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Asymmetric Base-Catalyzed Cycloaddition Between Anthrone and Some Dienophiles

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Abstract : Anthrone has been found to react with N-methylmaleimide in the presence of catalytic amounts of various chiral β-aminoalcohols. The cycloadduct **3a** has been obtained in excellent yield with enantiomeric excess of up to 61%. Its absolute configuration has been assigned by X-ray crystallography. Several features of the reaction have been studied: variation of dienophile; competition between cycloaddition and formation of the optically active Michael adduct **4**; solvent and temperature effects. Mechanistic studies are in agreement with a concerted [4+2] process, providing an unique case of a base-catalyzed asymmetric Diels-Alder reaction.

The asymmetric Diels-Alder reaction has been extensively studied especially when a chiral auxiliary is bound to one of the reactants.[2] Excellent results have also been obtained in the presence of stoichiometric amounts of chiral Lewis acids.[3-6] *Asymmetric catalysis* in the Diels-Alder reaction[7] has been mainly realized by chiral Lewis acids based on aluminum,[8-10] titanium,[11,12] europium,[13] boron[14,15] or iron.[16] We wish to describe a specific case where a formal [4+2] cycloaddition closely related to Diels-Alder reaction (*vide infra*) has been realized by *asymmetric base-catalysis*.

Base-catalyzed [4+2] cycloaddition

Base-catalyzed Diels-Alder reactions are unusual. However a class of reactions related to this process has been extensively studied of late by Rickborn and Koerner.[17,18] These authors found that the cycloaddition of anthrone **1** and naphthacene analogues proceeded easily with N-methylmaleimide **2a** at room temperature in DMF alone or in chloroform with catalytic amounts of triethylamine. The case of anthrone as a masked diene was already known, namely with ethylene (basic conditions),[19] dimethyl acetylenedicarboxylate and maleic anhydride (in refluxing acetic acid).[20] However the early work did not recognize the unusual reactivity of anthrone in base-catalyzed reactions. In a careful investigation Rickborn and Koerner gave convincing arguments that formation of cycloadduct **3a** occurs by an intermediate oxyanion **5** (formally a 1-oxido 1,3-diene) rather than through anthradienol **6**. This process was described as an oxyanion accelerated Diels-Alder reaction.[21]

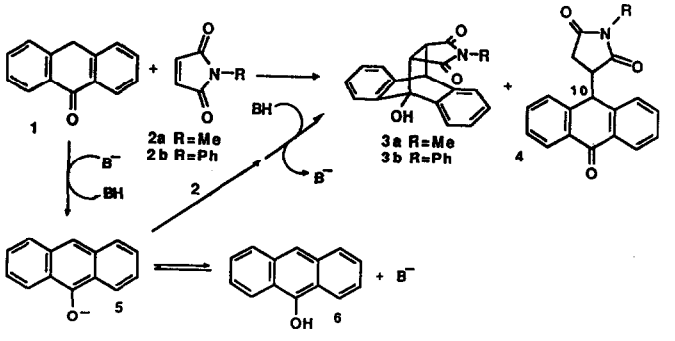

Fig. 1. Base -catalyzed reactions between anthrone and maleimides.

Cycloadditions between Michael acceptors and 1-oxido-1,3-dienes or 2-oxido-1,3-dienes (generated by treatment of suitable enones by LDA or similar bases) are known to occur under mild conditions (see ref.18 for leading references). These reactions, (Figure 2) which exhibit high regio- and stereoselectivities are usually interpreted as being tandem Michael-aldol or Michael-Michael reactions (from 1-oxido-1,3-dienes or 2-oxido-1,3-dienes respectively). However the Diels-Alder mechanism has been sometimes proposed.[27-29] Base-catalyzed cycloadduct formation from enones and a Michael acceptor are rare.[30]

