Chiral guanidine catalyzed Michael addition reaction and Diels-Alder reaction of anthrone and *N*-methylmaleimide

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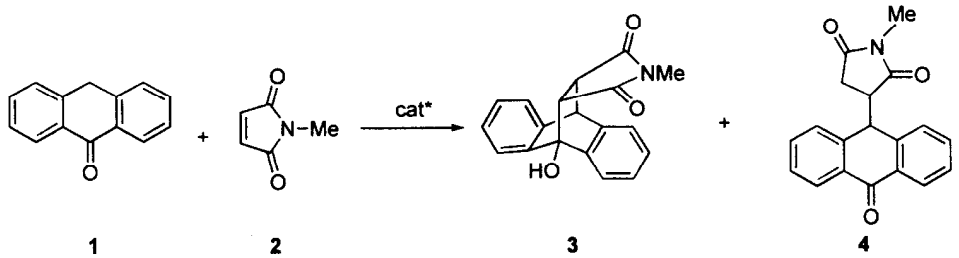
Two chiral guanidines were evaluated as catalysts for the reaction of anthrone (1) with *N*-methylmaleimide (2). When guanidine 5 was used, the Michael adduct 4 was isolated as a major product. The best enantioselectivity (70% *ee*) was obtained when the reaction was carried out in THF at −20℃.

Keywords Chiral catalysts, guanidine, cycloaddition, michael addition

About ten years ago, Rickborn and Koerner reported an unusual base-catalyzed Diels-Alder reaction.[1,2] They found that the cycloaddition of anthrone (**1**) and naphthacene analogues proceeded easily with *N*-methylmaleimide (**2**) at room temperature under the catalysis of various bases to give cycloadduct **3** and Michael adduct **4**. The ratio of **3** to **4** was highly dependent on reaction time and prolonging reaction time would only deliver the compound **4**. Later, Kagan,[3,4] Yamamoto[5] and their coworkers observed that this reaction proceeded enantioselectively if a suitable chiral base was used as catalyst and the enantiomeric excess of the product **3** was up to 61%. These results represent an example of chiral base catalyzed Diels-Alder reactions that were rarely reported. We have demonstrated that some chiral guanidines could catalyze asymmetric Michael addition reaction.[6] When we applied these chiral guanidines to the reaction of **1** and **2**, we found that in most cases the Michael adduct **4** was the major product and the enantiomeric excess of the product **4** was up to 70%. Herein we wish to detail our results.



1 **2** **3** **4**

As shown in Table 1, we chose chiral guanidines **5** and **6** as catalysts. When **6** was used, the cycloadduct **3** was obtained as the major product with very low *ee* value (Entry 9). This reaction result is quite similar to those using other amines as catalysts. However, when **5** was used, the Michael adduct **4** was formed exclusively and the major enantiomer has *R* configuration. Among the solvents tested, THF gave the best result and the enantiomeric excess of the product **4** was up to 70% if the reaction was carried out at −20℃ (Entry 1). Other

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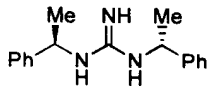
solvents such as methylene chloride, chloroform and ether gave worse outcome in enantioselectivity. Lower reaction temperature was also of benefit for enantioselectivity because if the reaction was carried out at 0℃ the *ee* value of the product **4** dropped greatly (compare Entries 1 and 2). The reason for different product selectivity caused by catalyst **5** with other base catalysts is not clear.

Table 1 Chiral guanidines catalyzed reaction of **1** and **2**[a]

Entry	Cat.	Solvent	Temperature (℃)	Yield of **4** (%)[b]	Yield of **3** (%)[b]	$[\alpha]_D$ of **4**	*ee* (%) of **4**
1	**5**	THF	-20	67	<3	+96.6	70[c]
2	**5**	THF	0	88	—	+31.0	22.4[d]
3	**5**	CH_2Cl_2	-20	95	—	+80.9	58.6[c]
4	**5**	$CHCl_3$	-20	63	—	+50.6	36.6[d]
5	**5**	CH_3CN	-20	80	4.5	+25.7	18.6[d]
6	**5**	Et_2O	-20	—[e]	—	—	—
7	**5**	Et_2O	-5	56	6.5	+39.9	41.3[d]
8	**5**	C_6H_6	-5	77	—	+12.6	13.1[d]
9	**6**	THF	-10	14	68[f]	-5.2	3.8[d]

[a] Reaction condition: **1** (1 mmol), **2** (1 mmol), guanidine (0.1 mmol), solvent (5 mol). The reaction completion was checked by TLC. [b] Isolated yield. [c] Determined by chiral HPLC analysis using a Chiralpak AD column. [d] Determined by comparing the rotation values. [e] No reaction occurred. [f] $[\alpha]_D = -1.1$, *ee* = 2%.



