



Asymmetric Base-Catalyzed Diels-Alder Reaction of 3-Hydroxy-2-pyrone with Chiral Acrylate Derivatives

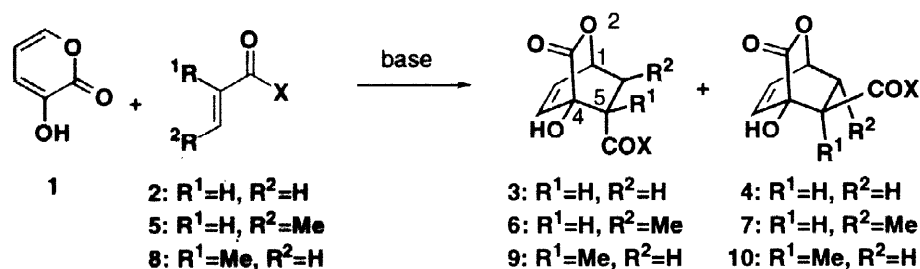
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Abstract: In the presence of a cinchona alkaloid as a catalyst, the Diels-Alder reaction of 3-hydroxy-2-pyrone with chiral *N*-acryloyl oxazolidinone afforded a bicyclic lactone adduct with high diastereoselectivities (up to 95%de) in almost quantitative yield. © 1998 Elsevier Science Ltd. All rights reserved.

Diels-Alder (DA) reactions of 2-pyrones¹ are superior method for preparing highly functionalized cyclohexene derivatives, which are attractive building blocks for natural product synthesis. Recent studies in our group have disclosed that the DA reaction of 3-hydroxy-2-pyrone² (**1**) with an electron deficient dienophile was catalyzed by a base and afforded DA adducts in nearly quantitative yield.³ In particular, when a cinchona alkaloid was used as an optically active base catalyst, up to 77%ee of the *endo* adduct was obtained in the reaction of **1** with *N*-methylmaleimide.⁴ In our continuous effort to obtain optically active adducts with other dienophiles, we found the highly stereoselective DA reaction of **1** with a dienophile having chiral oxazolidinone as an auxiliary⁵ (Scheme 1).



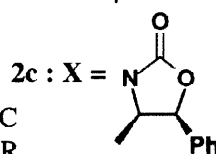
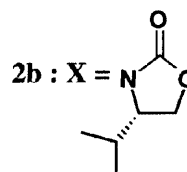
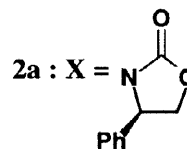
Scheme 1

We initially investigated the reaction of **1** with optically active *N*-acryloyloxazolidinone derivatives **2a-c**,⁶ and the results are summarized in Table 1. All the reactions proceeded smoothly at 0 °C and afforded bicyclic adducts with very high yields. The diastereoselectivities of the reactions were strongly dependent on the solvents. When the reactions were carried out in aprotic solvents, only the *endo* adducts (**3a-c**) were obtained, and their %de were moderate (53–69 %de, entries 1, 3–7, 9). However, when the reactions were executed in

isopropanol (i-PrOH), fairly good diastereoselectivities were observed. Interestingly, however, the reproducibility of %de was poor (73-86 %de for **3a**, 67-81 %de for **3b**).

Table 1. Et₃N catalyzed reaction of **2a-c** with **1**^a

entry	dienophile	solvent	yield (%) ^b	%de of 3 ^c
1	2a	CH ₂ Cl ₂	97	53
2	2a	i-PrOH	98 ^d	73-86
3	2b	CH ₂ Cl ₂	96	69
4	2b	Toluene	89	62
5	2b	THF	100	66
6	2b	AcOEt	97	62
7	2b	CH ₃ CN	79	54
8	2b	i-PrOH	88-100 ^d	67-81
9	2c	CH ₂ Cl ₂	95	62



a) All of the reactions were carried out with 1.0 eq Et₃N at 0 °C for 18-24h. b) Isolated yields for **3**. c) Determined by ¹H NMR analysis. d) Small amount of *exo* isomer **4** were contaminated.

