically active ketamine **1** with 2-[4-(*S*)-*tert*-butyloxazolin-2-yl]-pyridine coordinated Ni complexes but unfortunately the attempt resulted in failure, only giving a racemic product.[8] To the best of our knowledge, no successful synthesis of (*S*)-**1** has been reported.



racemic Ketamine **1** (*S*)-Ketamine **1**

Chart 1. Structure of target molecule.

On the other hand, a challenging methodology in organic synthesis prompted us to develop the enantioselective construction of quaternary carbon centers bearing a nitrogen atom, which are ubiquitous in naturally occurring pharmaceutical drugs (e.g., alkaloids),[9] but effective approaches are quite limited.[10] The difficulty on the case of (*S*)-**1** can be ascribed in part to the special requisite that the nitrogen-substituted quaternary carbon has an aryl group from the carbon and a carbonyl group adjacent to the carbon in the ring system. As part of our ongoing project to find a new reliable route to (*S*)-**1**, we applied a straightforward methodology, utilizing

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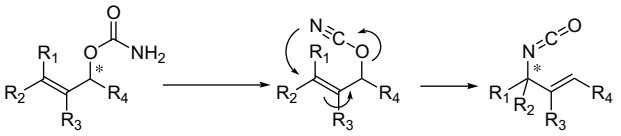


Scheme 1. 1,3-Chirality transfer via allyl cyanate-to-isocyanate rearrangement.

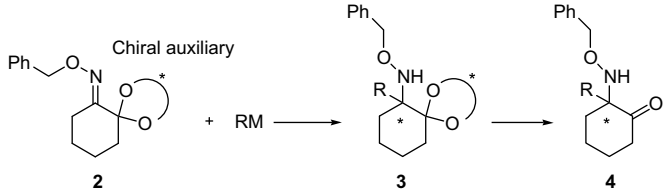
nucleophilic 1,2-addition to chiral α-ketoxime-ether acetals. The enantioselective 1,2-addition reaction of phenyllithium to the chiral imines proceeded with considerably high diastereoselectivity. After deprotection, the asymmetric synthesis of the chiral model compound was established. However, the reaction of 2-chlorophenyllithium did not work so that the method could not lead to the asymmetric synthesis of (*S*)-**1**. Then, we employed the plan using an allyl cyanate-to-isocyanate rearrangement (Scheme 1), recently developed by Ichikawa,[11] independent of the rearrangement developed by Stevens.[2] The strategy, with a combination of an enantioselective reduction and the rearrangement provided a novel and short route directed toward (*S*)-ketamine **1**. We describe herein the details of the foregoing 1,2-addition to chiral imines and disclose the first asymmetric synthesis of (*S*)-**1** by the sequential enantioselective reduction-rearrangement strategy.

2. Results and discussion

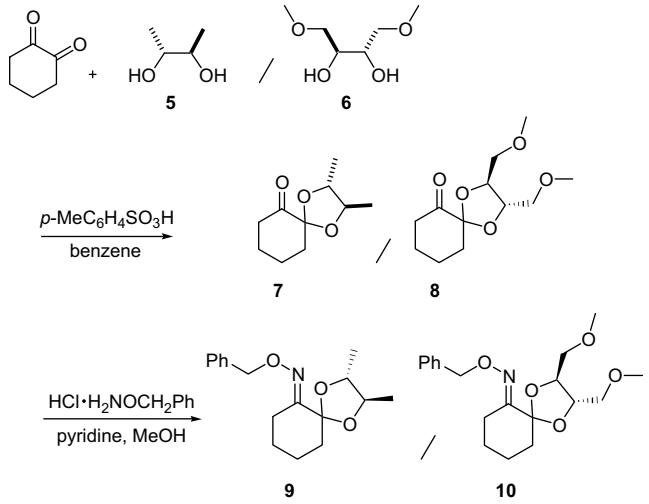
2.1. Enantioselective construction of quaternary carbon centers bearing a nitrogen atom by nucleophilic 1,2-addition to chiral α-ketoxime-ether acetals

Whereas chiral quaternary carbon centers have been generally realized by the asymmetric addition of nucleophiles to ketones, the enantioselective construction of nitrogen-substituted quaternary carbon centers by the straightforward addition to ketimines is regarded to be more difficult because of the poor electrophilic characteristic of ketimines in comparison with that of ketones.[12] As a model of simple routes to (*S*)-**1**, we considered employing nucleophilic addition of RM reagents to *N*-methylketimines, directly affording the*N*-methyl amine function necessary for **1**. After some preliminary studies, however, *N*-methylketimines turned out to be inadequate for the purpose because of their inherent instability. Then, the related ketoxime ethers were chosen as the starting electrophiles, which have the higher stability toward hydrolysis and can be efficiently purified by silica-gel column chromatography. While there are limited examples of the addition of organometallic reagents to chiral open-chain ketoxime ethers,[13,14] no example for the addition to cyclic ketoxime ethers has been reported. Thus, diastereoselective nucleophilic 1,2-addition reactions were designed to the ketoxime ethers modified the α-carbonyl group with chiral diol auxiliaries, as depicted in Scheme 2.

The availability of the chiral diol auxiliary has been reported[15] for the Grignard addition reactions to a chiral α-keto acetal and to a chiral α-aldoxime-ether acetal in the presence of $CeCl_3$. However, the utilization of such a chiral auxiliary has not been reported for the enantioselective addition to ketimines with regard to the asymmetric



Scheme 2. Diastereoselective addition with chiral auxiliaries.



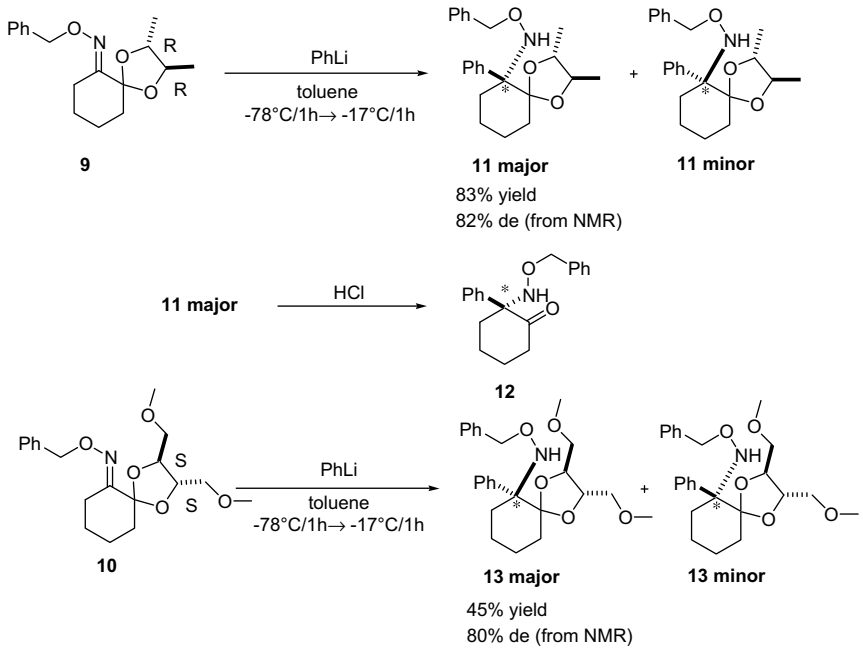
Scheme 3. Preparation of chiral α-ketoxime-ether acetals.

construction of nitrogen-substituted quaternary carbon centers. We chose C2-symmetric diols, (−)-(2*R*,3*R*)-2,3-butanediol **5** and (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol **6**, suitable for our purposes. Chiral α-ketoxime-ether acetals **9** and **10** were prepared via the corresponding **7** and **8**, as shown in Scheme 3.

The results of the diastereoselective addition are shown in Scheme 4. The reaction of α-ketoxime-ether acetal **9** with PhLi proceeded well in toluene (−78 °C/1 h and then −17 °C/1 h) to afford a diastereomeric mixture **11** in 83% yield. A diastereoselectivity of 82% was determined using the methyl proton signals of the relative acetal moieties in the ^{1}H NMR spectra. After separation using silica-gel column chromatography, the **11 major** was subjected to acid hydrolysis with HCl to afford amino ketone **12** in a quantitative yield. The enantioselectivity of **12** was confirmed to be 82% ee by using HPLC with a DAICEL CHIRALPAK IA column (mobile phase: *n*-hexane/dichloromethane/diethylamine=90/10/0.1, retention times: 19 min for *S* and 27 min for *R* under a flow rate of 1.0 mL/min). Determination of the absolute configuration of the stereogenic center in **11 major** using NMR spectroscopy techniques was quite difficult because of its quaternary carbon. Then, using fine crystals recrystallized from *n*-hexane, the absolute configuration of the chiral center was determined to be ***R*** by X-ray diffraction analysis,[16] as shown in Figure 1.