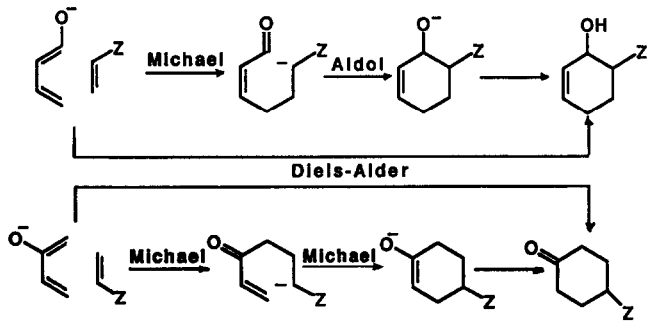

Fig. 2. Mechanistic possibilities (concerted *versus* tandem reactions) in the formation of six-membered products from oxido-1,3-dienes and electron-poor olefins (Z=electron withdrawing group).

In the light of the detailed mechanistic study of Rickborn and Koerner[17,18] of the base-catalyzed cycloadditions of anthrone (Figure 1) it seemed highly probable that the process was concerted, leaving room for asymmetric catalysis, since cycloadduct **3** is a chiral molecule (bearing two asymmetric centers in the succinimide ring) One can envisage some enantioselectivity for the reaction if a *chiral base* is used. The putative intermediate **5** should be chiral because of association to the conjugated acid of the chiral base by coulombic force and hydrogen bonding; anthradienol **6** is also able to interact with the chiral base by hydrogen bonding. There are encouraging precedents in the literature of asymmetric base-catalyzed reactions where the stereodetermining step is related to the formation of organized chiral ion-pairs.[31-35] We wish to show that interesting levels of enantioselectivity can be reached from anthrone **1** by using chiral bases.[36]

Asymmetric catalysis in the formation of cycloadduct 3a

At room temperature, a rapid formation of optically active **3a** occurs upon addition of 1 to 10% equiv. of a cinchona alkaloid to a chloroform solution containing equimolar amounts of **1** and N-methylmaleimide **2a**. Isolated yields are in the range of 84-100%. Representative results are listed in Table 1. Minor amounts (0-2%) of Michael adduct **4** were also detected in the crude reaction mixtures (TLC and ^{1}H nmr analysis). The specific rotation of cycloadduct **3a** formed at 20°C varied from 18 to 25, it could reach 43 by decreasing the temperature to -50°C (entry 5). Optically active **3** has not previously been described in the literature, thus it was necessary to develop a method to measure the enantiomeric excess of the experiments described in Table 1. We were unable to find a chiral shift reagent capable of separating the peaks in the ^{1}H nmr spectra of **3**. Fortunately enantiomer separation can be achieved by HPLC on Sumipax OA-2000, and it was therefore possible to calculate the specific rotation of enantiomerically pure **3a** : $[\alpha]_D = \pm 71.5$ (c 1, $CHCl_3$). The enantiomeric excesses listed in Table 1 were obtained either by HPLC or polarimetry.

In some of the experiments of Table 1 it was possible to detect minor amounts (up to 2%) of Michael adduct **4** when reactions are performed at room temperature ; the formation of **4** is fully suppressed at or below 0°C.

Table 1. Cinchona alkaloids-catalyzed cycloaddition between **1** and **2**.

	Catalyst [a]	Temp (°C) [b]	**3a** (%) [c]	**4** (%) [d]	$[\alpha]_D$ **3a**	Ee (%) **3a** [e,g]
1	Quinidine	20	99.5	0.5	+25.5	35.5 [f]
2	Quinidine	-23	99.5	nd	+35.5	50
3	Quinidine	-35	98	0	+40.7	57
4	Quinidine	-50	97	nd	+43.5	61
5	Quinidine [h]	0	99.5	0	+31.5	44
6	Quinidine [h,i]	20	99.5	0	+18.4	8
7	Quinine	20	90	1-2	-19	26
8	Quinine	0	96	nd	-23	32
9	Cinchonine	20	84	0	-11	9
10	Cinchonine	-23	90	nd	-4.5	6.5
11	Cinchonine[i]	20	97	0	-28	39
12	Cinchonidine	20	98	0.6	+21.6	30
13	Cinchonidine	-23	90	nd	+15.5	22
14	DHQ-PCB[j]	20	100	nd	-4.2	6