Table 2. Reaction of **1** and **2a** and **b** under various conditions^a

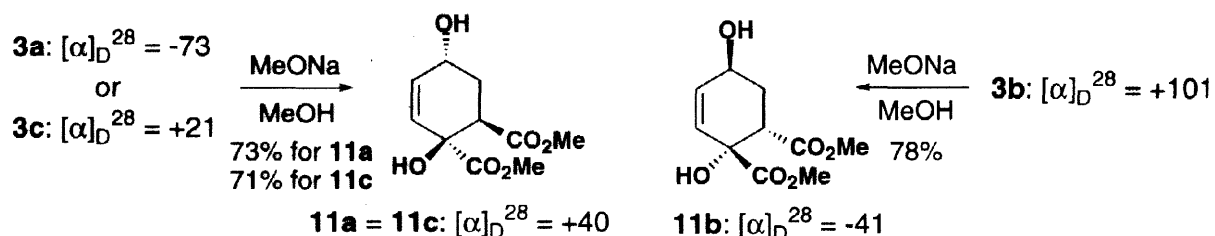
entry	dienophile	base	solvent	yield (%) ^b	3 : 4 ^c	%de of 3 ^c
1	2a	Et ₃ N	dry i-PrOH	100	.. ^e	69
2	2a	Et ₃ N	i-PrOH : H ₂ O = 95 : 5	99	.. ^e	82
3	2a	Et ₃ N	i-PrOH : H ₂ O = 90 : 10	98 ^d	7.6:1	76
4	2a	Et ₃ N	i-PrOH : H ₂ O = 80 : 20	87 ^d	2.2:1	61
5	2a	Et ₃ N	i-PrOH : H ₂ O = 70 : 30	72 ^d	0.96:1	53
6	2a	cinchonidine	dry i-PrOH	100	.. ^e	89
7	2a	cinchonidine	i-PrOH : H ₂ O = 95 : 5	93	.. ^e	95
8	2a	cinchonidine (0.1eq)	i-PrOH : H ₂ O = 95 : 5	94	.. ^e	95
9	2a	cinchonine (0.1eq)	i-PrOH : H ₂ O = 95 : 5	97	.. ^e	79
10	2a	quinine (0.1eq)	i-PrOH : H ₂ O = 95 : 5	100	.. ^e	94
11	2a	quinidine (0.1eq)	i-PrOH : H ₂ O = 95 : 5	97	.. ^e	84
12	2b	cinchonine	i-PrOH : H ₂ O = 95 : 5	100	.. ^e	95

a) All of the reactions were carried out at 0°C with 1eq of base, except for entries 8-11. b) Isolated yield for **3** and **4**. c) The ratio and the %de was determined by ¹H NMR analysis. d) The yield contained the *exo* isomer. e) No *exo* adduct was obtained.

From a detailed study of the reaction conditions, we found that the presence of H₂O in i-PrOH was an important factor in controlling the diastereoselectivity (**Table 2**). In the reaction with **2a**, the addition of a small amount of water (i-PrOH : H₂O = 95 : 5) improved the diastereoselectivity up to 82 %de (entry 2),

whereas the reaction in dry *i*-PrOH afforded **3** with only moderate %de (entry 1). However, the further addition of water lowered the *endo/exo* ratio, the %de of the *endo* adduct and the chemical yield (entries 3-5). Improvement of the diastereoselectivity was accomplished by the addition of a chiral base (entries 6-11). When cinchonidine was used as the chiral base, the diastereoselectivity was improved up to 95 %de (entry 7), and no lowering of the selectivity was observed even by use of catalytic cinchonidine (0.1 eq) (entry 8). These conditions were also effective for the reaction with **2b**, but cinchonine was a more effective base than cinchonidine because of the double stereodifferentiation⁷ between the dienophile and the chiral base (entry 12).

The absolute stereochemistry of the bicyclic lactone moiety of **3a** was determined as *1R*, *4S*, *5R* by a conversion into (-)-pseudo- α -L-mannopyranose pentacetate.^{8,9} The stereochemistry of **3b** and **c** was also established by comparison of the $[\alpha]_D$ of their methanolized compounds **11b** and **c** with that of **11a** (Scheme 2). As expected from the stereochemistry of their chiral auxiliaries, the configurations of **11a** and **b** were exact opposites.



*All $[\alpha]_D$ values were measured for homochiral samples in CHCl_3 .

