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Enantioselective Construction of Octahydroquinolines via Trienamine-Mediated Diels−Alder Reactions

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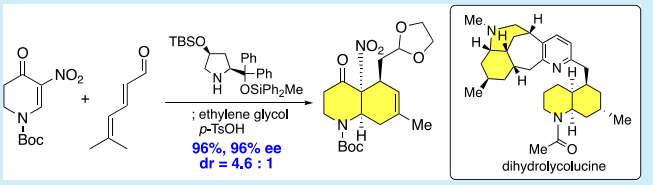
Supporting Information

ABSTRACT: A trienamine-mediated asymmetric Diels−Alder reaction using a 5-nitro-2,3-dihydro-4-pyridone derivative as a dienophile in the presence of a secondary amine organocatalyst derived from *cis*-hydroxyproline was discovered. The reaction provides optically active octahydroquinolines through an *endo*-selective [4 + 2] cyclization pathway. The following stereoselective denitration, isomerization, and/or hydrogenation generated divergent stereoisomers of decahydroquinolines, which are useful synthons for the total synthesis of *Lycopodium* alkaloids.



Decahydroquinoline scaffolds are present in a wide range of natural products, and they are important pharmacologically active structural units. In particular, *Lycopodium* alkaloids, which are composed of complex ring structures and present interesting biological activities, possess a multiply substituted decahydroquinoline moiety (Figure 1a).[1] These alkaloids contain not only *cis*- or *trans*-fused decahydroquinolines but also several diastereomers at the C8 methyl group and C10 alkyl group. Thus, the enantioselective synthesis of various stereoisomers of decahydroquinolines is an important issue in current natural product chemistry. Indeed, several synthetic protocols to access optically active decahydroquinolines have been reported.[2] Since the advent of the 21st century, interest in organocatalyzed asymmetric reactions has grown rapidly.[3] Asymmetric Diels−Alder reactions are commonly used methods that involve the application of organocatalysts to construct multiply substituted ring systems. In 2011, Jørgensen and Chen reported an enantioselective Diels−Alder reaction that proceeded via a trienamine intermediate with a secondary amine organocatalyst.[4] Since their findings, several trienamine-mediated Diels−Alder reactions including hetero-Diels−Alder reactions have been reported.[5] In this context, we envisaged that 2,3-dihydro-4-pyridones may be suitable dienophiles against activated chiral trienamines derived from a secondary amine organocatalyst and *α,β,γ,δ*-unsaturated aldehydes to provide chiral multiply substituted octahydroquinolines in one step (Figure 1b). In 2002, the Diels−Alder approach to construct octahydroquinolines using 5-ethoxycarbonyl-2,3-dihydro-4-pyridone **1** in the presence of Danishefsky's diene was reported by the group of Dhimane et al.[6] These methods were carried out under Lewis acid conditions or at elevated temperatures to provide achiral octahydroquinolines. To our knowledge, this is the only example of 2,3-dihydro-4-pyridones functioning as a dienophile.

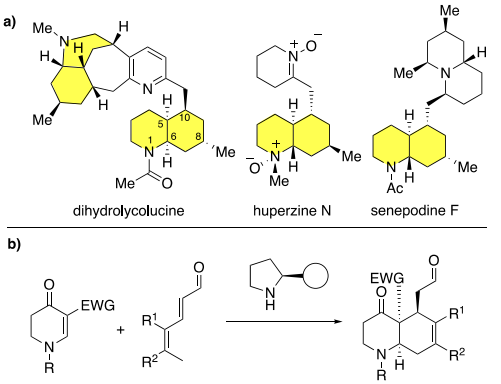


Figure 1. (a) Alkaloids containing decahydroquinoline scaffolds isolated from *Lycopodium* plants. (b) Enantioselective approach to a multiply substituted decahydroquinoline scaffold.