In the result, it was shown that the (*R*,*R*)-chiral acetal auxiliary induces (*R*)-configuration at the newly created stereocenter. A stable conformer of the encountered complex, comprised of **9** and phenyllithium, was optimized by the calculation at the Density Functional Theory B3LYP/6-31G* level: all computations have been done using the GAUSSIAN 03 code, 98,[17] as shown in Figure 2. The trajectory of the phenyl anion responsible for the resulting (*R*)-configuration can be explained with its approach to the upper site of the C=N double bond so as to avoid the steric hindrance induced by the coordinated phenyllithium. On the other hand, the reaction of **10** with phenyllithium also proceeded with nearly the same de but the yield was comparatively low presumably owing to the excessive steric bulkiness of the acetal moiety bearing additional methoxy groups.

Unexpectedly, the 1,2-addition reaction of chiral α-ketoxime-ether acetal **9** with 2-chlorophenyllithium, prepared from 2-bromochlorobenzene with *n*-butyllithium in THF at −78 °C,[18] did not proceed because of the increased steric hindrance arising from the *ortho*-chloro substituent of the nucleophile (Scheme 5). The addition of $BF_3{\cdot}OEt_2$[19] could not apparently improve the addition reaction. This method, based on the enantioselective construction of



Scheme 4. Diastereoselective addition of phenyllithium to α-chiral ketoxime-ether acetals.

nitrogen-substituted quaternary carbon centers by the straightforward addition to chiral α-ketoxime-ether acetals, was conclusively found to be less promising for the asymmetric synthesis of (*S*)-ketamine **1**.

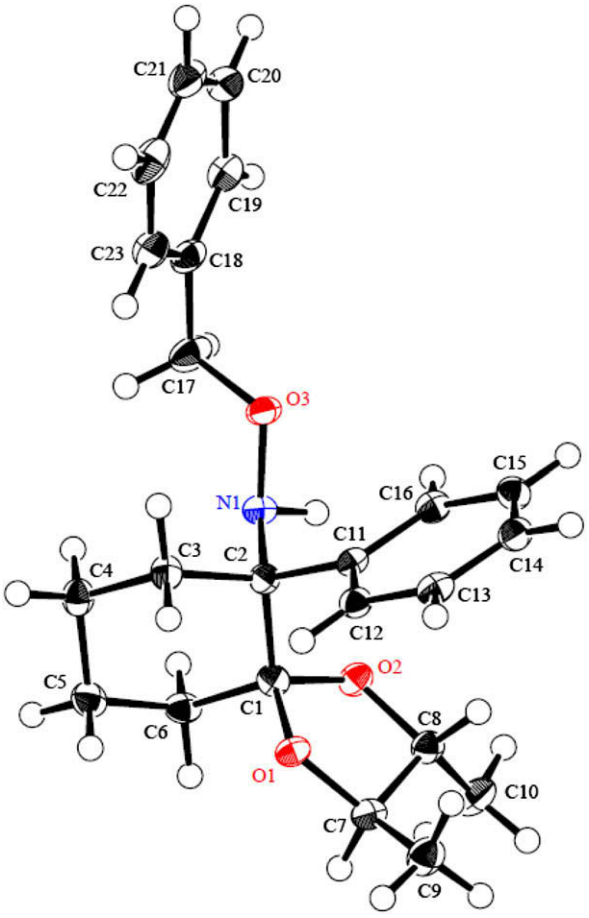


Figure 1. ORTEP drawing of **11 major**.

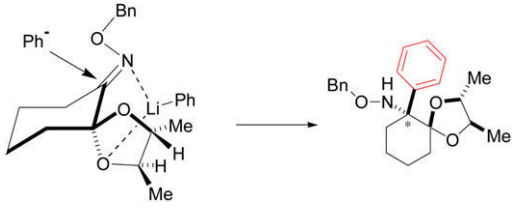
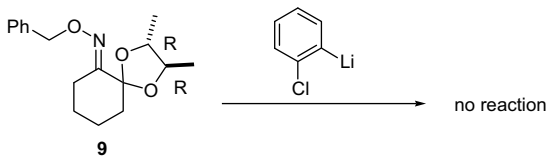


Figure 2. Trajectory of nucleophile to afford (*R*)-enantiomer.

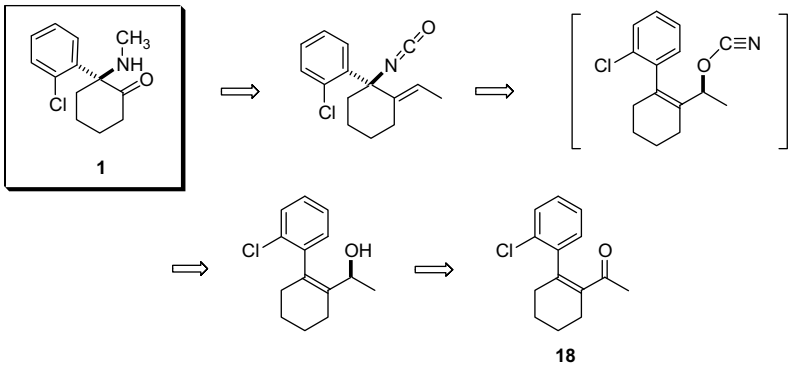
2.2. Asymmetric synthesis of (*S*)-ketamine by the strategy of enantioselective reduction and sequential allyl cyanate-to-isocyanate rearrangement

*2.2.1. Synthetic strategy directed toward (S)-1 and preparation of synthetic intermediate ketone **18***

As appeared in the Stevens' first synthesis of racemic ketamine, it looks promising to utilize a rearrangement reaction for constructing such a structure with highly converged steric features. Recently, Ichikawa et al. have presented the validity of applying allyl cyanate-to-isocyanate rearrangement to the construction of quaternary carbon centers bearing a nitrogen atom.[20] They confirmed, through the adaptation to acyclic systems, that the [1,3]-chirality transfer in the rearrangement takes place in a stereospecific manner without any scrambling at the stereogenic centers. The efficiency of the rearrangement persuaded us to adapt it in an effective and novel route directed toward (*S*)-ketamine **1**, as shown in Scheme 6. The retrosynthesis of (*S*)-**1** revealed that ketone **18** is suitable as a starting material. As outlined in Scheme 7, the synthetic intermediate **18** was prepared from ethyl (2-chlorobenzoyl)acetate **14**,[21] according to Fleming's procedure.[22]



Scheme 5. Difficult 1,2-addition of 2-chlorophenyllithium to **9**.

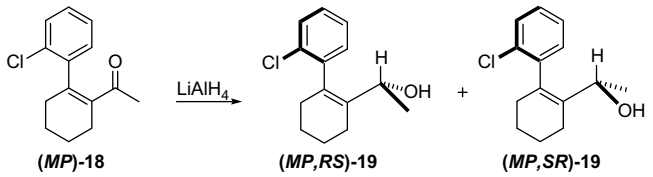


Scheme 6. Retrosynthesis on synthetic strategy directed toward (*S*)-ketamine.

2.2.2. *Atropisomerism on alcohol **19***

Before choosing an appropriate enantioselective reduction of ketone **18**, we prepared racemic alcohol **19** by lithium aluminum hydride reduction as a standard sample for chiral HPLC analysis to check the selectivity of the following enantioselective reduction. The reduction of **18** in diethyl ether or THF occurred without any problems at room temperature under usual conditions but the product was found to be a mixture of diastereomers. The appearance of the diastereoisomers is attributable to a new stereocenter induced by an atropisomerism[23] resulting from hindered rotation about the single bond between the *ortho*-substituted phenyl and cyclohexene rings, which were related to (*MP*,*RS*)-**19** ((*aRaS*,*RS*)-**19**) and (*MP*,*SR*)-**19** ((*aRaS*,*SR*)-**19**),[24] as represented in Scheme 8. The diastereoisomers had a ratio of almost 1 to 1, which was estimated from the two doublet peaks corresponding to the methyl groups in the ^{1}H NMR spectra. The ratio suggests that the reaction stereochemistry in the reduction was scarcely affected by the direction of the *ortho*-chloro substituent. Unfortunately, the diastereoisomers could not be separated to each pure state where the interconversion of them took place under the conditions of silca-gel column chromatography. It has become apparent that the steric hindrance to rotate could be considerably low for the isolation of the diastereoisomers.

