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STEREOSPECIFIC SYNTHESIS OF PIPERIDINE SKELETON BY [4+2] CYCLOADDITION, LEADING TO THE SYNTHESIS OF PIPERIDINES OF BIOLOGICAL INTERESTS†

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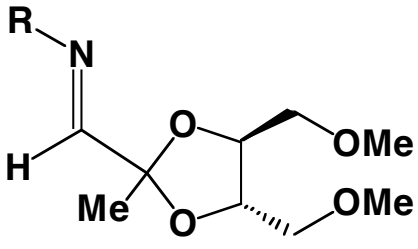
†*This paper is dedicated to Professor Teruaki Mukaiyama in recognition of his remarkable contributions to organic synthesis*

Abstract - [4+2] Cycloaddition reaction between a chiral imine possessing an auxiliary derived from tartaric acid and Danishefsky diene was studied, and the reaction promoted by boron trifluoride etherate gave 2,3-dehydropiperidin-4-one in a stereospecific manner. The adduct thus obtained was converted into (*S*)-coniine derivatives without loss of the stereochemical integrity.

The potentiality of the Dields-Alder reaction for the construction of the cyclic molecule has been well recognized in connection with the creation of multiple asymmetric centers stereoselectively in a single step. In particular, the recent examples demonstrate that the cycloaddition between an imino compound and a diene constitutes a rapid access to a 2,3-dehydropiperidin-4-one skeleton.[1] We have recently introduced an imine (**1**) possessing a chiral dioxolane derived from tartaric acid for the enolate-imine condensation method of synthesis of β-lactams in a highly stereodivergent manner.[2] We have found that the reaction of Danishefsky diene **2**[3] with the imine (**1**) gave the adduct (*R*-**3**) in a highly sterereocontrolled manner, and would like to disclose herein a stereoselective access to 2,3-dihydropiperidin-4-one and a stereocontrolled synthesis of a (*S*)-coniine derivative (**10**).[4]



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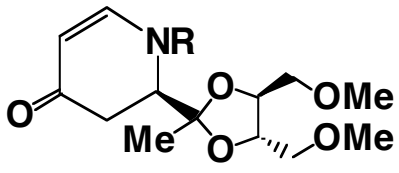
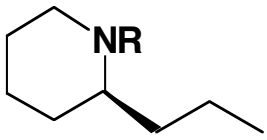


R-**3**



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The cycloaddition reaction was carried out by mixing solutions of the diene (**2**) and the imine (**1**) in the presence of a Lewis acid at -78 ℃. The adduct (**3**) was obtained as a mixture of diastereomers, and the results are summarized in Table 1.[5]

