The First Enantioselective Hetero Diels–Alder Reaction of Nitroso Compound Utilizing Tartaric Acid Ester as a Chiral Auxiliary

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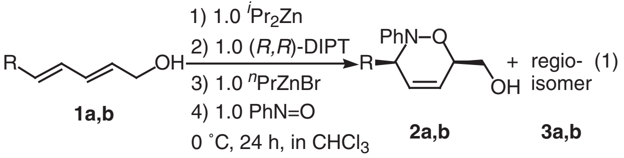
The first regio- and enantioselective hetero Diels–Alder reaction of nitroso compound with dienol has been realized utilizing tartaric acid ester as a chiral auxiliary and the corresponding cycloadduct was obtained in complete regioselectivity with excellent enantioselectivity up to 92% ee.

The hetero Diels–Alder reaction provides a very convenient approach to the synthesis of six-membered partially saturated heterocycles, a class of compounds that have found extensive use as starting materials for total syntheses of natural products.[1] A wide range of nitroso compounds have been proven to be useful dienophiles for the hetero Diels–Alder reaction to afford dihydro-1,2-oxazine derivatives. Development of asymmetric hetero Diels–Alder reaction of nitroso compound was for a long time restricted to only diastereoselective reactions using chiral dienes or chiral nitroso compounds in spite of the great potential of this synthetic methodology.[2,3] To the best of our knowledge, metal-catalyzed enantioselective hetero Diels–Alder reaction of arylnitroso dienophile has not been reported so far.[4]

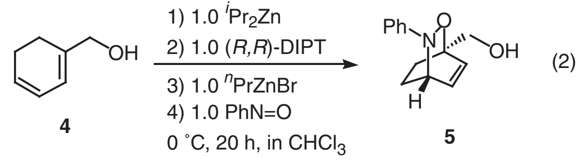
A novel chiral multinucleating system utilizing tartaric acid ester as a chiral auxiliary was developed in our laboratory and it has been successfully applied to the asymmetric 1,3-dipolar cycloaddition reactions.[5] The promising results obtained from the 1,3-dipolar cycloadditions tempted us to apply this strategy for the enantioselective hetero Diels–Alder reaction with nitroso compound by the use of tartaric acid ester as a chiral auxiliary. When acyclic dienols **1** were successively treated with diisopropylzinc, a stoichiometric amount of diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT], propylzinc bromide, and nitrosobenzene as shown in Eq 1, the corresponding dihydro-1,2-oxazine derivatives were obtained as a mixture of regioisomers **2** and **3** with different N–O orientation in favor of isomers **2**, in which oxygen of the nitroso group oriented toward the diene carbon bearing CH_2OH moiety. To our delight, the enantioselectivity of the major product **2b** was over 50% ee. This modest enantioselectivity encouraged us to further optimize the reaction conditions.



1a,b **2a,b** **3a,b**

a R = H, 37%, 33% ee 13% yield
b R = Me, 57%, 55% ee 28% yield

When (cycohex-1,3-dienyl)methanol (**4**) was used as a diene component as shown in Eq 2, we were pleased to find that the reaction proceeded in complete regioselective manner to afford the corresponding bicyclic dihydro-1,2-oxazine **5** as a sole product in excellent chemical yield with higher enantioselectivity of 63% ee.



4 **5**

91%, 63% ee

A number of conditions have been surveyed in attempt to improve the reactivity and selectivity of the present hetero Diels–Alder cycloaddition reaction. An alternative procedure by successive treatment of (*R*,*R*)-DIPT with propylzinc bromide and diisopropylzinc, followed by addition of dienol **4** and nitrosobenzene was tried as shown in Eq 3. The effect of solvent and chiral auxiliary was examined as listed in Table 1.

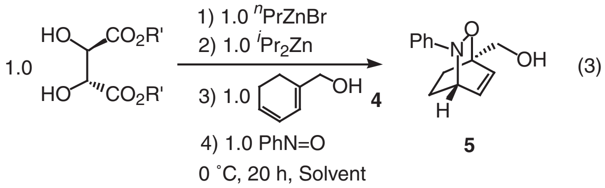
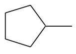
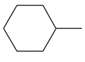
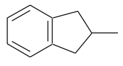


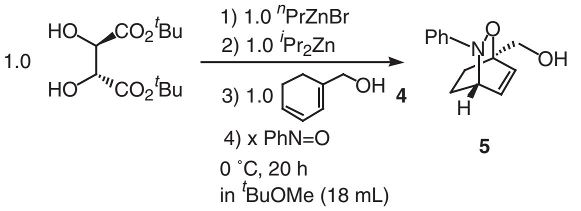
Table 1. The effect of solvent and chiral auxiliary

Entry	R′	Solvent[a]	Yield/%	ee/%[b]
1	^{i}Pr	$CHCl_3$	86	72
2	^{i}Pr	CH_2Cl_2	80	74
3	^{i}Pr	Toluene	82	69
4	^{i}Pr	^{i}Pr$_2$O	51	64
5	^{i}Pr	THF	18	57
6	^{i}Pr	DME	64	20
7	^{i}Pr	CH_3CN	64	37
8	^{i}Pr	Et_2O	69	77
9	Et	Et_2O	43	60
10	Bn	Et_2O	17	11
11		Et_2O	83	46
12		Et_2O	67	67
13		Et_2O	69	70
14	^{t}Bu	Et_2O	76	88
15	^{t}Bu	^{t}BuOMe	56	91

[a] The reaction was carried out on a 0.5 mmol scale in 9 mL of solvent.
[b] Optical yields were determined by HPLC analysis (Daicel Chiralcel OJ-H).

