Base-Catalyzed Asymmetric Diels–Alder Reaction of 3-Hydroxy-2-pyrone and Simple Aryl Vinyl Sulfoxide: Asymmetric Synthesis of Carbaketopyranoses

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A highly stereoselective base-catalyzed asymmetric Diels–Alder reaction of 3-hydroxy-2-pyrone and simple aryl vinyl sulfoxide is reported. Furthermore, the synthetic utility of the resulting product was demonstrated by the efficient asymmetric synthesis of β-L-carbafructopyranose and β-L-carbapsicopyranose.

The base-catalyzed Diels–Alder (DA) reaction is a unique cycloaddition, which comprises the combination of electron-deficient dienophiles and dienes that are activated by a base.[1,2] It is quite the opposite of the well-known Lewis acid-catalyzed DA reactions that include electron rich dienes and dienophiles that are activated by a Lewis acid. Our research group has been conducting studies to develop base-catalyzed DA reactions[2] and has reported several synthetic applications of these reactions.[3]

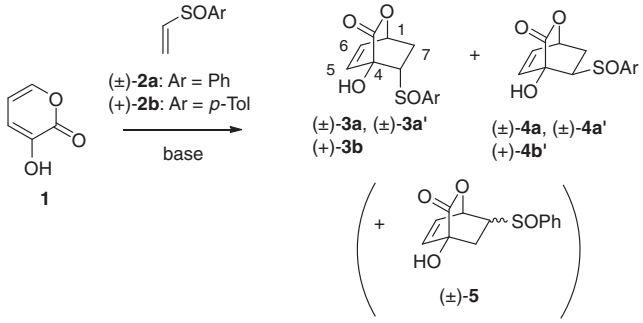
Vinyl sulfoxides are known as attractive chiral molecules for asymmetric synthesis.[4] They are easily available in optically pure form,[4b,4c] and their sulfur stereogenic center, which is close to the reactive vinyl group, can provide high stereoselectivity. Asymmetric DA reactions using vinyl sulfoxides as dienophiles are also well known to give optically active compounds, but in most cases, one or more activating groups, such as a carbonyl group and/or a nitro group, are needed to increase the reactivity of dienophiles.[5] To the best of our knowledge, there are very few reports on the asymmetric DA reaction using simple aryl vinyl sulfoxide and the stereoselectivity of the reaction is moderate.[6]

In this paper, we report a new efficient base-catalyzed asymmetric DA reaction of 3-hydroxy-2-pyrone[7] (**1**) and simple aryl vinyl sulfoxides **2**, and the concise enantioselective synthesis of two carbaketopyranoses **8** and **13** from the homochiral DA adduct (+)-**4b′** as its application.

Results and Discussion

The results of the base-catalyzed DA reaction of **1** and (±)-**2a** are listed in Table 1. Because (±)-**2a** is a less reactive dienophile,[5b,6] no product was obtained by the reaction without a base-catalyst. Even the reaction carried out in diluted solutions (CH_2Cl_2, THF, etc.) with 1.0 equiv of Et_3N, which was successful for the reaction of **1** and methyl acrylate,[2a,2c] gave no product (Entry 1). However, under a highly concentrated condition (neat condition), Et_3N and other amine catalysts were effective in affording a mixture of four or five DA adducts[8] (*endo* isomers, (±)-**3a** and (±)-**3a′** (a diastereomer of the sulfur stereogenic center of (±)-**3a**), *exo* isomers, (±)-**4a** and (±)-**4a′** (a diastereomer of the sulfur stereogenic center of (±)-**4a**), and a small amount of regioisomer (±)-**5** in Entries 2–5) in moderate yields after 3 days (Entry 2). The yields of the products were improved by gentle warming, but at higher temperature (above 80 °C) both of the products and pyrone **1** were decomposed and gave only tarry product.

