

Intramolecular bromo-amination of 1,4-cyclohexadiene aминаl: one-pot discrimination of two olefins and concise asymmetric synthesis of (–)- γ -lycorane†

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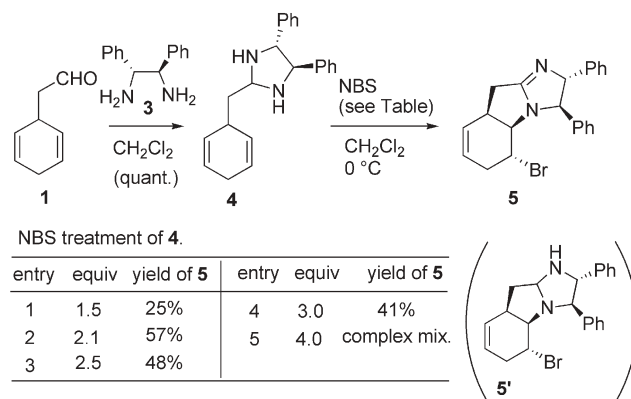
The reaction of cyclohexa-2,5-dienyl-1-methylaldehyde and optically pure 1,2-diaryl-1,2-diamine followed by intramolecular bromo-amination produced a one-pot discrimination of two olefins in the cyclohexane system, which was used for the asymmetric synthesis of (–)- γ -lycorane.

The symmetrization–desymmetrization concept is very useful for synthesizing optically active compounds. The development of this methodology is quite desirable.¹ We have recently developed efficient methods for desymmetrization of σ -symmetric dienes based on the intramolecular halo-etherification of a cyclohexadiene acetal having a 1,4-cyclohexadiene aldehyde **1** and a chiral hydrobenzoin unit.^{2,3} The obtained desymmetrized products served as useful chiral building blocks because the remaining olefin and newly introduced halogen were used for the next transformations.² If a similar reaction would occur in the 1,4-cyclohexadiene aминаl, we could obtain chiral building blocks for synthesizing nitrogen-containing skeletons. We now present the novel transformation of the 1,4-cyclohexadiene aldehyde **1** to the cyclohexene imidazoline, a tetrahydroindoline analogue, **2** in a one-pot operation and the concise asymmetric synthesis of (–)- γ -lycorane (Scheme 1).

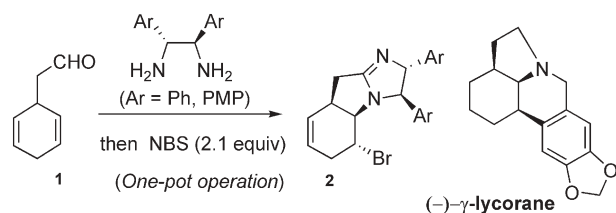
The reaction of the 1,4-cyclohexadiene aминаl **4**, prepared from the 1,4-cyclohexadiene aldehyde **1** and (\pm)-1,2-diphenyl-1,2-diamine **3** (1.0 equiv.) in a quantitative yield, was first examined. To our surprise, the expected product **5'** was not obtained at all and the product **5** was formed by two reactions, the intramolecular bromo-cyclization and successive oxidation of the aминаl unit. The best yield of **5** was obtained using 2.1 equiv. of *N*-bromosuccinimide (NBS) (entry 2). An increase in the quantity

of NBS decreased the yield of **5** because of further reaction of the remaining olefin (entries 3–5) (Scheme 2).