a) 10 % equiv unless stated.
b) Standard reaction performed in chloroform, with [**1**] = 0.1 M, for 15 min, at 20°C. At lower temperature the reaction completion was checked by tlc.
c) Isolated yield, after flash-chromatography on silica gel (Cy / AcOEt = 1:1).
d) Measured by ^{1}H nmr on crude product.
e) Measured by hplc (Sumipax OA-2000, solvent: hexane / 1,2-dichloroethane / EtOH = 450:50:2,detect. 230 nm), unless otherwise stated. Hplc and polarimetry (as in g)) data are in good agreement.
f) Same value when [**1**] = 0.25 M or 0.05 M.
g) Measured by polarimetry, using $[\alpha]_D$ = +71.5 (c=1, $CHCl_3$) for 100 % ee **3a** .
h) 1 % equiv catalyst.
i) In toluene.
j) DHQ-PCB = (-)-dihydroquinidine p-chlorobenzoate.

Solvent effect
It was found that the nature of the solvent exerted a strong influence on the enantiomeric excess of cycloadduct **3a**, in a standard reaction performed at room temperature with 10% equiv. of quinidine as catalyst (Table 2). The best ee (44%) was obtained in CCl_4 or in cyclohexane (46%), whilst the lowest values were observed in THF (11%), or in methanol (racemic composition).

Temperature influence
Hoping to optimize the enantiomeric excess of the cycloadduct some catalytic reactions with quinidine, quinine, cinchonine and cinchonidine were performed below room temperature. It was not possible to work at very low temperature because of a strong decrease in the reaction rate. The major results are listed in Table 3.

Table 2. Influence of the solvent on the ee of cycloadduct **3a** (catalysis by 10 % equiv of quinidine)

Solvent [a]	Z value [37]	ee (%) of (+)-**3a** [c]
CCl_4	32.5	44
$CHCl_3$	39.1	35.5
CH_2Cl_2	41.1	31.4
Cyclohexane	31.2	46
Toluene	33.9	23.5
1,4-dioxane	36	14.7
EtOAc	38.1	14.3
THF	37.1	10.3
Methanol	55.5	0

(a) Experimental conditions as in Table 1 (entry 4), reaction performed at 20°C.
(b) Cyclohexane / $CHCl_3$= 4:1, because of the insolubility of the catalyst.
(c) See note c, Table 1.

With quinidine and quinine there is a marked increase of ee with a decrease of temperature; the reverse effect was observed for cinchonine and cinchonidine. The data for quinidine (entries 1-4) gave a Eyring type correlation Ln[(1+ee)/(1-ee)] = 1/T (T : absolute temperature). This plot allows calculations of thermodynamic parameters concerned with the competing transition states : $\Delta\Delta H^{\neq}$=−1.32 kcal / mol, $\Delta\Delta S^{\neq}$= −3 eu. This data shows that enthalpic factors are predominant but that entropic factors are also of importance. One predicts ee = 96% at -111°C, but this prediction was not checked because of the marked decrease of reactivity at low temperature. For cinchonidine and cinchonine the isokinetic point (where ee=0) is located at low temperature. The increase of ee should parallel an increase of temperature above room temperature, this prediction has also not been tested.

Table 3. Temperature dependency of enantiomeric excess of cycloadduct **3a** prepared by asymmetric catalysis

	Catalyst [a]	Temperature (°C)	Ee (%) of **3a** [b]	Sign of $[\alpha]_D$ of **3a**
1	Quinidine	20	35.5	+
2	Quinidine	0	44	+
3	Quinidine	-23	50	+
4	Quinidine	-35	57	+
5	Quinine	20	26	-
6	Quinine	0	32	-
7	Cinchonine	20	16	-
8	Cinchonine	-23	6.5	-
9	Cinchonidine	20	27	+
10	Cinchonidine	-23	22	+

(a) Experimental conditions as in Table 1, with 10 % equiv catalyst in $CHCl_3$. Isolated yields are quantitative.
(b) Measured by polarimetry (see note g, Table 1).