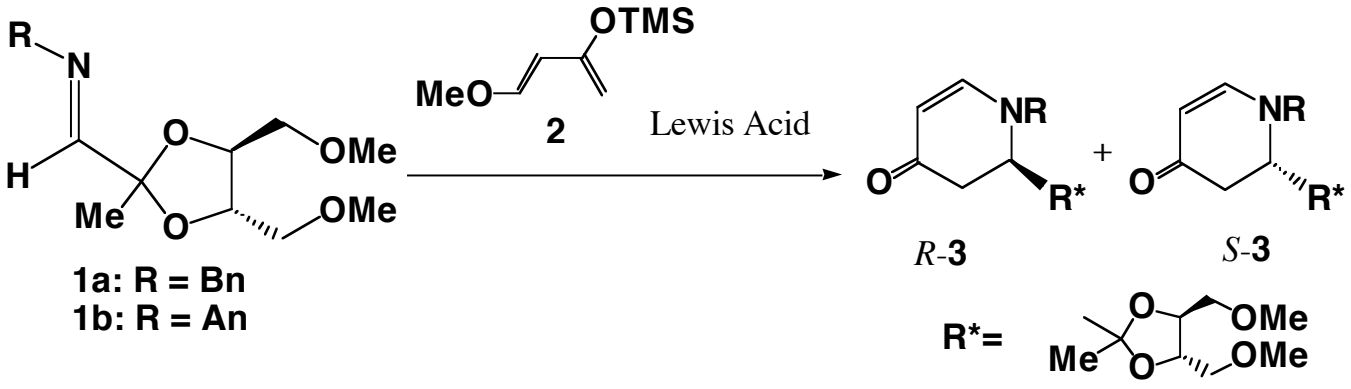


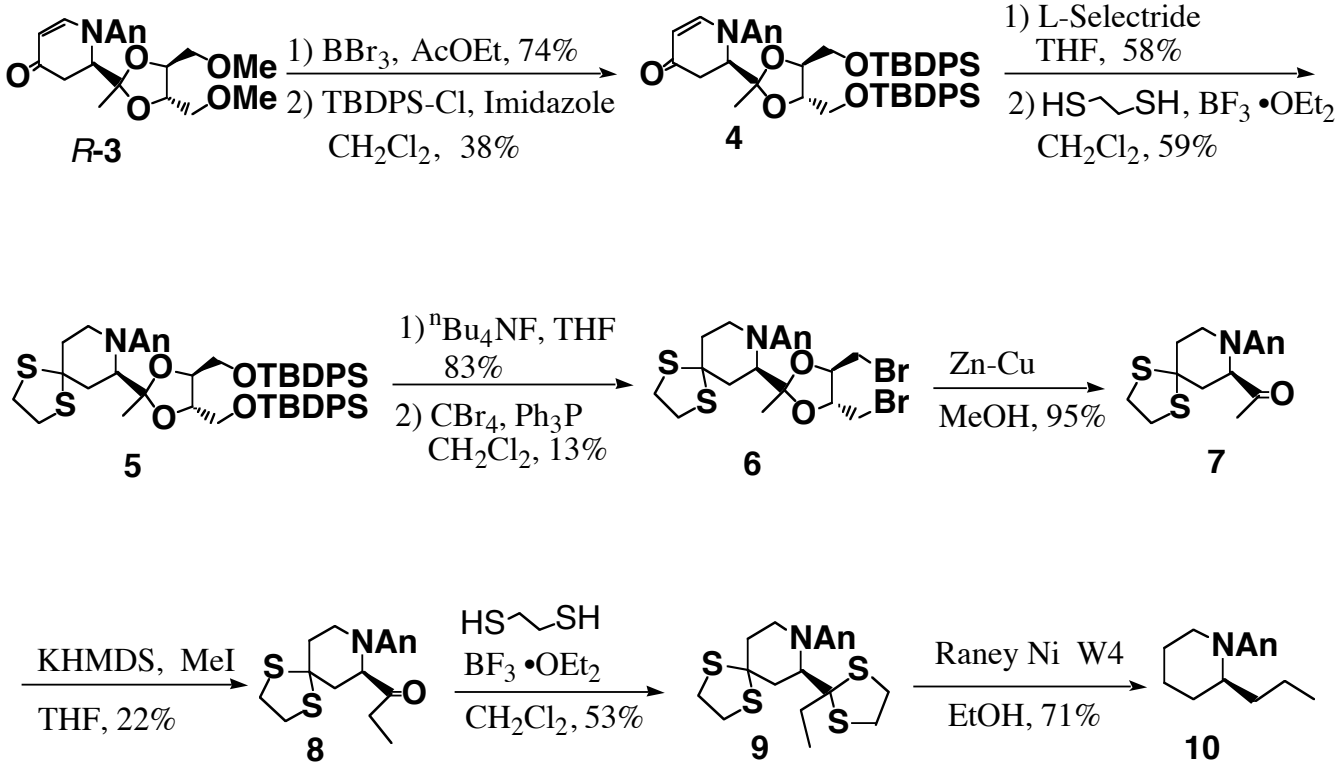
Table 1. Cycloaddition of the Imine (1) with the Diene (2).[a)]

entry	Imine	Lewis Acid (equiv.)	Solvent	Temp. /°C	Time	Yield (%)[b)]	*R*-**3**: *S*-**3**[c)]
1	**1a**	$ZnCl_2$ (1.1)	THF	-78~rt	26 h	20	63 : 37
2	**1a**	$EtAlCl_2$ (1.1)	CH_2Cl_2	-78	5 min	13	82 : 18
3	**1a**	BF_3•Et_2O (1.1)	CH_2Cl_2	-78	5 min	27	87 : 13
4	**1a**	BF_3•Et_2O (2.2)	CH_2Cl_2	-78	5 min	27	>99 : <1
5	**1a**	BF_3•Et_2O (3.3)	CH_2Cl_2	-78	5 min	32	>99 : <1
6	**1b**	$EtAlCl_2$ (1.1)	CH_2Cl_2	-78	40 min	30	77 : 23
7	**1b**	$Cl_2Ti(O$*i*-$Pr)_2$ (1.1)	THF	-78	3.5 h	52	83 : 17
8	**1b**	TMSOTf (1.1)	CH_2Cl_2	-78	10 min	73	94 : 6
9	**1b**	BF_3•Et_2O (1.1)	CH_2Cl_2	-78	5 min	100	>99 : <1
10	**1b**	BF_3•Et_2O (2.2)	CH_2Cl_2	-78	30 min	66	>99 : <1
11	**1b**	BF_3•Et_2O (3.3)	CH_2Cl_2	-78	20 min	52	>99 : <1
12	**1b**	$ZnCl_2$ (1.1)	CH_2Cl_2	-78~0	13 h	57	>99 : <1
13	**1b**	$ZnCl_2$ (1.1)	THF	-78~0	23 h	95	>99 : <1

a) The reaction was carried out according to the typical experimental procedure. b) Isolated yield. c) Ratio determined by ^{13}C and/or ^{1}H NMR.