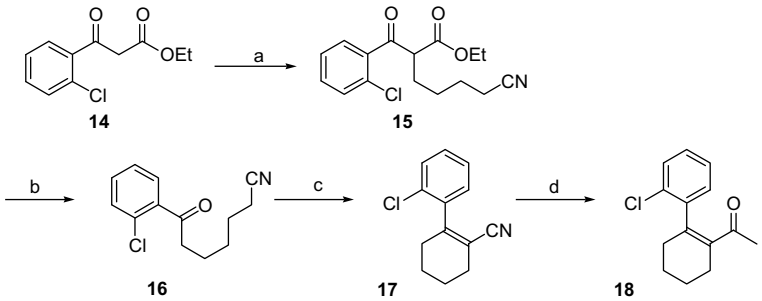
The phenomenon of the interconversion was confirmed by HPLC measurement through the interaction of the four enantiomers with the chiral material packed in the column: the four peaks were observed in the chromatogram of a DAICEL CHIRALCEL OD-H. Excessive overlaps were observed in their peaks between **I** and **IV** and between **II** and **III**, respectively (Fig. 3). These two pairs correspond to each distinguishable epimerization on atropisomerism, where the assignment of the structures; ***P*–*S***, ***M*–*S***, ***M*–*R***, and ***P*–*R***, to the corresponding peaks remains unclear at this stage. We observed an additional interesting finding with regard to the partial epimerization on the atropic axis that a diastereomer isomerized toward the more stable another diastereomer in a ratio of 5 to 1 after standing in the solid state at room temperature for 2 months.[25] The



Scheme 8. Preparation of racemic alcohols **19**.

ideal rotational barrier on the atropisomers and the related structures were investigated by the Density Functional Theory, as mentioned above.[17] The results are illustrated in Figure 4. The calculation of the potential energy was performed every 10° along the dihedral angle around the atropic axis. Two stable structures of **A** and **B** were optimized: **A** was more stable than **B** by 4.7 kcal/mol, where in **A** the *ortho*-chloro substituent and the alcohol moiety were situated at opposite side (*anti*) and the reverse was found for **B** (*syn*). The rotational energy barrier was 22.8 kcal/mol.

As a result, the enantiomeric purity of the product alcohol obtained in the expected enantioselective reduction could not be directly determined. Then, in order to enable the determination of the enantioselectivity by preventing the rotation, the resulting racemic alcohols **19** were transformed into the corresponding benzoyl derivatives **20** in almost quantitative yields; the mixture of **20** showed only one spot on the TLC, and the two isomers could not be separated by silica-gel column chromatography. By the ^{1}H NMR measurement, the isomeric ratio (2.66:1) of **20** was found to be changed from the original ratio (1:~1) of **19**, which is presumably due to the isomerization during the process of benzoylation. The more stable isomer of **20** was confirmed to be *anti* by the calculation study. However, the interconversion between the two atropisomers of **20** was found to be surely restricted due to the steric bulkiness of the introduced benzoyl group by checking their chromatogram of a DICEL CHIRALPAK IA column (mobile phase: *n*-



Scheme 7. Synthesis of synthetic intermediate ketone **18**. Reagents and conditions: (a) 5-bromovaleronitrile, NaH, NaI, THF, reflux, 24 h, 85%; (b) aq NaOH, 80 °C, 12 h, 76%; (c) *t*-BuOK, THF, reflux, 4–5 h, 57%; (d) Mg, MeI, ether then toluene, reflux, 3 h, 82%.

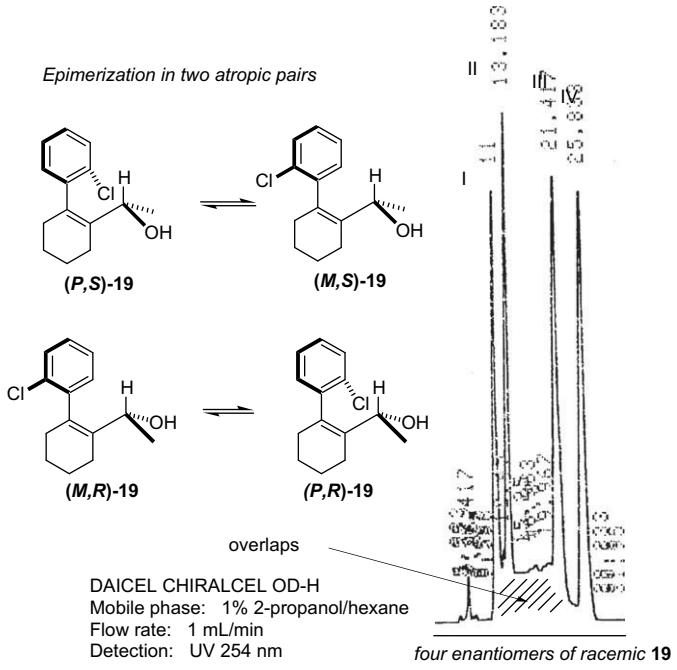


Figure 3. Epimerization on diastereomeric atropisomers **19**.

hexane, retention times: 6 min for (*P*,*S*)-**20** and 7 min for (*M*,*R*)-**20** and 10 min for (*M*,*S*)-**20** and 14 min for (*P*,*R*)-**20** under flow rate of 2.0 mL/min), in which the ratios of two diastereoisomers were observed to be almost the same as those of NMR (Fig. 5).

2.2.3. Chirality introduction by enantioselective reduction

On the basis of the above results, we next focused our attention on the enantioselective reduction of ketone (*MP*)-**18**. Our first choice for the enantioselective reduction was the Noyori's classical BINAL-H reduction,[26] which is known to be effective for α,β-olefinic ketones. Considering the concerted six-membered cyclic transition state of 1,3-chirality transfer in the subsequent rearrangement, we were aware that (*S*)-configuration is necessary for alcohol **19** for the

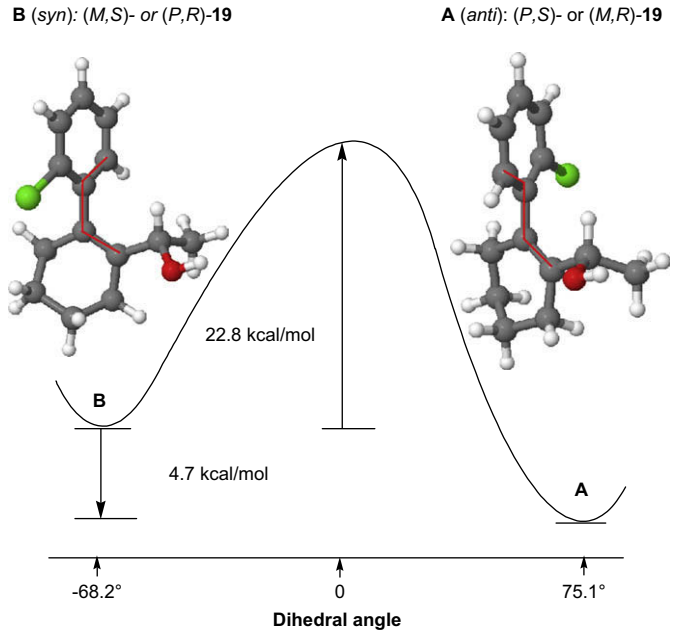


Figure 4. Rotaional barrier and optimized structures of atropisomers (B3LYP/6-31G* level).