Michael adduct 4

It has recently been demonstrated by Rickborn and Koerner[18] that compound **4** could be obtained in good yield from anthrone **1** and N-methylmaleimide **2a** in the presence of a basic catalyst (triethylamine, NaOMe). The Michael adduct **4** was also formed in excellent yield in toluene at room temperature in conditions of phase-transfer catalysis (solid-liquid).[36] The reaction required one equiv. of base (KF) and a catalytic amount (0.02 equiv.) of N-benzylquinium chloride (Quibec[31]). Cycloadduct **3a** was produced in minor amounts while the Michael adduct **4** has been isolated in 80% yield and is optically active ($[\alpha]_D$ = +26, (c 0.55 ,$CHCl_3$). The enantiomeric excess of **4** could be measured by chiral HPLC (OT(+), Daicel Co) and was found to be 16%.

Rickborn and Koerner have demonstrated that cycloadduct **3a** is transformed into Michael adduct **4** under the catalytic influence of Et_3N in methanol (but not in the other solvents examined). We were able to effect the conversion of **3a** into **4** in excellent yield by heating at reflux a solution of racemic **3a** in ethanol. A similar procedure has also been applied to enantiomerically enriched cycloadduct **3a** (*vide infra*).

Absolute configuration of 3a and 4

Enantiomerically enriched cycloadduct (-) (30%ee) **3a** could be ring-opened into the Michael adduct (-)-**4** (30%ee) by refluxing in ethanol. This chemical correlation clearly does not affect the stereochemistry of the common asymmetric center of **1** and **3a**. This is in agreement with the catalytic interconversion of **3a** into **4** by NEt_3/MeOD which has been shown to involve a full deuteration at C_{10}, some deuteration at the methylene group and no deuteration at the methine site of the succinimide ring.[18]

In order to assign absolute configuration to (-)-**3** and (-)-**4** a chemical correlation was first envisaged with a known compound such an α–substituted succinic acid derivative. In order to avoid a multi-step process we turned to the use of X-ray crystallography. For that purpose it was necessary to prepare a sample of enantiomerically pure **3a** or **4**. It was not possible to increase the ee of cycloadduct **3a** by crystallization (50-60%ee). However enantiomerically pure **4** ($([\alpha]_D$ = -160, $CHCl_3$) was isolated by fractional crystallization from a sample of 45 % ee (see experimental section). Unfortunately the X-ray diffraction pattern was not suitable for application of the map difference method. In order to be in a better position to assign the absolute configuration by the X-ray method it was necessary to introduce a heavy atom in the molecule. This was realized by bromination of (-)-**4** (100%ee) by molecular bromine in dichloromethane-acetic acid. Monobrominated compound **7** ($[\alpha]_D$ = - 54.5, $CHCl_3$) was isolated (quantitative yield) and recrystallized. The crystalline compound is suitable for X-ray analysis. This method demonstrated the location of bromine at C_{10} position and hence the (R) configuration for the asymmetric center (Figure 3).

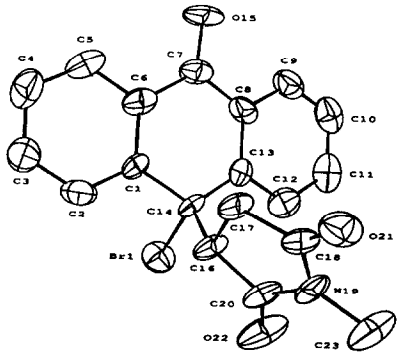

Fig. 3. Crystal structure of (-)-**7** (ORTEP, ellipsoids at the 50 % probability level), establishing the absolute configuration as shown.

The stereochemical correlations between cycloadduct (-)-**3a** and (-)-**7** are indicated in Figure 4.