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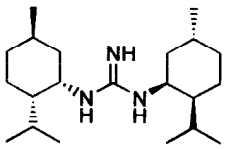
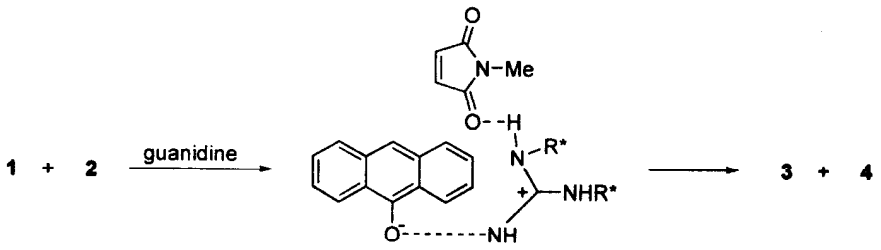


6

Although it was put forward that the Michael adduct **4** might form from the intermediate **3**, in our case it was also possible that the product **4** might directly form by the Michael addition reaction. In Kangan's report,[4] a possible doubly hydrogen bonded system model is proposed to explain the reaction mechanism. It is reasonable to extend this model to the present case. In our reaction, the chiral guanidine, anthrone (**1**) and *N*-methylmaleimide (**2**) might form **A** through two hydrogen bonds and then the Michael addition or Diels-Alder reaction occurred in an enantioselective manner. This model could be employed to explain the difference in enantioselectivity caused by the guanidines **5** and **6**. Due to the steric hindrance, the guanidine **6** might not easily form the transition state **A** and thereby giving poor enantioselectivity.



A

As a conclusion, we have demonstrated that chiral guanidine **5** is a good catalyst for reaction of anthrone (**1**) and *N*-methylmaleimide (**2**) to give the Michael adduct **4**. The enantiomeric excess of this product was up to 70%. This result is better than what have been observed.[3-6] Further application of these catalysts to other reactions is in progress.

Experimental

(*R*, *R*)-*N*, *N'*-Bis(1-phenylethyl)guanidine (**5**) and (1*R*,2*S*,5*R*)-*N*, *N'*-bis(2-isopropyl-5-methylcyclohexyl)guanidine (**6**) were prepared according to the procedures as described in the previous paper.[6] The enantiomeric purity of the reaction products were determined by chiral HPLC analysis using a Chiralpak AD column with 2/3 isopropyl alcohol/hexane for elution at 25℃. The configuration of each product was assigned by comparing its rotation with that reported. ^{1}H NMR spectra were recorded with TMS as an internal standard at a Brucker AM-300 spectrometer. MS spectra were determined on a Finnigan 4201 spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter.

General procedure for chiral guanidine catalyzed reaction of **1** *and* **2** To a mixture of anthrone (**1**, 194 mg, 1 mmol) and *N*-methylmaleimide (**2**, 111 mg, 1 mmol) in 5 mL of appropriate solvent was added chiral guanidine **5** (0.1 mmol) at −20℃ under nitrogen. The resultant mixture was stirred at the same temperature until the starting material disappeared monitored by TLC. After the reaction completed, 5 mL of 1 N aqueous HCl was added and the mixture was diluted with 30 mL of ethyl acetate. The organic layer was separated and washed with brine. After it was dried over Na_2SO_4, the solution was concentrated via rotavapor. The residue was chromatographed with elution by 1/6 ethyl acetate/petroleum ether to afford **3** and **4**.

3 δ_H($CDCl_3$): 2.51(s, 3H), 3.14(d, J = 8.1 Hz, 1H), 3.35(dd, J = 8.2, 3.6 Hz, 1H), 4.48(s, 1H), 4.75(d, J = 3.4 Hz, 1H), 7.03—7.81(m, 8H). *m/z*(%): 305(M^+), 193, 165, 83.

4 δ_H($CDCl_3$): 1.85(dd, J = 18.3, 4.9 Hz, 1H), 2.22(dd, J = 18.3, 9.1 Hz, 1H), 2.88(s, 3H), 3.45(ddd, J = 9.0, 4.9, 3.5 Hz, 1H), 5.18 (d, J = 3.5 Hz, 1H), 7,38—8.35(m, 8H). *m/z* (%): 305(M^+), 194, 165, 83.

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