Asymmetric Base-Catalyzed Diels-Alder Reaction of 3-Hydroxy-2-Pyrone with *N*-Methylmaleimide

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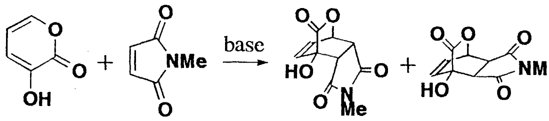
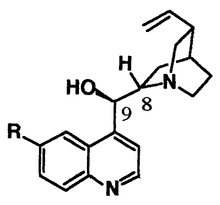
An asymmetric base-catalyzed Diels-Alder reaction of 3-hydroxy-2-pyrone with *N*-methylmaleimide was achieved by using cinchona alkaloids as asymmetric catalysts. The reaction catalyzed by cinchonidine afforded *endo*-adduct in 77% ee, and opposite enantiomer of 71% ee was obtained with cinchonine.

Diels-Alder (DA) reactions are usually catalyzed by Lewis acids, and several asymmetric acid-catalyzed reactions have been reported.[1] However, DA reactions catalyzed by bases are unusual,[2] and only one asymmetric base-catalyzed reaction is known.[3]

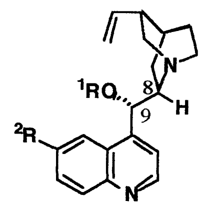


(1)

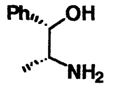
1 **2** **3a** *endo*-adduct **3b** *exo*-adduct



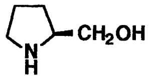
4: R = H, cinchonidine
5: R = OMe, quinine



6a: R^1, R^2 = H, cinchonine
6b: R^1 = CH_3CO, R^2 = H
6c: R^1 = PhCO, R^2 = H
7: R^1 = H, R^2 = OMe, quinidine



8: (+)-norephedrine



9: (+)-prolinol

A DA reaction of 3-hydroxy-2-pyrone[4] (**1**) with dienophile affords highly functionalyzed bicyclic lactones. Since the adducts are anticipated to be useful building blocks for natural product syntheses, several reactions which give bicycloadducts have been developed.[5] We recently found that the reaction of **1** with dienophile was catalyzed by base (eq. 1).[6] In particular, when triethylamine was used as a catalyst, the adducts were obtained in almost quantitative yields. This method is quite efficient, since it can be applied to practical large-scale synthesis with a wide range of dienophiles.

In addition to the various functionalities, the resulting adducts have four consecutive asymmetric centers. Therefore, if the adducts can be obtained in an optically pure form, this reaction will make an effective synthetic tool for asymmetric synthesis. In this letter, we wish to describe the asymmetric base-catalyzed DA reactions of **1** with *N*-methylmaleimide (**2**).

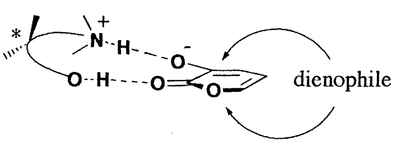


Figure 1. Expected complex of **1** and aminoalcohol.

The intermediate of the base-catalyzed DA reaction of **1** is presumed to be an oxyanion of **1** which constitutes an ion-pair with the conjugated acid of the base-catalyst in the solvent. Therefore, when optically-active base is used as a catalyst, the asymmetric intermediate which is expected to cause enantioselective cycloaddition can be obtained. In this study, we chose optically-active aminoalcohols **4**-**9** as asymmetric catalysts. These catalysts were expected to form rigid complexes with **1** by ionic and hydrogen bondings (Figure 1).

The results of the reactions with optically active aminoalcohols are listed in Table 1. All the reactions afforded *endo*-bicycloadduct **3a** as a major product, and its enantiomeric excess was determined with ^1H NMR by using *R*-(+)-binaphthol as a chiral shift reagent.[7] A considerable level of enantioselective reactions was achieved by cinchona alkaloids (entries 1-4). The sense of asymmetric induction of cinchonidine (**4**) and quinine (**5**) was opposite to that of cinchonine (**6a**) and quinidine (**7**), which reflected the stereochemistry of C-8 and C-9 in cinchona alkaloids.[8] Cinchona alkaloid esters **6b** and **6c** (entries 7 and 8), however, showed only poor asymmetric induction (17 and 0% ee, respectively). This indicates that the hydrogen bonding between hydroxyl group in cinchona alkaloid and carbonyl oxygen of **1** is necessary to form a rigid complex of **1** with catalyst.