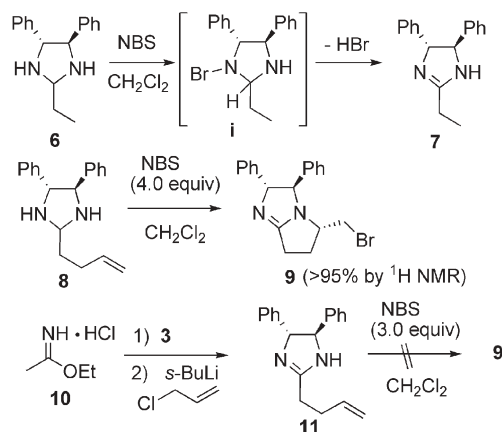
The formation of **5**, not **5'**, suggested the easy oxidation of the aминаl unit to the imidazoline unit. To clarify the reaction mechanism of **4** to **5**, the following reactions were carried out (Scheme 3). The treatment of the aминаl **6** with 1.05 equiv. of NBS afforded the dihydroimidazole **7** in a quantitative yield.⁴ NBS treatment of the ene aминаl **8**, which has one olefin, also gave the product **9** (> 95% by ¹H NMR)⁵ formed by the reactions of the intramolecular bromo-cyclization followed by oxidation of the aминаl unit. The reaction of the ene dihydroimidazole **11**, prepared by condensation of the Pinner salt⁶ **10** and **3** followed by allylation, with NBS did not give the cyclized product **9** thus showing the



Scheme 2



Scheme 1



Scheme 3

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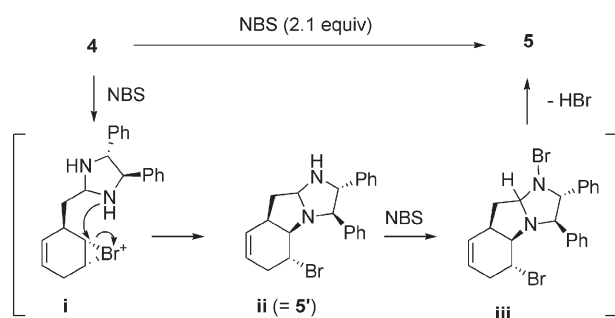
† Electronic supplementary information (ESI) available: experimental section. See DOI: 10.1039/b512161b

order of the reaction of **4** to **5**, first cyclization then oxidation of the amination.

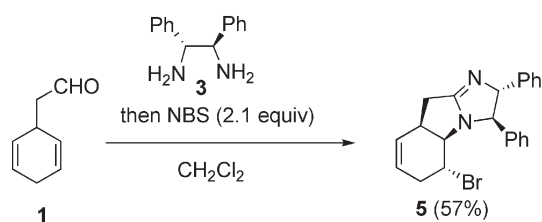
From the results in Scheme 3, the plausible reaction mechanism from **4** to **5** was rationalized as shown in Scheme 4. First, the formation of the bromonium ion **i** by NBS attack at the olefin, and subsequent cyclization by attack of the nitrogen atom at the bromonium ion formed the intermediate **ii** (= **5'**). The amination unit of **ii** was quite easily oxidized in the presence of NBS to give the dihydroimidazole **5** via **iii**.

Since the formation of the diene amination **4** from **1** proceeds in a quantitative yield in CH_2Cl_2 without a catalyst, and the next intramolecular bromoetherification of **4** to **5** can be done in the same solvent, CH_2Cl_2 , the one-pot transformation of **1** to **5** was next studied. The condensation of **1** with **3** (1.0 equiv.) was conducted for 1 h at 0°C , and then NBS (2.1 equiv.) was added to the reaction mixture at 0°C . Stirring the reaction mixture for 15 min afforded **5** in 57% yield (Scheme 5).[‡] The one-pot operation in three steps, *i.e.*, 1) amination formation, 2) bromo-amination, and 3) oxidation of amination, proceeded without any problems.