Table 1. Base-Catalyzed DA Reaction of **1** and **2a**



Entry	Catalyst, equiv	Conditions	Yield /%[a]	*endo* /*exo*[b]	% de[b]
1	Et_3N, 1.0	CH_2Cl_2, rt, 3 days	0[c]	—	—
2	Et_3N, 1.0	neat, rt, 3 days	35[d]	2.7/1.0	80 (for **3a**) 69 (for **4a**)
3	Et_3N, 1.0	neat, 50 °C 3 days	70[d]	1.5/1.0	>95 (for **3a**) 73 (for **4a**)
4	Et_2NH, 1.0	neat, 50 °C 3 days	59[d]	1.8/1.0	77 (for **3a**) 51 (for **4a**)
5	*i*-Pr_2NEt, 1.0	neat, 50 °C 3 days	63[d]	2.3/1	65 (for **3a**) 46 (for **4a**)
6	DBU, 1.0	neat, 50 °C 3 days	73	1.4/1	>95 (for **3a**) >95 (for **4a**)
7	Li salt of **1**, 0.1	THF, 50 °C 3 days	66	1.6/1	85 (for **3a′**) >95 (for **4a′**)
8	Na salt of **1**, 0.1	DMF, 50 °C 3 days	55	1/1.7	35 (for **3a′**) 80 (for **4a′**)
9	K salt of **1**, 0.1	DMF, 50 °C 3 days	38	1.5/1	58 (for **3a′**) 14 (for **4a′**)
10	Mg salt of **1**, 0.1	THF, rt 3 days	38	1.7/1	>95 (for **3a′**) >95 (for **4a′**)
11	Mg salt of **1**, 0.1	THF, 50 °C 3 days	69	1/4.3	87 (for **3a′**) >95 (for **4a′**)
12	Mg salt of **1**, 1.0	THF, 50 °C 3 days	20	1/1.7	>95 (for **3a′**) >95 (for **4a′**)

a) Isolated yield of DA adducts mixture after SiO_2 column chromatography. b) The ratio was determined by ^{1}H NMR. c) The starting materials were recovered. d) Small amount (2%–3%) of **5** was a contaminant.

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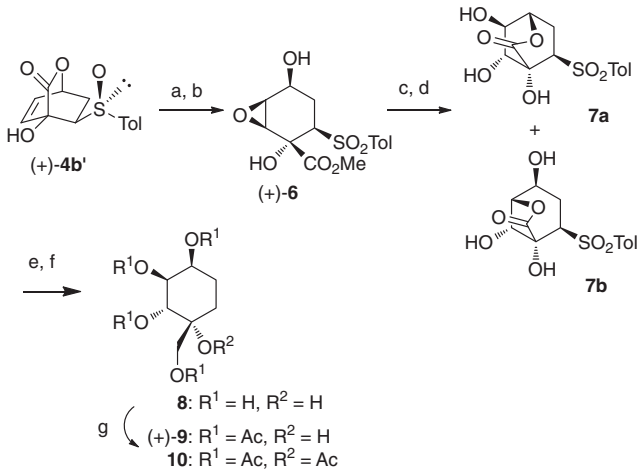
The catalysts listed in the table as "[metal salts] of **1**" were prepared by mixing **1** and the corresponding metallic bases such as *n*-BuLi, *t*-BuONa, *t*-BuOK, and MeMgBr in appropriate solvents (Entries 7–12). The reactions were carried out with 0.1 equiv of catalyst and gave mixtures of DA adducts in moderate to poor yields. By increasing the amounts of catalysts, the yields of the products significantly dropped as exemplified by Entry 12.