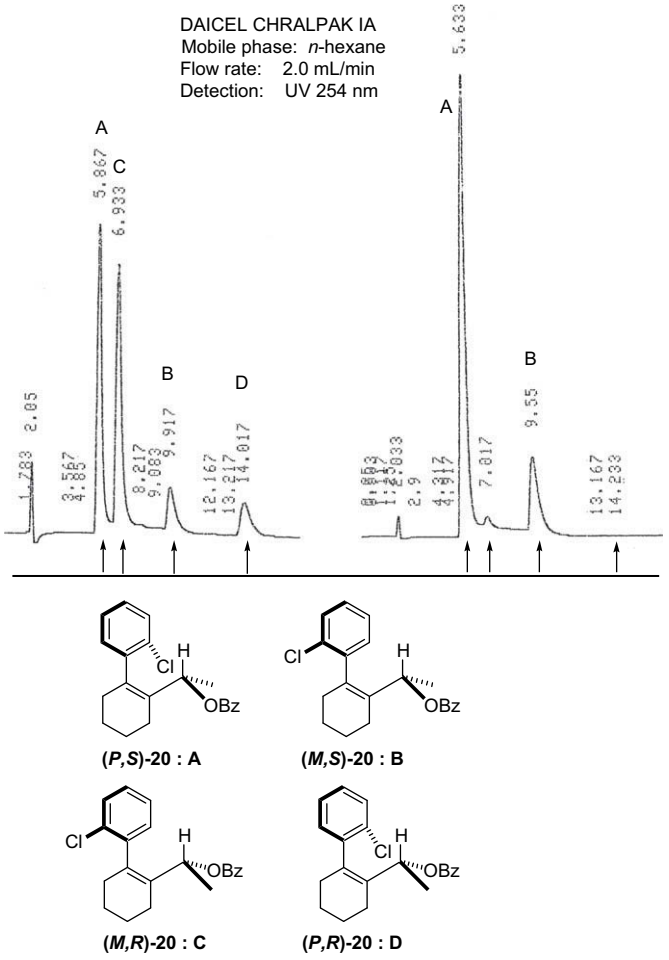
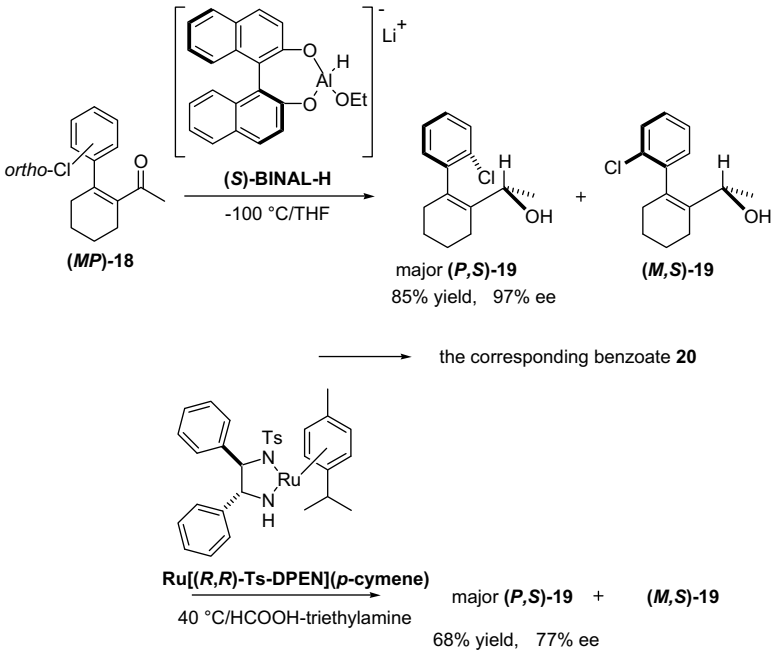


Figure 5. Determination (97% ee of *S*) of enantioselectivity by a chiral HPLC method with the benzoates **20** derived from the alcohols **19**, obtained in (*S*)-BINAL-H reduction.

asymmetric synthesis of (*S*)-**1**, and therefore (*S*)-BINAL-H is a suitable reagent. Treatment of **18** with (*S*)-BINAL-H in THF at −100 °C resulted in the production of atropisomeric alcohols **19** in 85% yield, as shown in Scheme 9. The resulting alcohols were transferred into the corresponding benzoyl derivatives **20** in a quantitative yield in order to determine the enantioselectivity of the reduction. Judging from the methyl signals of the ^{1}H NMR spectra of **20**, the diastereomeric ratio was determined to be 1.93:1. Needless to say, the change of the ratio can be ascribed to the epimerization on the atropisomerism during the benzoylation process. Determination of the enantiomeric purity was performed by chiral HPLC analysis using a mixture of **20**, as shown in Figure 5. By direct comparison with an authentic chromatogram of the racemates, the major pair (A and C) and the minor pair (B and D) of the diastereisomers turned out to have 96% ee of (*S*)-isomer and >99% ee of (*S*)-isomer, respectively. As a whole, the total enantioselectivity in the (*S*)-BINAL-H reduction of **18** was calculated to be 97% ee. This excellent enantioselection suggests that the newly created chiral center is almost completely controlled by the chirality of the catalyst,[27] regardless of the stereochemistry of the substrate ketone concerned with the atropisomeric *ortho*-chloro substituent. In addition, we explored Noyori's ruthenium-catalyzed asymmetric transfer hydrogenation[28] of **18** as a more practical catalytic method. [(1*R*,2*R*)-*N*-(*p*-Toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium(II), Ru[(*R*,*R*)-Ts-DPEN](*p*-cymene), served as an efficient catalyst for the enantioselective reduction of **18** to (*S*)-alcohol in a 5 to 2 formic acid-triethylamine azeotropic mixture at 40 °C. The enantioselectivity of the conversion, however, was not excellent (77% ee).

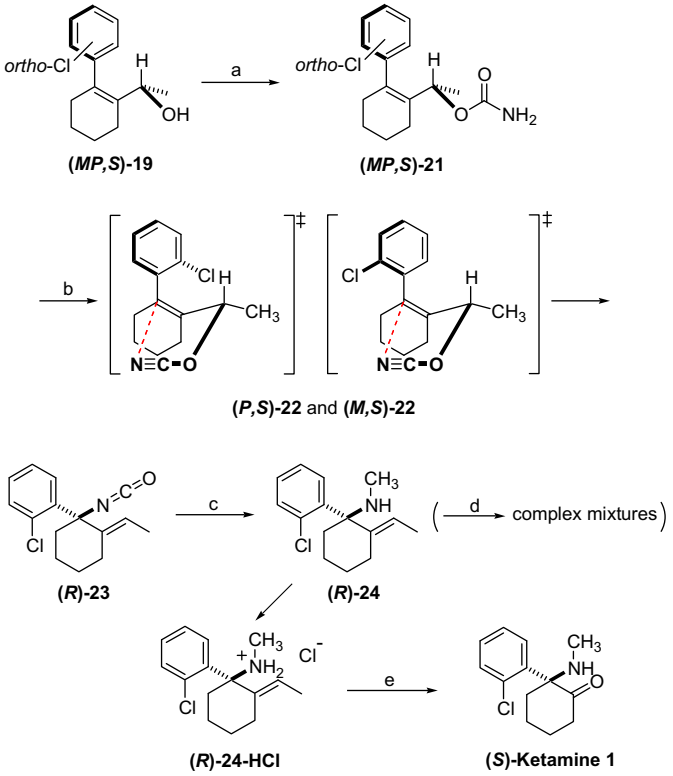


Scheme 9. Stoichiometric and catalytic 'Noyori' enantioselective reductions of ketone **18**.

2.2.4. Completion of asymmetric synthesis of (S)-ketamine

The reaction sequence from the diastereomeric optically active alcohols (*MP*,*S*)-**19** to (*S*)-ketamine **1** is as follows (Scheme 10). Reaction of **19** with trichloroacetyl isocyanate in dichloromethane at 0 °C and subsequent hydrolysis with potassium carbonate in an aqueous methanol provided carbamate (*MP*,*S*)-**21** in 96% yield. The carbamate **21** was also a diastereomeric mixture of the atropisomers and without further purification was employed as a precursor to the cyanates, (*P*,*S*)-**22** and (*M*,*S*)-**22**, for the successive allyl cyanate-to-isocyanate rearrangement. According to Ichikawa's procedure,[11,20] dehydration of **21** was carried out with triphenylphosphine, carbon tetrabromide, and triethylamine at 0 °C for 20 min as to provide the transient allyl cyanate. During the one-pot procedure, the expected sigmatropic rearrangement took place to convert **22** to the corresponding isocyanate (*R*)-**23**. Fortunately, the isocyanate was quite stable for the isolation process using an aqueous work-up and isolated as a single isomer in 98% yield. The stability of **23** is ascribed to its clearly inherent sterically hindered structure. This easy isolation of **23** led to a shortening of the reaction path to the methyl amine moiety necessary for ketamine. In practice, treatment of **23** with lithium aluminum hydride in THF provided the methyl amine (*R*)-**24** in 92% yield.