Herein, we disclose secondary amine catalyzed enantio- and diastereoselective Diels−Alder reactions using 5-nitro-2,3-dihydro-4-pyridone as a dienophile in the presence of *α,β,γ,δ*-unsaturated aldehydes to provide octahydroquinolines. In addition, a wide variety of *α,β,γ,δ*-unsaturated aldehyde substrates and derivatization to decahydroquinolines are described together with an application of the method toward the total synthesis of *Lycopodium* alkaloids.

Initially, 5-ethoxycarbonyl-2,3-dihydro-4-pyridone derivative **1**, which was reported as a dienophile in the Diels−Alder reaction by Dhimane et al., was employed as a substrate in the presence of methylhexadienal **2** and a catalytic amount of diphenylprolinol silyl ether **A**, which is known as the Hayashi−

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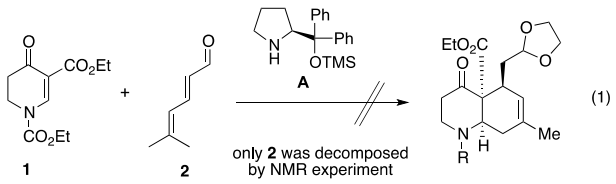
Org. Lett. XXXX, XXX, XXX−XXX

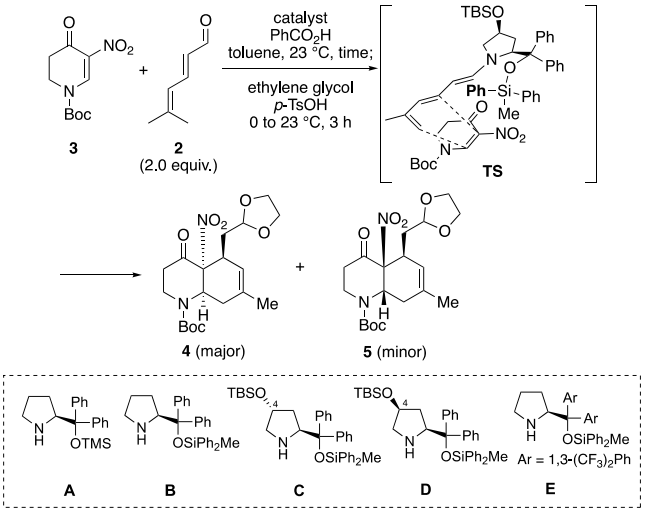
Jørgensen catalyst (eq 1). The reaction was attempted under various conditions, but no target compound was obtained. NMR spectroscopic studies showed that dihydropyridone **1** did not react and that only aldehyde **2** decomposed by a self-condensation reaction over time. Thus, it was suggested that the ethoxycarbonyl group on the dihydropyridone was not sufficiently electron-withdrawing to promote the desired Diels–Alder reaction. Thus, a suitable dienophile with a lower LUMO energy was required.



Considering alternative dienophile candidates, 5-nitro-2,3-dihydropyridone derivative **3** was designed and synthesized. Dihydropyridone **3** was prepared from commercially available *N*-Boc-*β*-alanine in 58% yield as stable yellow crystals through the application of two, one-pot operations (see details in the Supporting Information). Thus, when the reaction was performed with 5-nitro-2,3-dihydropyridone derivative **3** and 2.0 equiv of aldehyde **2** in the presence of 20 mol % catalyst **A** in toluene for 9 h at ambient temperature, the desired Diels–Alder product was obtained as a mixture of two diastereomers. The obtained aldehyde was unstable on silica gel, and therefore the crude mixture was treated with ethylene glycol in the presence of 1 equiv of *p*-TsOH to provide acetal compounds **4** and **5** in 68% yield (two steps, dr = 1.4:1; isolatable major isomer **4** in 40% yield, minor isomer **5** in 28% yield; Table 1, entry 1). The enantiomeric excesses of compounds **4** and **5** were 83% and 40% *ee*, respectively. The structure of **4**, including relative and absolute stereochemistries, was determined by X-ray analysis (Figure S1). We recognized that the major isomer **4** was produced via an *endo*-cyclization pathway. However, after recrystallization of compound **5**, crystals were obtained as a racemic mixture. The relative stereochemistry of **5** was determined by X-ray crystallographic analysis, although the absolute stereochemistry was not clear (Figure S1). In addition, it is apparent that the minor product was produced through an *exo*-cyclization pathway.