It was found that enantioselectivity of the cycloadduct was profoundly influenced by the solvent employed. The good chemical yield was observed in halocarbon solvents and the highest optical yield was attained in diethyl ether as solvent when (*R*,*R*)-DIPT was used as a chiral auxiliary (Entries 1, 2, 8). Optimization of reactivity and enantioselectivity was further achieved by variation of the chiral auxiliaries. The use of bulky di(*tert*-butyl) (*R*,*R*)-tartrate [(*R*,*R*)-DTBT] as a chiral auxiliary exhibited dramatically increased enantioselectivity of the corresponding cycloadduct up to 88% ee with 76% yield (Entry 14). Moreover, the resulting cycloadduct was obtained with more than 90% ee when diethyl ether was replaced by *tert*-butyl methyl ether as a solvent, though the chemical yield dropped a little (Entry 15).

It was reported that dimerization of nitrosobenzene strongly depends on the concentration of the solution; the monomer predominantly exists in diluted solution.[6] Dilution of the reaction mixture was thus expected to be effective to suppress the undesirable dimerization of nitrosobenzene. Therefore, the reaction was performed under the diluted conditions using *tert*-butyl methyl ether as a solvent as shown in Table 2. Under the diluted conditions, the reaction was conducted on a 0.5 mmol scale in 18 mL of *tert*-butyl methyl ether as a solvent. Gratifyingly, the chemical yield was remarkably increased from 56% to 73% with high enantioselectivity (Entry 1). Furthermore, it was found that the slow charge of excess amount of solid nitrosobenzene deeply influenced the reactivity: when the 1.5 molar amounts of solid nitrosobenzene was added to the reaction mixture over a period of 3 h, the chemical yield was improved to 94% with excellent enantioselectivity up to 92% ee (Entry 2).



(4)

Table 2. The effect of the amount of nitrosobenzene under the diluted conditions[a]

Entry	*x*	Yield/%	ee/%[b]
1	1.0	73	89
2[c]	1.5	94	92
3[c]	2.0	92	91

[a] The reaction was carried out on a 0.5 mmol scale in 18 mL of solvent.

[b] Optical yields were determined by HPLC analysis (Daicel Chiralcel OJ-H).

[c] The solid nitrosobenzene was added over a period of 3 h.

The absolute configuration of **5** was determined to be *3S*,*6R* as follows: the enantiomerically pure **5** obtained by recrystallization from AcOEt was treated with (*S*)-*N*-(4-nitrophenylsulfonyl)-phenylalanyl chloride and triethylamine in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine in CH_2Cl_2 to give the corresponding condensation product **6** (71%). The absolute stereochemistry of **6** was determined to be *3S*,*6R* by X-ray crystallographic analysis of its single crystal shown in Figure 1.[7]

Although the precise reaction mechanism is not yet clear, the plausible transition state is shown in Figure 2 to rationalize the absolute configuration of **5** determined above.

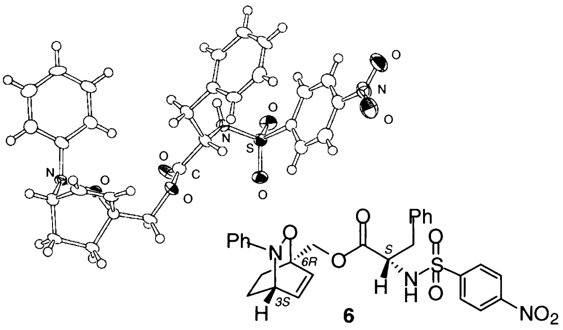


Figure 1.

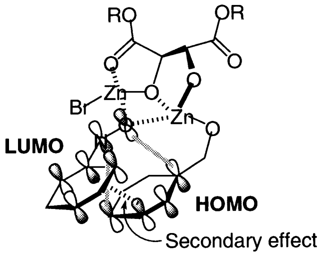


Figure 2.

In conclusion, we established the first successful example of enantioselective hetero Diels–Alder reaction of nitroso compound by utilizing tartaric acid ester as a chiral auxiliary, and the corresponding cycloadduct could be obtained with complete regioselectivity in excellent chemical yield and enantioselectivity. This approach will offer an appealing entry to the synthesis of six-membered heterocycles that are versatile synthetic intermediates for total syntheses of many natural products. Efforts to explore the scope of this novel process and to develop catalytic variants are currently in progress in our laboratory.

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References and Notes

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7 Single crystal of **6**·AcOEt was obtained by recrystallization from AcOEt. Mp: 89.2–91.5 °C. Found: C, 60.29; H, 5.54; N, 6.53%. Calcd for $C_{32}H_{35}N_3O_9S$: C, 60.27; H, 5.53; N, 6.59%. Crystal data: $C_{32}H_{35}N_3O_9S$, fw 637.70, orthorhombic, $P2_12_12_1$, $a = 8.568(2)$ Å, $b = 11.395(3)$ Å, $c = 31.586(9)$ Å, $V = 3083(1)$ Å^3, $Z = 4$. $D_{\text{calcd}} = 1.373$ g/cm^3. $R = 0.048$ ($Rw = 0.059$) for 3338 reflections with $I > 3.00s(I)$ and 406 variable parameters.

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