The final stage toward ketamine is only the conversion of the functional group from the double bond to the carbonyl group. Ozonolysis of **24** in dichloromethane at −18 °C followed by a reductive work-up with dimethyl sulfide resulted in a miserable mixture. Presumably, the participation of the basic allylic amino function to the intermediate ozonide might have disturbed the normal ozonolysis. Then, the hydrogen chloride salt of **24** was furnished for the ozonolysis in methanol. Expectedly, the reaction proceeded smoothly to give the final product of **1**, as the hydrogen chloride salt, which was crystallized from ethanol-*n*-hexane in 95% yield. The synthetic ketamine **1** was determined to be >99% ee with the almost complete enantiomeric purity of the (*S*)-configuration by chiral HPLC analysis, as illustrated in Figure 6. Here, the first asymmetric synthesis of (*S*)-ketamine has been accomplished via a short path with excellent selectivity. On the basis of the production of (*S*)-**1** in maintaining the level of the chirality of the starting alcohol **19**, the 1,3-chirality transfer in the [3,3]-sigmatropic rearrangement was reevaluated to be stereospecific with the concerted mechanism via the six-membered cyclic transition state in this investigation. Optically pure (*R*)-ketamine was also synthesized by starting with (*R*)-alcohol **19** from the enantioselective reduction of ketone **18** with (*R*)-BINAL-H.



Scheme 10. Completion of asymmetric synthesis of (*S*)-ketamine via rearrangement. Reagents and conditions: (a) CCl_3CONCO, CH_2Cl_2, aq K_2CO_3/MeOH, 96%; (b) PPh_3, CBr_4, Et_3N, CH_2Cl_2, 0 °C, 98%; (c) $LiAlH_4$, THF, 92%; (d) O_3, CH_2Cl_2, 50 min, Me_2S; (e) O_3, MeOH, 50 min, Me_2S, 95%.

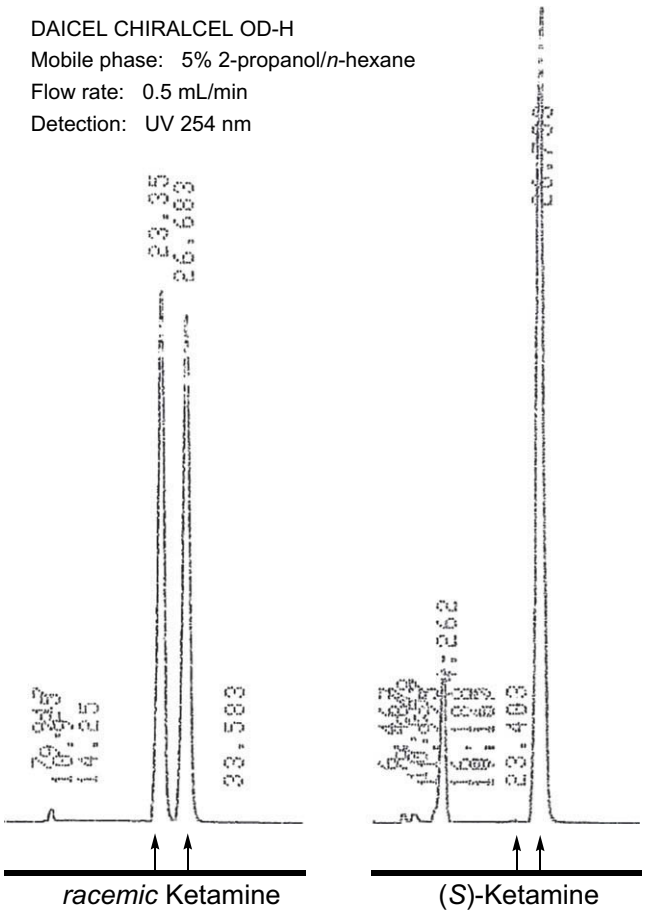


Figure 6. Determination of enantiopurity of synthetic (*S*)-ketamine.

3. Conclusion

The enantioselective construction of nitrogen-substituted quaternary carbon centers in the ring like (*S*)-ketamine was a very difficult challenge. First, we have established a straightforward method for the construction of a chiral nitrogen-substituted quaternary carbon center using an enantioselective 1,2-addition reaction of phenyllithium to chiral α-ketoxime-ether acetals, **9** and **10**, having α-chiral acetal auxiliary. After deprotection, the approach provided the chiral compound with a nitrogen-substituted quaternary carbon bearing α-carbonyl group. However, the reaction of 2-chlorophenyllithium did not work so that this route was unavailable for the synthesis of (*S*)-ketamine **1**. An alternative strategy was adapted to the synthesis, consisting of the enantioselective reduction of the atropisomeric intermediate ketone **18** and the sequential allyl cyanate-to-isocyanate rearrangement with 1,3-chirality transfer. The enantioselective reduction using (*S*)-BINAL-H gave (*S*)-alcohol **19** with 97% ee. Subsequently, the complete 1,3-chirality transfer of the carbamate **21**, derived from the alcohol, was observed to afford the corresponding isocyanate **23** in the [3,3]-sigmatropic allyl cyanate-to-isocyanate rearrangement. Thus, the first asymmetric synthesis of (*S*)-ketamine **1**, after reduction and ozonolysis, was accomplished with excellent selectivity (>99% ee).

4. Experimental

4.1. General

All reactions unless otherwise noted were carried out under an argon atmosphere. Flash column chromatography was carried out using Merck 60 silica-gel (230–400 mesh). Unless otherwise noted, all infrared spectra (IR) are reported in wave number (cm^{-1}). ^1H and ^{13}C NMR spectra are reported; chemical shifts are expressed in parts per million relative to internal standard tetramethylsilane (coupling constants: Hz). High resolution mass spectra (HRMS) are reported in *m*/*z*.

4.2. Synthesis of ketones having an acetal moiety

A solution of 1,2-cyclohexanedione (22.4 mmol, 2.51 g) and diol (22.4 mmol) in benzene (30 mL) was refluxed overnight with *p*-TsOH (8 mg) under a Dean–Stark water separator. Ether (30 mL) was added and unchanged diketone was extracted with 10% NaOH (aq) (15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residual oil was purified by flash column chromatography on silica-gel.

*4.2.1. 2-Oxocyclohexanone (1R,2R)-1,2-dimethylethylene acetal (**7**)*

Colorless oil; (3.62 g, 88%): $[\alpha]_D^{22}$ 15.0 (*c* 1.00, $CHCl_3$); IR (neat): 2972, 2870, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, d, *J*=7.3), 1.28 (3H, d, *J*=7.3), 1.82–1.97 (6H, m), 2.48–2.54 (1H, m), 2.58–2.62 (1H, m), 3.61–3.73 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.4, 22.2, 25.9, 37.6, 39.2, 78.6, 78.7, 105.7, 206.0.

*4.2.2. 2-Oxocyclohexanone (1S,2S)-1,2-dimethoxyethylene acetal (**8**)*

Colorless oil; (4.45 g, 80%): $[\alpha]_D^{22}$ −29.0 (*c* 1.00, $CHCl_3$); IR (neat) 2939, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70–1.79 (1H, m), 1.80–1.92 (3H, m), 1.95–2.05 (2H, m), 2.48–2.55 (1H, m), 2.59–2.67 (1H, m), 3.37 (3H, s), 3.40 (3H, s), 3.43 (1H, d, *J*=4.4), 3.51–3.56 (3H, m), 4.01–4.05 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 26.4, 37.9, 39.7, 59.3, 59.5, 72.4, 73.2, 77.8, 78.5, 107.9, 206.8.

4.3. Synthesis of α-ketoxime-ether acetals

To a solution of ketone (10.2 mmol) in MeOH (30 mL) were added $HCl{\cdot}H_2NOCH_2Ph$ (10.2 mmol, 1.63 g) and pyridine (30.6 mmol, 3 mL). The reaction mixture was refluxed for 30 min. After solvent evaporation, water (15 mL) was added to the residue. The mixture was extracted with ether (30 mL). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was subjected to flash column chromatography on silica-gel.

*4.3.1. 2-Benzyloxyiminocyclohexanone (1R,2R)-1,2-dimethylethylene acetal (**9**)*

Colorless oil; (2.51 g, 85%): $[\alpha]_D^{22}$ −24.2 (*c* 0.33, $CHCl_3$); IR (neat): 2970, 2935, 2865, 1496, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, *J*=5.6), 1.23 (3H, d, *J*=5.6), 1.62–1.52 (2H, m), 1.70–1.76 (2H, m), 1.85–1.90 (2H, m), 2.56 (1H, ddd, *J*=14.0, 7.4, 5.5), 2.67 (1H, ddd, *J*=14.0, 7.4, 5.5), 3.6 (1H, dq, *J*=8.9, 5.6), 3.63 (1H, dq, *J*=8.9, 5.6), 5.14 (2H, dd, *J*=14.0, 12.0), 7.27–7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.7, 22.8, 24.1, 24.9, 38.5, 75.6, 78.0, 79.2, 105.5, 127.5, 128.0, 138.3, 158.7; HRMS (FAB) calcd for $C_{17}H_{23}NO_3$ $[M+H]^+$ 290.1757, found 290.1763.