For optimization of the yield and enantioselectivity, a number of catalysts were screened. When diphenylprolinol diphenylmethylsilyl ether (**B**)[7] was employed in the reaction, a significant improvement in the yield was observed (85%; Table 1, entry 2; see also solvent screening in Table S1). With satisfactory yields for the two-step protocol in hand, we focused on improving the enantioselectivity to over 90% *ee*. Then, 4-siloxycatalyst **C**[8] which was prepared from *trans*-hydroxy proline was employed. As a result, the enantiomeric excess was slightly improved to 90% *ee* (Table 1, entry 3). Next, *cis*-hydroxy proline derivative **D** was designed and synthesized, because the steric bulk of the *cis*-4-siloxy group on the proline core was expected to favor one orientation of the diphenylmethylsilyl group (see details in the Supporting Information for the synthesis of **D**). As expected, when catalyst **D** was employed in the Diels–Alder reaction, the enantiomeric excess was improved to 96% *ee* (Table 1, entry 4). In addition, the diastereomeric ratio was slightly improved to 2.4:1. On the other hand, diarylprolinol silyl ether catalyst **E** was not suitable for the reaction (Table 1, entry 5) because, although both diastereomeric ratio and enantiomeric excess were excellent, the reaction rate was too slow and the yield was under 10% after 5 days of stirring.

Table 1. Optimization of Diels–Alder Reaction Using 2,3-Dihydro-4-pyridone[a]



entry	cat.	cat. amount [mol %]	equiv of $PhCO_2H$	time [h]	dr[b]	yield [%]	*ee* of **4** [%]
1	**A**	20	–	9	1.4:1	68	83
2	**B**	20	–	6.5	1.6:1	85	87
3	**C**	20	–	6.5	1.8:1	80	90
4	**D**	20	–	6	2.4:1	86	96
5	**E**	20	–	120	4.0:1	<10	95
6	**D**	20	1.0	2.5	4.6:1	96	96
7	**D**	5	1.0	15	4.3:1	80	96
8[c]	**D**	5	0.75	15	4.4:1	88	96

[a]Reaction conditions: **3** (0.1 mmol), **2** (0.2 mmol), and catalyst **A**–**E** (0.02 or 0.005 mmol) in the presence of benzoic acid in toluene (0.25 mL) was stirred at 23 °C. Ethylene glycol (1.5 mmol) and *p*-TsOH·H_2O (0.1 mmol) were added to the crude mixture at 0 °C. See details in the Supporting Information. [b]The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. [c]1 g of **3** was employed. See details in the Supporting Information.

After optimization of the reaction with respect to yield and enantioselectivity, we then focused on reducing the catalyst loading while maintaining an acceptable reaction time. Thus, a number of acid additives were screened in an attempt to accelerate the reaction (Table 1 and Table S2). When 1 equiv of benzoic acid was added to the reaction mixture, the reaction time decreased to 2.5 h (Table 1, entry 6). Fortunately, the addition of benzoic acid had a positive effect, not only on the reaction rate but also on both the yield and diastereoselectivity. Thus, the yield was improved to almost quantitative and the diastereomeric ratio reached 4.6:1. We then attempted to reduce the catalyst loading. When the reaction was carried out with 5 mol % catalyst under the above conditions, the reaction reached completion in 15 h (80% yield, 94% *ee*; Table 1, entry 7). Given that the chemical yield was slightly decreased, the amount of benzoic acid was reinvestigated. As a result, the use of 75 mol % benzoic acid led to an excellent result (dr = 4.4:1, 88% yield, 96% *ee*; Table 1, entry 8; major compound **4** was isolated in 72% in gram-scale quantities; see details in Supporting Information).