The stereochemistries of the *exo* products, (±)-**4a** and (±)-**4a′** were unambiguously determined as 1*R**,4*R**,8*S**,S*R** and 1*S**,4*S**,8*R**,S*R**, respectively, by comparing their ^{1}H NMR spectra with those of (+)-**4b**, which was established as 1*S*,4*S*,8*R*,S*R* by the asymmetric synthesis of β-L-carbafructopyranose tetracetate (+)-**9**[10b] (vide infra). For the *endo* products, (±)-**3a** and (±)-**3a′**, their stereochemistries were ascertained as 1*R**,4*R**,8*R**,S*R** and 1*S**,4*S**,8*S**,S*R**, respectively, by the chemical shift in the ^{1}H NMR signals of H7*endo*. The signal of H7*endo* in (±)-**3a′** showed a remarkable upfield shift compared to that in (±)-**3a**, which was explained by the shielding effect of the nearby phenyl group.[8] The structure of (±)-**5** was suggested to be a regioisomer by the chemical shift of H7 that appeared at a lower field (δ 3.97) and by the H1–H7 coupling in its ^{1}H–^{1}H COSY spectrum.[8]

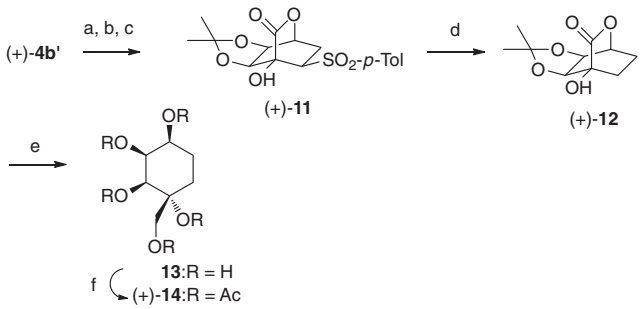
The stereoselectivity of the reaction was predominantly controlled by the catalyst and the reaction conditions. In the amine-catalyzed reactions (Entries 1–5), the *endo* isomers were slightly dominant over the *exo* isomers, and the diastereomers (±)-**3a** and (±)-**4a** were obtained as major stereoisomers. Although the change in the diastereomeric excess of (±)-**3a** listed in Entries 2 and 3 seemed to suggest that the diastereoselectivity was improved by heating, it could be explained by the decomposition of the products and isomerization of the *endo* isomer to a sterically less hindered *exo* isomer. Indeed, the Et_3N treatment of the products that was obtained from the reaction listed in Entry 2 at 50 °C for 3 days, decomposed a considerable amount of the products. The diastereomeric excesses of the recovered (±)-**3a** and (±)-**4a** were changed to 91% de and 65% de, respectively, and the *endo*/*exo* ratio dropped to 1.5/1.0.

In contrast, the reactions catalyzed by metal salts of **1** (Entries 7–12) gave (±)-**3a′** and (±)-**4a′** as major isomers. The best diastereoselectivity was observed in the reactions catalyzed by the Mg salt of **1**. The reaction carried out at room temperature (Entry 10) provided (±)-**3a′** and (±)-**4a′** in >95% de, although yield and *endo*/*exo* ratio were low (38% and 1.7/1, respectively). The reaction at 50 °C (Entry 11) increased the yield and the ratio of the *exo* isomer (69% and 1/4.3, respectively) and gave (±)-**4a′** in >95% de, which can again be explained by the thermal decomposition and *endo*–*exo* isomerization of the products.[9] The reactions catalyzed by Et_3N or DBU gave the product(s) in high diastereoselectivity, but their *endo*/*exo* ratio was low (Entries 3 and 5).

To demonstrate the synthetic utility of the resulting DA adduct, the concise asymmetric synthesis of two carbaketopyranoses were carried out as shown below. β-L-Carbafructopyranose **8**[10] was synthesized in six steps from an optically pure (+)-**4b′** that was obtained in 49% isolated yield by reacting **1** with (+)-**2b**[11] using the Mg salt of **1** as a catalyst (Scheme 1). The lactone ring of (+)-**4b′** was cleaved by



Scheme 1.