To find appropriate conditions, the reactions with **4** and **6a** were further examined (Table 2). As expected from the ionic nature of the reaction intermediate, the polarity of solvents strongly affected the optical purity of **3a**. The highest enantioselectivity (77% ee) was achieved with 1eq. of **4** in

Table 1. DA reactions of **1** and **2** with aminoalcohols[a]

entry	catalysts (eq)	time/h	yield/%[b]	**3a**:**3b**[c]	%ee[d]
1	**4** (1.0)	0.5	91	7.8:1	74 (-)
2	**5** (1.0)	0.5	100	8.2:1	53 (-)
3	**6a** (0.1)[e]	0.5	95	7.1:1	71 (+)
4	**7** (1.0)	0.5	100	7.2:1	42 (+)
5	**8** (1.0)	0.5	84	9.6:1	14 (+)
6	**9** (1.0)	0.5	98	8.5:1	9 (-)
7	**6b** (1.0)	1.0	93	5.9:1	17 (+)
8	**6c** (1.0)	1.5	93	6.6:1	0

[a] All the reactions were carried out in CH_2Cl_2 at 0 °C. [b] Isolated yields of a mixture of **3a** and **b**. [c] Ratios of **3a**:**3b** were determined by ^1H NMR. [d] % ee of **3a**. Signs of optical rotation of **3a** measured in acetone are shown in parenthesis. [e] The amount of catalyst is dependent on its solubility in the solvent.

Table 2. Reactions with cinchonidine (**4**) and cinchonine (**6a**) under various conditions[a]

entry	catalysts	solvent	temp/°C	yield/%[b]	**3a**:**3b**	% ee[c]
1	**4** (1.0)	CH_2Cl_2	-78--20	98	11:1	77
2	**4** (1.0)	CH_2Cl_2	0	91	7.8:1	74
3	**4** (0.1)	CH_2Cl_2	0	100	6.9:1	66
4	**4** (<0.1)[d]	toluene	0	89	2.6:1	63
5	**4** (1.0)	THF	0	96	2.1:1	33
6	**4** (1.0)	MeOH	0	98	7.7:1	0
7	**6a** (<0.1)[d]	CH_2Cl_2	-78--20	95	12:1	51
8	**6a** (0.1)[d]	CH_2Cl_2	0	95	7.1:1	71
9	**6a** (<0.1)[d]	toluene	0	93	3.7:1	44
10	**6a** (0.5)[d]	THF	0	95	4.6:1	35
11	**6a** (1.0)	MeOH	0	100	10:1	0

[a] All the reactions were completed within 30 min except for entries 1 and 7 which required 18 h to finish. [b] Isolated yields. [c] % ee of **3a**. [d] The amount of catalyst is dependent on its solubility in the solvent.

CH_2Cl_2 at -78 to -20 °C (entry 1), and the opposite enantiomer with 71% ee was obtained with 0.1eq. of **6a** in CH_2Cl_2 at 0 °C (entry 8). On the other hand, when MeOH was used as a solvent, racemic **3a** was obtained (entries 6 and 11). In addition to the solvent polarity, the amount of catalyst also affected the enantioselectivity. For example, despite its lower polarity, toluene was not as an effective solvent as CH_2Cl_2 (entries 4 and 9), since the catalysts were barely soluble in toluene (less than 0.1eq.). Actually, the effect of catalyst equivalence was confirmed from the results of entry 3. Lower enantioselectivity of **6a** at low temperature (entry 7) was also explained from the poor solubility of the catalyst at the temperature.

In addition to the enantioselectivity, diastereoselectivity of this reaction also varied by reaction conditions, particularly by solvent. Relatively high diastereomeric ratios of **3a** and **b** were observed with CH_2Cl_2 (entries 1, 2, 3, 7, and 8) and MeOH (entries 6 and 11), and poor selectivities appeared in toluene (entries 4 and 9) and THF (entries 5 and 10). At present the reason is not clear.

In conclusion, asymmetric base-catalyzed DA reaction of 3-hydroxy-2-pyrone (**1**) with *N*-methylmaleimide (**2**) was achieved by using cinchona alkaloids as asymmetric catalysts. Since (-)- and (+)-enantiomers of the adduct **3a** can be obtained with cinchonidine (**4**) and cinchonine (**6a**), respectively, this reaction is expected to become a useful method for asymmetric synthesis.

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References and Notes

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7 The enantiomeric excess of **3a** was determined from the integral of ^1H NMR of 6-H signal. When ^1H NMR of **3a** was measured in a saturated $CDCl_3$ solution of *R*-(+)-binaphthol, the signal corresponding to (+)-enantiomer of **3a** appeared at 3.58 ppm and the signal of (-)-enantiomer was observed at 3.50 ppm.

8 Similar reversal of asymmetric induction was also observed for asymmetric Diels-Alder reaction of anthrone and dienophiles.[3]