Having established fully optimized conditions, the substrate scope of the reaction with respect to the aldehyde was examined (Figure 2). Simple hexadienal could be employed as

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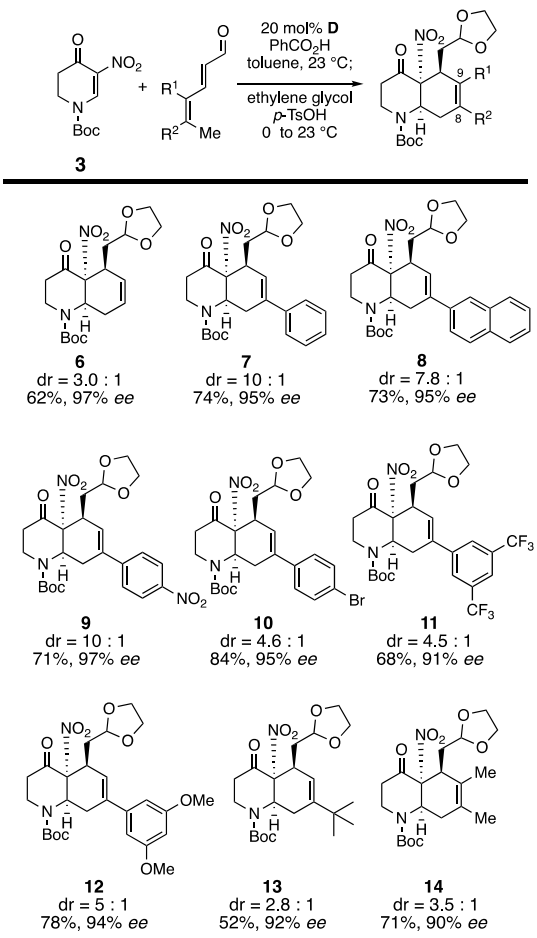
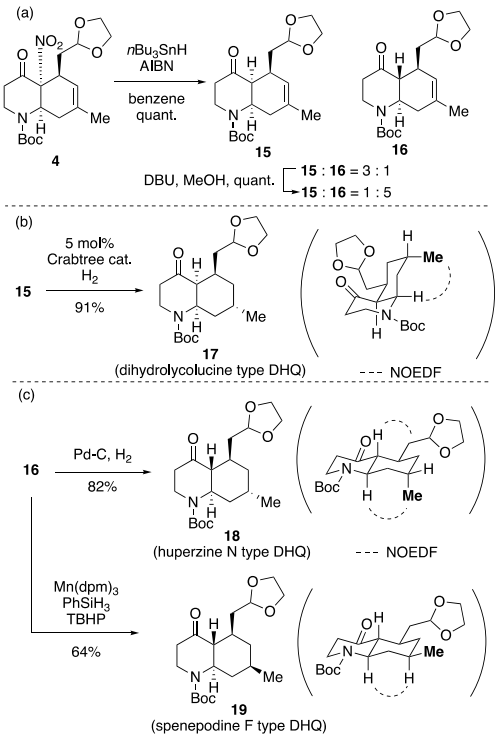


Figure 2. Substrate scope.

a diene to provide **6** in good yield and with excellent enantioselectivity (dr = 3.0:1, 62% yield, 97% *ee*). In addition, several aromatic groups were inserted at the C8 position of octahydroquinolines. Thus, C8-phenyl- and naphthyl-substituted octahydroquinolines (**7**, **8**) were obtained with high diastereo- and enantioselectivity in good yield [**7**: dr = 10:1, 74% yield, 95% *ee* (Diels–Alder reaction was performed at 0 °C); **8**: dr = 7.8:1, 73% yield, 95% *ee*]. Substrates with an electron-withdrawing group on the phenyl, such as *p*-nitro, *p*-bromo, and 3,5-bis(trifluoromethyl)phenyl groups, promoted the Diels–Alder reaction; compounds **9**–**11** were obtained in satisfactory yield with excellent stereoselectivity (**9**: dr = 10:1, 71% yield, 97% *ee*; **10**: dr = 4.6:1, 84% yield, 95% *ee*; **11**: dr = 4.5:1, 68% yield, 91% *ee*). Furthermore, compound **12**, with a 3,5-dimethoxyphenyl group as an electron-rich aromatic group at the C8 position, was efficiently obtained under the optimized reaction conditions (dr = 5:1, 78% yield, 94% *ee*). The presence of a sterically bulky substituent led to a slight decrease in both the chemical yield and diastereoselectivity, although the enantiomeric excess was excellent. Thus, compound **13**, which has a *tert*-butyl group at the C8 position, was isolated in moderate yield and diastereomeric ratio (dr = 2.8:1, 52% yield, 92% *ee*). Finally, the preparation of product **14**, which was substituted with methyl groups at the C8 and C9 positions, was achieved (dr = 3.5:1, 71% yield, 90% *ee*).