*4.3.2. 2-Benzyloxyiminocyclohexanone (1S,2S)-1,2-dimethoxyethylene acetal (**10**)*

Colorless oil; (2.73 g, 76%): $[\alpha]_D^{25}$ −18.0 (*c* 1.00, $CHCl_3$); IR (neat): 3030, 2934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53–1.61 (2H, m), 1.72–1.78 (2H, m), 1.88–1.91 (2H, m), 2.53–2.62 (1H, m), 2.64–2.73 (1H, m), 3.16 (1H, dd, *J*=10.0, 5.0), 3.34–3.41 (1H, m), 3.26 (3H, s), 3.38 (3H, s), 3.51 (2H, d, *J*=4.4), 3.90–3.96 (2H, m), 5.13 (2H, dd, *J*=14.8, 11.8), 7.26–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 24.0, 24.9, 38.3, 59.2, 59.4, 72.8, 73.6, 75.5, 78.0, 78.1, 107.2, 127.6,

128.0, 128.3, 138.5, 158.5; HRMS (FAB) calcd for $C_{19}H_{27}NO_5$ $[M+H]^+$ 350.1968, found 350.1977.

4.4. Typical 1,2-additon reaction of PhLi to chiral α-ketoxime-ether acetals

To a stirred solution of chiral α-ketoxime-ether acetal **9** (0.98 mmol, 283 mg) in toluene (5 mL) was PhLi (2.94 mmol) at −78 °C. The solution was stirred for 1 h at −78 °C and then was allowed to warm to −17 °C. After stirring for 1 h, the reaction mixture was quenched by the addition of satd $NaHCO_3$ (aq) (5 mL) at −7 °C. The reaction mixture was extracted with Et_2O (10 mL). The combined organic layers were dried over anhydrous K_2CO_3. After evaporation of the solvent, the resulting residue was purified by silica-gel column chromatography to give a mixture of **11** (305 mg, 83% yield). The diastereoselectivity of **11** was determined to be 82% de by using the relative methyl doublet signals (7.25 (major) and 8.23 (minor) ppm) in its ^{1}H NMR spectrum. The isomers were separated by silica-gel column chromatography. The major isomer was recrystallized from *n*-hexane to afford the fine crystals (mp 78 °C), adequate for X-ray study.

*4.4.1. (2R)-2-Benzyloxyamino-2-phenylcyclohexanone (1R,2R)-1,2-dimethylethylene acetal ((R,R,R)-**11**)*

Colorless crystals; Mp 78 °C (*n*-hexane): $[\alpha]_D^{23}$ 24.5 (*c* 2.00, $CHCl_3$); IR (KBr) 2950, 2927, 2898, 2859, 1496, 1445 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, d, *J*=6.5), 0.91 (3H, d, *J*=6.5), 1.43 (1H, d, *J*=12.8), 1.53–1.70 (3H, m), 1.92 (1H, tq, *J*=12.7, 3.1), 2.03 (1H, dt, *J*=12.7, 5.7), 2.15–2.24 (1H, m), 2.25–2.27 (2H, m), 3.34 (1H, dq, *J*=8.6, 5.7), 4.74 (2H, dd, *J*=20.8, 11.5), 6.46 (1H, m), 7.20–7.34 (8H, m), 7.50–7.52 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 16.9, 20.7, 23.8, 29.5, 33.7, 68.6, 76.3, 77.3, 78.7, 108.6, 126.3, 126.9, 127.4, 128.1, 128.2, 128.8, 138.6, 140.8; HRMS (FAB) calcd for $C_{23}H_{29}NO_3$ $[M+H]^+$ 368.2227, found 368.2231.

*4.4.2. (2S)-2-Benzyloxyamino-2-phenylcyclohexanone (1S,2S)-1,2-dimethoxyethylene acetal ((S,S,S)-**13**)*

Colorless paste: IR (KBr) 2928, 1497, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.54 (2H, m), 1.69 (2H, br s), 1.86–1.91 (1H, m), 1.86–1.91 (1H, m), 1.98–2.01 (1H, m), 2.22–2.25 (1H, m), 2.29–2.36 (1H, m), 2.70 (2H, br s), 2.74–2.78 (1H, m), 3.21 (3H, s), 3.24–3.30 (2H, m), 3.28 (3H, s), 3.72–3.75 (1H, m), 4.70 (2H, dd, *J*=22.0, 13.0), 6.46 (1H, s), 7.23–7.38 (8H, m), 7.51 (2H, d, *J*=8.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 23.7, 29.4, 33.8, 59.1, 59.3, 68.6, 72.8, 73.3, 76.3, 77.1, 78.8, 111.6, 126.5, 127.0, 127.1, 127.3, 127.4, 128.2, 138.6, 140.9; HRMS (FAB) calcd for $C_{25}H_{33}NO_5$ $[M+H]^+$ 428.2438, found 428.2431.

4.5. (2*R*)-2-Benzyloxyamino-2-phenylcyclohexanone (12) from deacetalization of (*R*,*R*,*R*)-11

To a stirred solution of (*R*,*R*,*R*)-**11** (100 mg, 0.27 mmol) in MeOH (3.6 mL) was added 36% HCl (aq) (5.7 mL). The solution was stirred at 50 °C overnight. After solvent evaporation, the resulting mixture was extracted with ether (10 mL). The organic layer was washed with satd K_2CO_3 (aq) (3 mL) and dried over anhydrous Na_2SO_4. The crude was purified by flash column chromatography on silica-gel to give **12** (271 mg, 92% yield). Colorless oil: $[\alpha]_D^{23}$ −163.0 (*c* 2.00, $CHCl_3$); IR (neat) 2943, 2864 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (2H, m), 1.84 (1H, m), 1.94 (1H, m), 2.29 (2H, m), 2.49 (1H, m), 2.75 (1H, ddd, *J*=14.4, 5.6, 3.2), 4.59 (2H, s), 6.35 (1H, s), 7.40–7.24 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 26.9, 32.9, 40.5, 73.8, 77.2, 127.5, 127.6, 128.2, 128.3, 128.4, 128.9, 136.8, 137.7, 210.7; HRMS (FAB) calcd for $C_{19}H_{21}NO_2$ $[M+H]^+$ 296.1651, found 296.1650.

4.6. Ethyl (2-chlorobenzoyl) (4-cyanobutyl)acetate (15)

Ethyl (2-chlorobenzoyl)acetate **14** (3.20 g, 14.1 mmol), [IR (film) 2982, 1741, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.27 (3H, t, *J*=7.7), 4.00 (2H, s), 4.19–4.25 (2H, q, *J*=7.7), 7.47–7.96 (5H, m)], was added dropwise to a stirred THF (60 mL) slurry of NaH (408 mg, 17.0 mmol) at 0 °C. To the resulting solution were added 5-bromovaleronitrile (2.12 mL, 18.3 mmol) and solid NaI (417 mg, 2.8 mmol) and then the reaction mixture was heated at reflux. After 24 h, the reaction was allowed to cool, a saturated aqueous NH_4Cl solution (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with AcOEt (20 mL×3). The combined organic layers were dried (Na_2SO_4). After concentration of the solvent under reduced pressure, the residue was purified by flash chromatography on silica-gel (20% AcOEt/hexane) to afford ketoester **15** (3.69 g, 85%). IR (film) 2245, 1736, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.16 (keto: 3H, t, *J*=6.8), 1.37 (enol: 3H, t, *J*=6.8), 1.45–1.60 (m), 1.69–1.74 (m), 1.98–2.04 (m), 2.16 (enol: 2H, t, *J*=7.2), 2.36 (keto: 2H, t, *J*=7.2), 4.13 (keto: 2H, q, *J*=6.8), 4.27 (enol: 1H, t, *J*=6.8), 4.34 (enol: 2H, q, *J*=6.8) 7.30–7.50 (4H, m). ^{13}C NMR ($CDCl_3$): δ Keto form: 13.8, 16.8, 25.1, 26.4, 27.3, 57.3, 61.4, 119.3, 126.8, 129.2, 130.3, 130.5, 132.1, 138.1, 173.0, 197.6; Enol form: 14.1, 16.6, 24.6, 25.5, 28.3, 60.9, 102.4, 119.4, 126.7, 129.6, 129.8, 130.8, 132.0, 133.9, 168.6, 168.9.