As shown in Table 1 the initial reaction of the *N*-benzyl derivative (**1a**) proceeded with good to excellent selectivity. In particular, in the presence of BF_3•Et_2O, the adduct (**3**) was obtained as a single isomer (entries 4 ~ 5). However, the low yields of the product called for the use of other derivatives. Among other *N*-protecting groups *p*-anisyl group appears to be attractive due to the electron-donating and hence oxidative degradation abilities. With the anisyl derivative (**1b**) the reaction went readily to give the adduct (**3**) in good to excellent yields, in which the selectivity was usually high. The reaction was sensitive to the amount of the Lewis acid. In contrast to the cases with the benzyl derivative (**1a**), using 1.1 equivalents of BF_3•Et_2O, the reaction gave the adduct (*R*-**3**) quantitatively, whereas the use of an increased amount of BF_3•Et_2O considerably decreased the product yields (entries 9 ~ 11). The presence of $ZnCl_2$ in THF also recorded an excellent result (entry 13). From the standpoint of the reaction time, BF_3•Et_2O (1.1 eq) appears to be the Lewis acid of choice.

With the diastereomerically pure cycloaddition product (*R*-**3**) in hand, we next applied the present procedure to the synthesis of biologically interesting piperidines involving a (*S*)-coniine derivative.[4] The dimethyl ether moiety of the adduct (*R*-**3**) was removed with BBr_3 in AcOEt to give the diol, which was protected with bis-TBDPS groups. The olefin part of the bis-silyl ether (**4**) was reduced with L-Selectride® followed bythioketal formation with 1,2-ethanedithiol and BF_3•Et_2O to give the dithiolane (**5**). The removal of the bis-TBDPS groups was effected with TBAF to give the diol. The diol was brominated with CBr_4 and PPh_3 to give the dibromide (**6**), which upon treatment with Zn-Cu, gave the methyl ketone (**7**). The alkylation was carried out with $KN(TMS)_2$ and MeI to give the ethyl ketone (**8**). The subsequent thioketalization with 1,2-ethanedithiol and BF_3•Et_2O gave the bis-dithiolane (**9**). Reductive removal of the bis-dithiolane moieties was carried out with Raney Ni (W4) to give the (*S*)-*N*-anisylconiin (**10**) in enantiomerically pure form.[6]



In conclusion, the cycloaddition using the chiral imine (**1**) possessing a chiral auxiliary, (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol, derived from (2*S*,3*S*)-tartaric acid offers the adduct (**3**) in diastereomeraically pure form in quantitative yield. The subsequent manipulation of the functionalities affords piperidines of biological interests.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. a) S. Danishefsky, M. E. Langer, and C. Vogel, *Tetrahedron Lett.*, 1985, **26**, 5983; b) S. Danishefsky and C. Vogel, *J. Org. Chem.*, 1986, **51**, 3916; c) H. Waldmann and M. Braun, *Ibid.*,

1992, **57**, 4444; d) K. Hattori and H. Yamamoto, *J. Org. Chem.*, 1992, **57**, 3264; e) K. Hattori and H. Yamamoto, *Tetrahedron*, 1993, **49**, 1749; f) P. N. Devine, M. Reilly, and T. Oh, *Tetrahedron Lett.*, 1993, **34**, 5827; g) K. Ishimaru, K. Watanabe, Y. Yamamoto, and K.-y. Akiba, *Synlett*, 1994, 495.

2. a) T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron Lett.,* 1991, **32**, 7563; b) T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron*, 1992, **48**, 5629; c) M. Shimizu, Y. Ukaji, J. Tanizaki, and T. Fujisawa, *Chem. Lett.*, 1992, 1349; d) T. Fujisawa, R. Hayakawa, and M. Shimizu, *Tetrahedron Lett.,* 1992, **33**, 7903; e) T. Fujisawa, K. Higuchi, and M. Shimizu, Synlett, 1993, 59; f) T. Fujisawa, M. Ichikawa, Y. Ukaji, and M. Shimizu, Tetrahedron Lett., 1993, 34, 1307; g) T. Fujisawa, D. Satou, and M. Shimizu, *BioMed. Chem.* Lett., 1993, 3, 2343; h) M. Shimizu, T. Ishida, and T. Fujisawa, *Chem. Lett.*, 1994, 1403; i) T. *Fujisawa and M. Shimizu, Rev. Heteroatom Chem.*, 1996, **15**, 203, and the references cited therein.
3. J. Kervin, Jr. and S. Danishefsky, *Tetrahedron Lett.,* 1982, **23**, 3739.
4. S. M. Weinreb, *Acc. Chem. Res.*, 1985, **18**, 16; S. M. Weinreb and S. S. Staib, *Tetrahedron*, 1982, **38**, 3087.
5. A typical procedure for the [4+2] cycloaddition reaction is as follows: To a solution of BF_3•Et_2O (123 mg, 0.869 mmol) in CH_2Cl_2 (3.0 mL) was added a solution of the imine (**1b**) (244 mg, 0.790 mmol) in CH_2Cl_2 (10 mL) at -78 ˚C, and the mixture was stirred at that temperature for 20 min. A solution of the diene (**2**) (204 mg, 1.184 mmol) in CH_2Cl_2 (5.0 mL) was added to the resulting mixture at -78 °C, and the mixture was stirred for 5 min. After usual work-up followed by purification on silica gel TLC, the adduct ((*R*)-**3**) was obtained as a colorless oil (276 mg, 100%).
6. Analyzed by HPLC using a chiral stationary column (Daicel OJ, eluent: *n*-hexane : *i*-PrOH = 50 : 1).