Next, cycloadduct **4** was transformed into decahydroquinoline toward the total synthesis of *Lycopodium* alkaloids (Scheme 1). To construct the *cis*- and *trans*-decahydroquinoline scaffold, diastereoselective removal of the nitro group was

Scheme 1. Derivatization of Cycloadduct 4 toward Total Synthesis of *Lycopodium* Alkaloids



examined (Scheme 1a). Thus, when cycloadduct **4** was treated with catalytic 2,2′-azobisisobutyronitrile (AIBN) and 1 equiv of *n*-Bu_3SnH,[9] *cis*-fused octahydroquinoline **15** was obtained predominantly as the kinetic product (quant, dr = 3:1). The *cis*-fused product **15** could be isomerized to thermodynamically stable **16** by treatment with DBU in MeOH. Thus, after addition of DBU to a diastereomer mixture of **15** and **16**, the diastereomeric ratio was shifted to 1:5 without loss of any material. Next, diastereoselective hydrogenation of isolated *cis*-fused octahydroquinoline **15** was carried out (Scheme 1b). The concave-face-selective hydrogenation of **15** was accomplished by treatment with 5 mol % of Crabtree's catalyst under a hydrogen atmosphere to provide **17** in excellent yield (91%). The stereochemistry of decahydroquinoline (DHQ) **17** corresponded to that of dihydrolycolucine (Figure 1a). The *trans*-fused octahydroquinoline **16** was submitted to hydrogenation reaction conditions with Pd–C to give **18**, containing an axial methyl group on C8, in excellent yield (82%); hydrogenation proceeded at the equatorial site (Scheme 1c). The relative stereochemistry of **18** matched that of the DHQ ring of huperzine N. On the other hand, a senepodine F-type dihydroquinoline ring **19** was obtained through thermodynamic hydrogenation using $Mn(dpm)_3$ and $PhSiH_3$ in the presence of TBHP[10] with *trans*-fused octahydroquinoline **16** as a substrate (Scheme 1c, 64%). The stereochemistries of the obtained decahydroquinolines (**17**–**19**) were determined by differential NOE experiments.

In conclusion, we have developed trienamine-mediated asymmetric Diels–Alder reactions using 5-nitro-2,3-dihydro-4-pyridones as a dienophile. It is the first example in which 2,3-dihydro-4-pyridone was employed in an asymmetric Diels–Alder reaction. The C5-nitro group was required to decrease the LUMO level of the dienophile. In addition, our designed secondary amine organocatalyst, which was derived from *cis*-

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Org. Lett. XXXX, XXX, XXX–XXX

hydroxyproline, provided an excellent yield and enantioselectivity. Furthermore, several C8- and C9-substituted octahydroquinolines were prepared using our methodology. The subsequent stereoselective denitration, isomerization, and/or hydrogenation of multiply substituted octahydroquinolines generated divergent stereoisomers of decahydroquinolines, which are useful synthons for the total synthesis of *Lycopodium* alkaloids. Further synthetic studies of *Lycopodium* alkaloids are in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00932.

Figure S1, Tables S1 and S2, and experimental details and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1903409 and 1903439 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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