4.7. 2-Chlorophenyl 5-cyanopentyl ketone (16)

An aqueous NaOH (2 M, 14 mL) solution was added to an ethanolic solution (5 mL) of **15** (5.49 g, 17.8 mmol). The reaction mixture was heated at 80 °C for 12 h. The resulting solution was acidified at 0 °C by 1 M HCl until a pH of 2. The organic layer was separated, the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica-gel (10% EtOAc/hexane) to afford cyanoketone **16** (3.19 g, 76%). IR (film) 2245, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.54 (2H, m), 1.74 (4H, oct, *J*=7.0), 2.37 (2H, t, *J*=7.0), 2.97 (2H, t, *J*=7.0), 7.30–7.45 (4H, m); ^{13}C NMR ($CDCl_3$): δ 17.0, 23.2, 25.3, 28.1, 119.6, 127.0, 128.7, 130.6, 130.8, 131.7, 139.5, 203.1.

4.8. 1-(2-Chlorophenyl)-2-cyano-1-cyclohexene (17)

Solid *t*-BuOK (602 mg, 5.37 mmol) was added to a refluxing THF solution of **16** (900 mg, 4.47 mmol) in THF (200 mL). After 5 h, the solution was cooled to room temperature. A saturated aqueous NH_4Cl (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with ether (30 mL×3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica-gel (20% EtOAc/hexane) to give nitrile **17** (555 mg, 57%). IR (film) 2211, 1470, 1431 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.79 (4H, br s), 2.24 (1H, br s), 2.42 (2H, br s), 2.59 (1H, br s), 7.16–7.22 (1H, m), 7.26–7.34 (2H, m), 7.41–7.50 (1H, m); ^{13}C NMR ($CDCl_3$): δ 21.2, 21.5, 27.4, 30.9, 111.0, 118.4, 127.1, 129.1, 129.6, 129.9, 131.6, 139.2, 154.5; HRMS (FAB) calcd for $C_{13}H_{12}NCl$ $[M+H]^+$ 218.0737, found 218.0726.

4.9. 1-Acetyl-2-(2-chlorophenyl)-1-cyclohexene (18)

To an ethereal solution (1.5 mL) containing magnesium turning (104 mg, 4.31 mmol) was added a solution of methyl iodide (335 μL, 5.0 mmol) in Et_2O (1.0 mL). When the reaction was complete, dry toluene (4.5 mL) was added. After the ether solvent was evacuated under reduced pressure, nitrile **17** (468 mg, 2.15 mmol) was added. The resulting solution was stirred at 100 °C. After cooling, 5 M hydrochloric acid (5 mL) was added. Then, the mixture was stirred at 90 °C for 12 h. The separated organic layer was washed with a dilute aqueous $NaHCO_3$ solution (5 mL) and dried ($MgSO_4$). After

concentrated under reduced pressure, the crude was purified by flash chromatography on silica-gel (10% EtOAc/hexane) to give ketone **18** (439 mg, 87%). IR (film) 1663 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.67–1.76 (1H, m), 1.73 (3H, s), 1.98–2.00 (1H, m), 2.10–2.24 (1H, m), 2.25–2.33 (2H, m), 2.52–2.56 (2H, m), 7.08 (1H, dd, J=3.1, 5.4), 7.23 (2H, dd, J=3.1, 5.4), 7.38 (1H, dd, J=3.1, 5.4); ^{13}C NMR ($CDCl_3$): δ 21.9, 22.2, 25.7, 29.6, 32.1, 127.2, 128.7, 129.6, 129.7, 137.8, 141.8, 143.0 (×2), 203.1; HRMS (FAB) calcd for $C_{14}H_{15}OCl$ $[M+H]^+$ 235.0890, found 235.0883.

4.10. Major (*P,S*)- and minor (*M,S*)-1-[2-(2-chlorophenyl)-1-cyclohexenyl]ethanol ((*P,S*)-19 and (*M,S*)-19) from (*S*)-BINAL-H reduction of 18

To a 2.4 M THF solution (2.95 mL, 7.10 mmol) of $LiAlH_4$ at 0 °C was added dropwise a solution of ethanol (330 mg, 7.18 mmol) of THF (3.5 mL). After stirring for 10 min, a solution of (*S*)-binaphthol (2.07 g, 7.21 mmol) in THF (10 mL) was added and the resulting mixture was stirred for 30 min at room temperature. The reducing agent was cooled to −100 °C. A solution of ketone **18** (500 mg, 2.14 mmol) in THF (12 mL) was added dropwise over a period of 5 min at −100 °C. The resulting mixture was stirred for an additional 6 h at the temperature and at −78 °C for 24 h. After addition of 2 M HCl (20 mL), the mixture was extracted with ether. *The ligand, (S)-binaphthol, was recovered in a quantitative level without lowing the enantiopurity* by extracting the ethereal solution with 5% NaOH (20 mL×3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. A residual oil was purified by flash chromatography on silica-gel (20% AcOEt/hexane) to afford the optically active alcohol **19** (395 mg, 78%). IR (film) 3301, 1469, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (minor: 3H, d, J=6.8), 1.17 (major: 3H, d, J=6.8), 1.52 (minor isomer: 1H, s), 1.60 (major isomer: 1H, s), 1.62–1.80 (4H, m), 2.00–2.40 (4H, m), 4.16 (1H, m), 7.05–7.40 (4H, m); ^{13}C NMR ($CDCl_3$): Two isomers δ 20.0, 20.5, 21.4, 21.5, 22.5 (×2), 22.8, 23.0, 31.1, 31.3, 67.9 (×2), 126.8, 1269, 127.9 (×2), 129.4, 129.5, 129.6, 130.3, 131.9, 132.2, 132.8, 133.0, 136.7, 137.2, 141.7, 141.8; HRMS (FAB) calcd for $C_{14}H_{17}OCl$ $[M+H]^+$ 237.1047, found 237.1023. *The enantiomeric excess was determined to be **97%** by HPLC analysis (DAICEL CHIRALPAK IA) after conversion of the alcohol into the corresponding benzoate.*

4.11. Major (*P,S*)- and minor (*M,S*)-19 from Ru[(*R,R*)-Ts-DPEN](*p*-cymene) reduction of 18

To an azeotropic (5: 2) mixture[29] of formic acid and triethylamine (1 mL) was added a solution of ketone **18** (50 mg, 0.214 mmol) in CH_2Cl_2 (1 mL). A solution of (*R,R*)-Ru-[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) (6.4 mg, 0.011 mmol) in CH_2Cl_2 (1 mL) was added to the mixture at room temperature. After stirring at 40 °C for 15 h, the resulting solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica-gel to give the optically active alcohols **19** (34 mg, 68%). The enantiomeric excess was determined to be 77% by HPLC analysis after conversion of the alcohol into the corresponding benzoate.

4.12. (*PM,S*)-1-(1-Benzoylethyl)-2-(2-chlorophenyl)-1-cyclohexene ((*PM,S*)-20)

To a solution of alcohols **19** (30 mg, 0.127 mmol), obtained from enantioselective reduction, in CH_2Cl_2 (1 mL) was added pyridine (30 μL). After stirring at room temperature for 15 min, benzoyl chloride (29 μL, 0.255 mmol) was added to the solution. The resulting solution was sirred for 2 h. The mixture was quenched with 10% HCl (1 mL) and extracted with CH_2Cl_2 (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give benzoates **20** (42 mg, 98%). Colorless oil: IR (film) 1717, 1271 cm^{-1}; ^1H NMR ($CDCl_3$): δ (minor) 1.32 (3H, d, J=7.0), (major) 1.33 (3H, d, J=7.0), 1.70–1.79 (4H, m), 2.00–2.20 (1H, m), 2.23–2.35 (3H, m), (major) 5.40 (1H, q, J=7.0), (major) 5.42 (1H, q, J=7.0), 7.18–7.40 (4H, m), 7.43 (2H, t, J=6.8) 7.53 (1H, q, J=6.8), 8.00 (2H, t, J=6.8); ^{13}C NMR ($CDCl_3$): (major) δ 18.3, 22.3, 22.4, 22.7, 30.9, 72.0, 127.0, 128.1, 128.2, 129.3, 129.4, 130.0, 141.1, 165.3: (minor) δ19.0, 22.5, 22.8, 23.0, 31.1, 71.4, 126.5, 128.1, 128.2, 129.5, 129.7, 129.9, 141.0, 165.2.