Scheme 2.

methanolysis to give an ester, and its olefin and sulfoxide moieties were oxidized simultaneously by *m*CPBA to give epoxysulfone (+)-**6** as a single diastereomer. The stereochemistry of the resulting oxirane ring was supposed to be β because of the diastereomeric induction of the neighboring secondary hydroxy group. The direct acidic hydrolysis of the epoxide was very slow and gave a complex mixture, which could be explained by the lactone formation through the free hydroxy and carbomethoxy groups in (+)-**6**. The acetylation of the secondary hydroxy group, which might prevent the lactonization, improved the hydrolysis and gave a mixture of lactones **7a** and **7b** in high yield. The reductive elimination of the sulfone moiety and the subsequent LAH reduction of the lactone carbonyl group in **7a** and **7b** afforded the desired compound **8** that was isolated as its tetraacetate (+)-**9** and pentaacetate **10**. By comparing the $[\alpha]_D$ value of (+)-**9** ($[\alpha]_D^{18} = 40$ (*c* 0.33, $CHCl_3$), literature value[10b] $[\alpha]_D^{24} = 46$ (*c* 1, $CHCl_3$)) and ^{1}H NMR spectrum of **10**[10a] with their reported data, the stereochemistry of **8** has been established as shown in Scheme 1. The overall yield of (+)-**9** and **10** was 36%.

The synthesis of β-L-carbapsicopyranose **13** was carried out as shown in Scheme 2. The sulfoxide (+)-**4b′** was first converted into sulfone by *m*CPBA oxidation, which was further transformed into (+)-**11** exclusively by OsO_4 oxidation of the olefin moiety followed by acetonide protection of the product diol. The reductive elimination of the sulfonyl group proceeded smoothly by using Raney Ni to give lactone (+)-**12**. Finally,

the reduction of the lactone carbonyl group gave desired β-L-carbapsicopyranose (**13**) that was isolated as its pentaacetate (+)-**14** after acetylation. The overall yield of (+)-**14** was 45%.

In conclusion, we have developed a new base-catalyzed asymmetric DA reaction of **1** and phenyl vinyl sulfoxide (±)-**2a**, which gave (±)-**3a** and (±)-**4a′** selectively by changing the catalyst. It is an exceptional example of highly stereoselective DA reaction using non-activated vinyl sulfoxide as a dienophile. The synthetic utility of the homochiral DA adduct (+)-**4b′** was demonstrated by the asymmetric synthesis of β-L-carbafructopyranose **8** and β-L-carbapsicopyranose (**13**).

Experimental

Typical Experimental Procedures of the DA Reaction of 1 and (±)-2a. Amine-Catalyzed Reaction: A homogeneously mixed **1** (1.0 mmol), (±)-**2a** (0.50 mmol), and amine catalyst (1.0 mmol) in a tightly capped glass tube was left in an oil bath (50 °C) for 3 days. The reaction mixture was diluted with a small amount of CH_2Cl_2 and subjected to short SiO_2 column chromatography to remove tarry by-products, the amine catalyst, and the starting materials. The ratio of the products in the resulting mixture was determined by ^{1}H NMR.[8]

Metal Salt-Catalyzed Reaction: A catalytic amount of metal-containing base described in the text (0.050 mmol) was added to a solution of **1** (1.0 mmol) and (±)-**2a** (0.50 mmol) in the solvent listed in Table 1 (0.50 mL). The resulting suspended mixture was heated at 50 °C in an oil bath for 3 days. The reaction mixture was diluted with aq. H_3PO_4 (5%, 5 mL) and extracted with AcOEt (5 mL, three times). The collected AcOEt solution was dried with $MgSO_4$ and concentrated to a crude DA mixture that was purified by short SiO_2 column chromatography. The ratio of the products in the resulting mixture was determined by ^{1}H NMR.[8]

For a detailed discussion of the stereochemistry of the products and their ^{1}H and ^{13}C NMR and IR spectra, see Supporting Information.

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Supporting Information

Experimental details for the synthesis of carbaketopyranoses and spectral data are provided in Supporting Information that is available free of charge on the Web at http://www.csj.jp/journals/bcsj/.

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