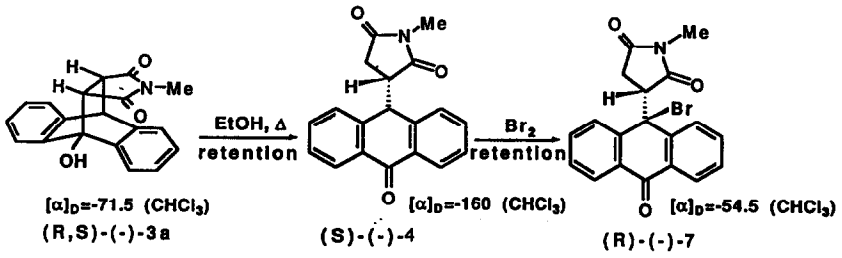

Fig. 4. Stereochemical correlations between enantiomerically pure **3a**, **4** and **7**.

Asymmetric catalysis by various chiral amines

In order to gain some insight into the catalytic formation of cycloadduct **3** several chiral amino-alcohols were tried (Figure 5). Catalytic activity was clearly established with only marginal formation of Michael adduct **4** (Table 4). The highest enantiomeric excess was obtained with (S)-prolinol at room temperature (47 %ee) while low ee's were observed with N-methyl prolinol (9 % ee) or other prolinol derivatives (entries 8,9,11). The compounds of the ephedrine series (entries 1-5), gave very poor results, below 20%ee.

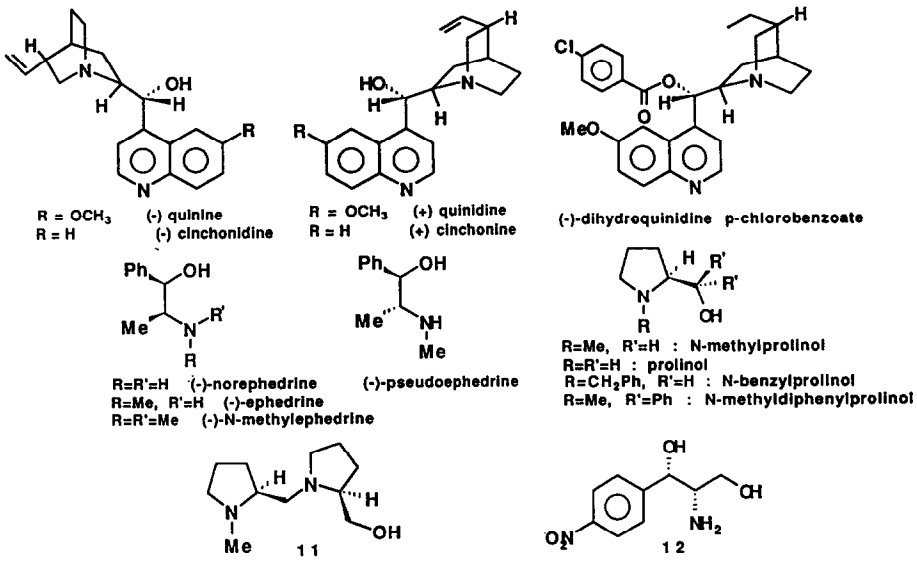

Fig. 5. Chiral amines used as asymmetric catalysts in the formation of **3a**.

Table 4. Chiral amines as asymmetric catalyst in the formation of cycloadduct **3a** from anthrone

	Catalyst [a]	Yield (%) **3a** [b]	Yield (%) **4**	$[\alpha]_D$ **3a** [c]	Ee (%) **3a** [d]
1	(-)-N-Me ephedrine	86	1.1	13.5	19
2	(-)-N-Me ephedrine [e]	>90	nd	12.0	17
3	(-)-ephedrine [e]	>90	nd	3.1	4.5
4	(-)-norephedrine [e]	>90	nd	-2.2	3
5	(-)-pseudoephedrine [e]	>90	nd	-1.4	2
6	(S)-prolinol [f]	85	15	-33.5	47
7	(S)-prolinol [g]	>95	<1	-29	43
8	(S)-N-Me diphenylprolinol [h]	>90	nd	-5.1	7
9	(S)-N-benzyl prolinol [h]	>90	nd	-10	14
10	(S)-N-Me prolinol [i]	>90	nd	-6.5	9
11	**11** [j]	98	3	-3	4.5
12	**12** [j]	98	nd	-1.3	2