4.13. Major (*P,S*)- and minor (*M,S*)-1-[2-(2-Chlorophenyl)-1-cyclohexenyl]ethyl carbamate ((*PM,S*)-21)

To a solution of alcohol (*MP,S*)-**19** (170 mg, 0.729 mmol) in CH_2Cl_2 (4.6 mL) at 0 °C was added trichloroacetyl isocyanate (172 μL, 1.46 mmol) and the reaction mixture was stirred at 0 °C for 15 min. After stirring at room temperature for 15 min, evaporation of the solvent gave a crude material. The residue was dissolved in an aqueous K_2CO_3 (811 mg) solution in water (2 mL) and MeOH (5 mL). The reaction mixture was stirred at room temperature for 1.5 h. After extraction with ether (10 mL×3), the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash chromatography on silica-gel (30% AcOEt/hexane) to afford allyl carbamate **21** (195 mg, 96%). IR (film) 3454, 1734, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.19 (3H, d, J=6.7), 1.68–1.78 (4H, m), 1.99–2.03 (1H, m), 2.17 (2H, brs), 2.30–2.35 (1H, m), 4.79 (2H, br s), 5.04 (1H, q, J=6.9), 7.15–7.35 (4H, m); only distinguishable methyl doublet 1.21 (3H, d, J=6.7) of minor diastereomer shows the ratio (3: 1) of the atropisomers; ^{13}C NMR ($CDCl_3$): (major) δ 18.3, 22.2, 22.3, 22.6, 30.8, 72.0, 126.8, 128.0, 129.2, 130.1, 132.6, 133.4, 133.5, 141.1, 156.3: (minor) δ 18.9, 22.4, 22.7, 22.8, 31.0, 71.6, 126.5, 128.0, 129.6, 129.9, 132.4, 133.5, 133.6, 141.0, 156.4; HRMS (FAB) calcd for $C_{15}H_{18}NO_2Cl$ $[M+H]^+$ 280.1105, found 280.1083.

4.14. (1*R*,2*E*)-1-(2-Chlorophenyl)-2-ethylidenecyclohexyl isocyanate ((*R*)-23)

To a solution of carbamate **23** (100 mg, 0.357 mmol), triphenylphosphine (288 mg, 1.10 mmol), and triethylamine (290 μL, 2.10 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C was added a solution of carbon tetrabromine (353 mg, 1.06 mmol) in CH_2Cl_2 (3.5 mL). After stirring at 0 °C for 30 min, the reaction mixture was diluted with hexane (20 mL). The resulting reaction mixture was washed with H_2O, an aqueous saturated $NaHCO_3$ solution, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a crude product, which was purified by flash chromatography on silica-gel (20% AcOEt/hexane) to afford isocyanate **23** (92 mg, 98%). Colorless oil: $[\alpha]_D^{19}$ −116.0 (*c* 1.00, $CHCl_3$); IR (film) 2256, 1464, 1431 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48–1.56 (1H, m), 1.59 (3H, dd, J=6.5, 1.3), 1.77–1.88 (4H, m), 2.23–2.29 (1H, m), 2.62–2.76 (2H, m), 5.04 (1H, dq, J=6.7, 1.9), 7.24 (1H, dt, J=7.6, 1.7), 7.30 (1H, dt, J=7.6, 1.7), 7.37 (1H, dd, J=7.6, 1.7), 7.73 (1H, dd, J=7.6, 1.7); ^{13}C NMR ($CDCl_3$): δ 12.9, 22.6, 24.8, 25.2, 39.0, 69.0, 120.9, 124.7, 126.8, 128.7, 129.2, 131.9, 132.8, 137.3, 140.1; HRMS (FAB) calcd for $C_{15}H_{16}NOCl$ $[M+H]^+$ 262.1000, found 262.9987.

4.15. (*R*)-1-(2-Chlorophenyl)-2-ethylidene-1-methylaminocyclohexane ((*R*)-24)

To a slurry of large excess $LiAlH_4$ (50 mg, 1.31 mmol) in THF (1 mL) was added dropwise a solution of isocyanate **23** (150 mg, 0.57 mmol) in THF (1 mL). The resulting solution was stirred at room temperature for 1 h and then reflux for 30 mn. After cooling, a 30% NaOH solution (1 mL) was added and the mixture was heated

to 90 °C for 1 h. The reaction mixture was extracted with ether (10 mL×3). The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure gave a residue, which was purified by flash chromatography to afford the corresponding methyl amine **24** (131 mg, 92%). Colorless liquid: $[\alpha]_D^{20}$ −48.8 (*c* 1.67, $CHCl_3$); IR (film) 1427, 1039, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46–1.50 (1H, m), 1.59 (3H, d, *J*=6.2), 1.60–1.83 (4H, m), 1.96 (1H, br s), 2.05 (3H, s), 2.27–2.40 (3H, m), 4.99 (1H, q, *J*=6.9), 7.16 (1H, dt, *J*=7.7, 1.7), 7.25 (1H, dt, *J*=7.7, 1.7), 7.32 (1H, dd, *J*=7.7, 1.7), 7.51 (1H, dd, *J*=7.7, 1.7),; ^{13}C NMR ($CDCl_3$): δ 12.7, 22.5, 25.3, 26.9, 29.3, 36.4, 65.6, 118.1, 126.4, 127.5, 130.4, 131.7, 133.9, 139.7, 141.7; HRMS (FAB) calcd for $C_{15}H_{20}NCl$ $[M+H]^+$ 250.1364, found 250.1366.

4.16. (*S*)-Ketamine (1)

Amine **24** (85 mg, 0.30 mmol) was dissolved in 10% HCl solution (2 mL). Concentration under reduced pressure gave the corresponding amine HCl salt. Ozone was passed into a solution of the amine HCl salt in MeOH (5 mL) at −78 °C, terminating the ozonolysis upon observing the distinctive blue color of ozone. After purging with nitrogen, dimethyl sulfide (400 μL) was added at −78 °C. The solution was allowed to warm up to room temperature and concentrated under reduced pressure to give the crude material, which was dissolved in EtOH (2 mL). When hexane was added, the HCl salt of (*S*)-**1** was immediately crystallized: Colorless crystals; Mp 276 °C (ethanol-*n*-hexane): $[\alpha]_D^{20}$ +91.7 (*c* 2.00, H_2O);[30] IR (film) 1722, 773 cm^{-1}; ^1H NMR (CD_3OD): δ 1.69–1.82 (2H, m), 1.90–2.00 (2H, m), 2.10–2.15 (1H, m), 2.50–2.59 (2H, m), 3.42 (1H, dd, *J*=14.2, 2.8), 7.60–7.70 (3H, m), 7.97 (1H, d, *J*=6.8); ^{13}C NMR (CD_3OD): δ 22.8, 28.0, 31.0, 37.5, 40.8, 73.7, 129.2, 129.7, 133.2, 133.3, 133.9, 135.8, 208.3. The salt was again dissolved in a 10% NaOH solution (3 mL) and the corresponding amine was extracted with ether (10 mL). After evaporation of the solvent, the amine was purified by flash chromatography (50% AcOEt/hexane) to afford (*S*)-ketamine (68 mg, 95%). The enantiomeric excess was determined to be >99% by HPLC analysis (DAICEL CHIRALCEL OD-H column). Colorless crystals; Mp 122 °C (*n*-hexane); $[\alpha]_D^{20}$ −56.3 (*c* 1.20, EtOH);[30] IR (film) 3353, 1701, 752 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72–1.78 (3H, m), 1.82–1.90 (1H, m), 1.96–2.05 (1H, m), 2.06–2.15 (1H, m), 2.11 (3H, s), 2.44–2.55 (2H, m), 2.76–2.82 (1H, m), 7.24 (1H, dt, *J*=7.5, 1.5), 7.32 (1H, dt, *J*=7.5, 1.5), 7.38 (1H, dd, *J*=7.5, 1.5), 7.55 (1H, dd, *J*=7.5, 1.5); ^{13}C NMR ($CDCl_3$): δ 21.7, 28.0, 29.0, 38.5, 39.4, 70.0, 126.5, 128.6, 129.3, 131.1, 133.6, 137.7, 209.1.

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