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ASYMMETRIC DIELS-ALDER REACTION CATALYZED BY CHIRAL BASES

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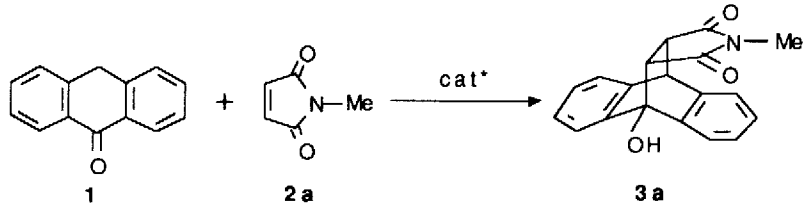
Abstract : Anthrone has been found to react with N-methyl maleimide in the presence of catalytic amounts of various chiral β-amino alcohols. The optically active cycloadduct **3a** has been obtained in excellent yield. Several features of the reaction have been studied.

The asymmetric Diels-Alder reaction has been extensively studied when a chiral auxiliary is bound to one of the reactants[2], and in the presence of stoichiometric amounts of chiral Lewis acids[3-6]. *Asymmetric catalysis* is obviously the most promising process in asymmetric synthesis. Asymmetric Diels-Alder reactions catalyzed by chiral Lewis acids based on aluminum[7-9], titanium[10,11], europium[12], or boron[13,14] have been recently described. We wish to present a unique case of asymmetric catalysis of the Diels-Alder reaction in which the catalyst is a chiral base such as an alkaloid.

Anthrone **1**, gives Diels-Alder adducts with various dienophiles under basic conditions[15,16], and a fast reaction between **1** and N-methylmaleimide **2a** occurs in DMF, pyridine or NEt_3, or in chloroform after addition of a small amount of NEt_3[15].This was ascribed to an oxyanion acceleration (presumably via the enolate of **1**)[15]. We report here our results concerning asymmetric cycloadditions between anthrone **1** and N-substituted maleimide **2** catalyzed by various chiral amines . This provides the first example of a *base-catalyzed asymmetric Diels-Alder reaction.*



1 **2a** **3a**

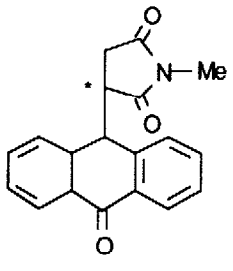
At room temperature, a fast reaction occurs when 1 to 10% equiv of an alkaloid is added to a chloroform solution of equimolar amounts of **1** and **2a**. Representative results are listed in Table 1. The isolated yields are in the range of 85-100%. Very often one recovers optically active cycloadduct **3a**. The measurement of the enantiomeric excess of **3a** could not be made on the basis of its specific rotation, since optically pure **3a** is unknown. However, enantiomer separation occurs by HPLC on Sumipax OA-2000. This allowed us to evaluate the ee's of the experiments in Table 1. The best result at room temperature was 35% ee, when using quinidine as catalyst. By decreasing the temperature to -50°C, the ee rises to 61%. With N-phenylmaleimide **2b**, the reaction is slower, and the ee is lower. A free OH group in the catalyst seems necessary for achieving a high optical yield. When quinidine is replaced by dihydroquinidine O-*p*-chlorobenzoate, the adduct **3a** is obtained in racemic form. Various types of β-aminoalcohols have been found to be catalytically active for the asymmetric synthesis of **3a** (Table 1). Quinidine and prolinol are the most enantioselective catalysts.

Table 1

Base-catalyzed asymmetric Diels-Alder reaction between **1** and **2a**

	Catalyst[a]	Temp. (°C)[b]	Isol. yield (%)[c]	$[\alpha]_D$ **3a**[d]	ee (%)[e]
1	Quinine	25	90	-19°	26
2	Quinine	0	96	-23°	32
3	Quinidine	25	100	+25.5°	35.5[f]
4	Quinidine	-20	100	+35.5°	50
5	Quinidine	-50	97	+43.5°	61
6	Quinidine	25[g]	95	+16.5°	23.5
7	Cinchonine	25	84	-11°	16
8	Cinchonine	-20	90	-4.5°	6.5
9	Cinchonidine	25	98	+20.5°	27
10	Cinchonidine	-20	90	+15.5°	21.5
11	(S)-Prolinol	-20	100	-30°	43
12	(1R,2S)-N-Me ephedrine	-20	86	+12°	17
13	Quinidine	25[h]	95	+31.5°	44
14	Quinidine	0[i]	100	+31.5°	44

[a] 10% mol equiv, except entry 14 (1% mol equiv). [b] Standard reaction performed in chloroform, with [**1**] = 0.1 M , for 15 min., at 25°C. At lower temperature the reaction completion was checked by tlc or polarimetry. [c] Flash-chromatography on silica gel (Cyclohexane / EtOAc 1:1). [d] $[\alpha]_D$ =+71.5° (C=1, $CHCl_3$) for enantiomerically pure **3a** (calculated from hplc measurements of ee). [e] Measured by hplc (Sumipax OA-2000, solvent : hexane / 1,2-dichloro-ethane / EtOH = 450 : 50 : 2, detect. 230 nm). [f] Same value when [**1**] = 0. 25 M or 0.05 M. [g] In toluene. [h] In CCl_4. [i] 1% equiv catalyst.