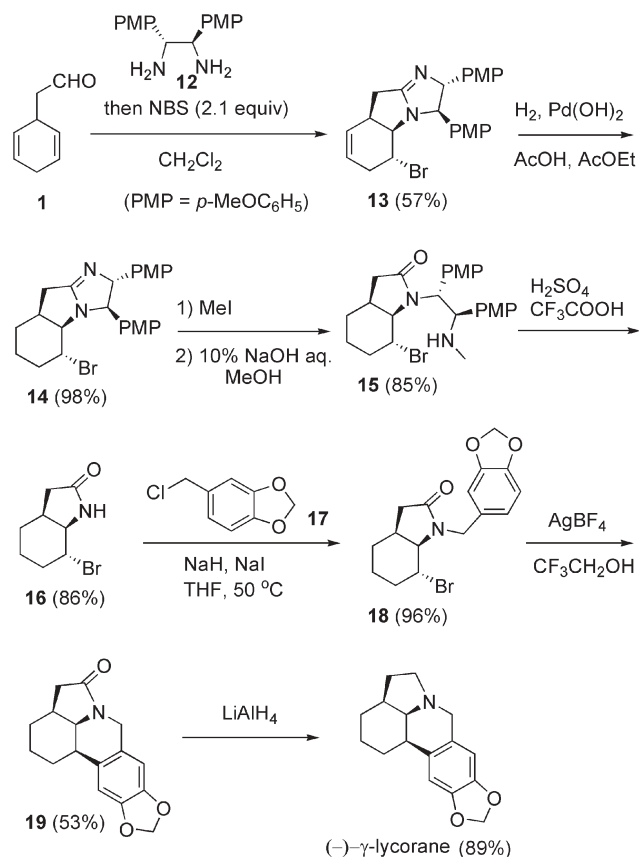
The potential of compound **5** as a chiral synthon for nitrogen-containing compounds was confirmed by the synthesis of (–)- γ -lycorane^{7,8} (Scheme 6). 1,2-Di(4-methoxyphenyl)-1,2-diamine **12** was chosen as a chiral diamine because of its easier removal with the intact olefin (*vide infra*). The one-pot operation of **1** with **12** and successive NBS treatment gave **13** in 57% yield as a single isomer. Hydrogenation of **13** afforded **14** (98% yield), which was transformed into the methyl ammonium salt, then alkaline hydrolysis produced the lactam **15** in 85% yield over two steps. Acid hydrolysis of **15** gave the bromo lactam **16** in good yield (86%). When **15** was treated with CAN, the yield of **16** decreased (55%). The condensation of **16** and the aromatic unit **17** afforded **18** in 96% yield. The intramolecular Friedel–Crafts type reaction of **18** proceeded to give **19** in moderate yield (53%). The LiAlH_4 reduction of **19** gave the γ -lycorane in 89% yield.



Scheme 4



Scheme 5 One-pot operation.



Scheme 6 Asymmetric synthesis of (–)- γ -lycorane.

Although there are many racemic syntheses⁷ of γ -lycorane, only three asymmetric syntheses,⁸ one of which contains an optical resolution step, are known, to the best of our knowledge. Our synthesis requires 8 steps, the same as the shortest one, and has a high ee. Therefore, ours is one of the best asymmetric syntheses.

In conclusion, a new asymmetric desymmetrization of two olefins in 1,4-cyclohexadiene has been developed using chiral 1,2-diamines. Especially, the one-pot operation in three steps provides a concise way to obtain an optically active nitrogen-containing carbon skeleton. The method was applied to the concise asymmetric synthesis of (–)- γ -lycorane, whose advantages are a high ee and short steps. Application of the method to the asymmetric total synthesis of natural products is now under investigation in our laboratory.

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Notes and references

[‡] **Experiment in Scheme 5 (One-pot Synthesis):** **3** (1.15 g, 5.43 mmol) was added to a solution of **1** (663 mg, 5.43 mmol) in CH_2Cl_2 (110 ml) at 0°C under N_2 . The mixture was stirred for 1 h. NBS (2.03 g, 11.4 mmol) was added to the mixture, and the resulting solution was stirred for 15 min at the same temperature. The mixture was quenched by the addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ and sat. aq. NaHCO_3 . The resulting solution was extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography using (AcOEt– Et_3N (20/1) to AcOEt–MeOH– Et_3N (20/1/1)) as the eluent to give **5** (1.22 g, 3.10 mmol) in 57% yield.

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- 5 Compound **9** is unstable and its yield was determined by ^1H NMR, whereas compounds **5** and **13** are stable. The structure of **9** was determined from the compound obtained by the reduction of **9** with Bu_3SnH , AIBN.
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