Scheme 2

We next examined the reaction with the less reactive dienophiles, *N*-crotonoyl- and *N*-methacryloyl-5-phenyloxazolidinones (**5a** and **8a**, respectively). The reaction of **5a** required three days at room temperature to complete, whereas the reaction of **8a** afforded only a trace amount of product even after a week. We therefore examined only **5a** in detail (Table 3). The use of a chiral base was also effective (entries 1 and 2), but when aqueous *i*-PrOH was used as a solvent, no bicyclic adduct was obtained because of the solvolysis of the product (entry 3). The reaction in more bulky alcohols, 2-methyl-2-butanol (*t*-Amyl alcohol) and 2-methyl-2-propanol (*t*-BuOH) afforded the bicyclic lactone **6a** in good yields (entries 4 and 5). Even with the addition of a small amount of H_2O , however, both the chemical yields and the selectivities were reduced (entries 6 and 7). Consequently, the highest selectivity (81%dc) was obtained by the reaction in *t*-BuOH with 1 eq. of cinchonidine (entry 5).¹⁰

In conclusion, we have developed a highly stereoselective base-catalyzed DA reaction of **1** with chiral *N*-acryloyl and *N*-crotonoyl oxazolidinones (**2** and **5**) which affords optically active and highly functionalized bicyclic lactones (**3** and **6**). In particular, the reaction with easily available **2a** and **b** afforded the adducts **3a**

and **b** in 95%de, which were easily purified by silica gel column chromatography to give homochiral bicyclolactones in gram quantities. These bicyclolactones, therefore, can be utilized as practical building blocks for the asymmetric synthesis of complex molecules. Indeed, we have achieved an asymmetric synthesis of pseudo-sugar from **3a**,⁸ and the further application of this reaction to an asymmetric synthesis of a bioactive compound is now underway.

Table 3. Reaction of **1** and **5a**.^a

entry	base	solvent	yield (%) ^b	%de of 6a ^c
1	Et ₃ N	CH ₂ Cl ₂	65	59
2	cinchonidine	CH ₂ Cl ₂	78	72
3	cinchonidine	i-PrOH : H ₂ O = 95:5	-	
4	cinchonidine	t-Amyl alcohol	96	72
5	cinchonidine	t-BuOH	87	81
6	cinchonidine	t-BuOH : H ₂ O = 99 : 1	81	73
7	cinchonidine	t-BuOH : H ₂ O = 95 : 5	59 ^d	71

a) All of the reactions are carried out at room temperature for 3-5 days with 1eq of base. b) Isolated yield of **6a** after chromatographic purification. In all cases, no *exo*-adduct **7a** was obtained. c) %de was determined by ¹H NMR analysis. d) Small amount of hydrolyzed compounds were contaminated.

References and Notes

1. K. Afarinkia, V. Vinader, T. D. Nelson, and G. H. Posner, *Tetrahedron*, **1992**, *48*, 9111-9171; J. A. Gladysz, S. J. Lee, J. A. V. Tomasello, and Y. S. Yu, *J. Org. Chem.*, **1977**, *42*, 4170-4172.; V. Prapansiri and E. R. Thoronton, *Tetrahedron Lett.*, **1991**, *32*, 3147-3150.; K. Narasaka, S. Shimada, K. Osoda, and N. Iwasawa, *Synthesis*, **1991**, 1171-1172.; K. C. Nicolaou, J. J. Liu, C.-K. Hwang, W.-M. Dai, and R. K. Guy, *J. Chem. Soc., Chem. Commun.*, **1992**, 1118-1120.
2. For preparation of 3-hydroxy-2-pyrone, see: J. A. Profitt, T. Jonse, and D. S. Watt, *Synthetic Commn.*, **1975**, *5*, 457-460.
3. H. Okamura, T. Iwagawa, and M. Nakatani, *Tetrahedron Lett.*, **1995**, *30*, 5939-5942.
4. H. Okamura, Y. Nakamura, T. Iwagawa, and M. Nakatani, *Chem. Lett.*, **1996**, 193-194.
5. For excellent review of chiral auxiliaries see: D. A. Evans, *Aldrichimica Acta*, **1982**, *15*, 318-327.
6. Chiral auxiliaries of **2a-c** were derived from D-phenylglycinol, L-valinol, and (+)-norepedrine, respectively.
7. S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **1985**, *24*, 1.
8. We have synthesized (-)-pseudo- α -mannopyranose pentacetate ($[\alpha]_D^{28} = -35$, mp. 85-87°C; lit.⁹ $[\alpha]_D^{28} = -38.5$, mp. 84-86°C) from **3a**. A detailed report of the asymmetric synthesis of pseudo-sugar is being preparing for publication.
9. K. Tadano, H. Maeda, M. Hoshino, Y. Iimura, and T. Suami, *J. Org. Chem.*, **1987**, *52*, 1946-1956.
10. The stereochemistry of **6a** was not established but should be the same as **3a** since the optical rotation of the methanolized compound ($[\alpha]_D^{28} = +55$) is similar with that of **11a** ($[\alpha]_D^{28} = +40$).