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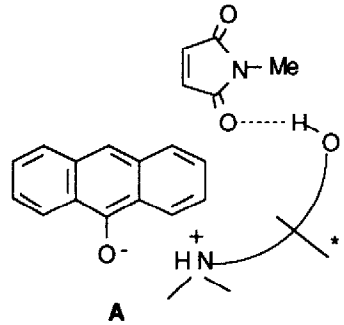

A

A typical catalyzed asymmetric Diels-Alder reaction is conducted as follows : 162 mg (0.5 mmol) of quinidine are added at room temperature to a solution of 970 mg - (5 mmol) of **1** and 555 mg (5 mmol) of **2a** in 50 ml of chloroform. After 15 min 1N HCl and dichloromethane are added, the organic phase is recovered and washed several times by aqueous 1N HCl. The crude product **3a** (1.45 g, $[\alpha]_D$ = +25.5°($CHCl_3$), 95% yield) is analyzed by chiral hplc , showing 35% ee. The ^1H nmr spectrum of **3a** showed it to be chemically pure .

KF (1 equiv) and Quibec (N-benzylquininium chloride[19]) (0.02 equiv) have also been used in conditions of phase-transfer catalysis in toluene. Surprisingly, the main product is then the Michael adduct **4** (80% isolated yield, $[\alpha]_D$ = + 26°, $CHCl_3$); cycloadduct **3a** was formed in minor amounts. The enantiomeric excess of **4** (16%) could be measured by chiral hplc (OT (+), Daicel Co).

The formation of **4** raises the possibility of a two-step mechanism in the asymmetric synthesis of cycloadduct **3a** (Michael addition followed by an intramolecular aldolization). This mechanism is not in agreement with the studies in ref.15 and with some of our experiments. Thus **4** could not be cyclized into **3a** by quinidine in chloroform under the conditions of the asymmetric synthesis. Cycloadduct (-)-**3a** (30% ee) reverses in excellent yield into (-)-**4** when heated at reflux in ethanol. Enantiomerically pure **4** ($[\alpha]_D$= -160°, $CHCl_3$) was isolated by fractional crystallization[17].

Our results clearly show that **3a** has been formed by a base-catalyzed Diels-Alder reaction, as previously stated by Koerner and Rickborn[15] when using small amounts of NEt_3. The asymmetric induction that we observed in the process could be related to a reactive intermediate such as **A** where the achiral dienolate is associate to a chiral counter-ion (protonated chiral amine) which itself is associated to **2a** (presumably by a hydrogen bond through the OH). The asymmetric synthesis will occur under the influence of the chiral backbone of the β-aminoalcohol, which will force the *re* and *si* prochiral centers on one face of **2a** to be regioselectively placed above the two ends of the dienolate. In absence of information on the absolute configuration of **3a** it is impossible to propose a more detailed picture for the preferred transition state[18]. Efficient asymmetric catalysis by chiral organic bases or by chiral phase-transfer catalysts mainly derived from alkaloids[19-21] usually requires the maximum association between ionic species in the organic phase. In our case, too, it is important to select the proper solvent. Thus, when chloroform is replaced by methanol, ee drops from 35 to 0%.

The dichotomy between the reaction pathways to Diels-Alder or to Michael adducts could be related to the structure (charge distribution) of the ionic species deriving from the dienol of anthrone **1**. An almost naked ion (such as formed with KF / Quibec) will react as a nucleophile[22], while the use of tertiary amines will give rise to an hydrogen-bonded ion-pair (because of $^+NHR_3$ cation), with a trend for [4 + 2] cycloaddition. It could be also possible to envisage that the reactive species for the Diels-Alder reaction is the anthrone dienol, hydrogen-bonded to amine[24].

In conclusion it has been established for the first time that chiral bases are able to act as catalyst in some Diels-Alder reactions. We are currently investigating the scope[26] and the mechanism of this class of asymmetric reactions, where "molecular engineering" of chiral catalysts offers numerous opportunities .

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