(a) Reaction performed with 10 % equiv catalyst in $CHCl_3$, at -20°C with [**1**] = 0.1 M, for 15 h.The reaction completion was checked by tlc or ^1H nmr. In Figure 6 are listed the structure and absolute configuration of the chiral amines used as catalyst.
(b) Isolated yield
(c) In $CHCl_3$.
(d) See note e, Table 1.
(e) At -20°C, reaction time: 48 h .
(f) Reaction time: 15 h, at 20°C.
(g) Reaction time: 3 days at -20°C.
(h) Reaction time: 15 h, at 0°C.
(i) Reaction time: 15 min, at 20°C.
(j) At room temperature.

Discussion

In the catalytic reaction of anthrone **1** with N-methylmaleimide **2a** the product is almost exclusively the cycloadduct **3a** in the presence of catalytic amount of chiral amines (tertiary or secondary amines) while a stoichiometric amount of insoluble base (KF) and a catalytic amount of a quaternary ammonium salt (Quibec as phase-transfer catalyst) provides exclusively the Michael adduct **4**. This raises the possibility of a two-step mechanism for the asymmetric synthesis of **3a** (Michael addition followed by an intramolecular aldolization). In view of the detailed mechanistic work of Rickborn and Koerner[38] when the catalyst is triethylamine which favored the Diels-Alder mechanism (oxyanion acceleration through **5**) this will be the working hypothesis. The authors also gave good evidence for the formation of formal Michael adduct **4** by the ring opening of cycloadduct **3**, **4** being a thermodynamic sink under the reaction condition (Et_3N in methanol). Our observation that **3a** is converted into **4** by heating in ethanol is also in agreement with this hypothesis. One strong argument is the full stereospecificity encountered in the cycloadducts derived from fumaronitrile and malononitrile.[38] The formation of Michael adduct **4** (16%ee) from anthrone and N-methylmaleimide in the presence of KF/Quibec is surprising.[40] Its formation is explained by a further transformation of the initially produced cycloadduct **3a** (16%ee). It was also checked if the ion-pair between oxyanion **5** and the chiral quaternary ammonium N-benzyl-quininium chloride (Quibec) acts as a catalyst for the formation of cycloadduct **3a** from **1** and **2** in dichloromethane at -78°C. **3a** is the only product (5%ee, (R) configuration) at 40% conversion and there is no Michael adduct formed. This result clearly supports an initial Diels-Alder cycloaddition of an ion-pair involving

5. It has also been found that lithium salt of **1** (10 % mol equiv) catalyzes the cycloaddition of N-methylmaleimide and anthrone (quantitative yield at -78°C in THF, after 24 h).

As expected, the Michael adduct **4** was unable to revert to cycloadduct **3a** by quinidine in chloroform under the conditions of the asymmetric synthesis. The intramolecular aldolization has been achieved only in very special conditions (Figure 6), by prior formation of the titanium enolate of the Michael adduct **4** prepared by the Evans method for formation of titanium enolates.[39] Reactions performed in dichloromethane at 0°C for one hour gave 44% of cycloadduct **3a** and 56% of starting material. At -78°C for 2 h 19% of **3a** was formed together with 81% unreacted **4**. Interestingly there was no deuterium incorporation at carbons when the workup was with CH_3CO_2D/D_2O. The tentative mechanism for the titanium-induced cyclisation is given in Figure 6. The reaction begins by formation of an insoluble complex between anthrone and $TiCl_4$; this complex dissolves after addition of triethylamine. The recovered **4** is ascribed to deprotonation at C_{10}.

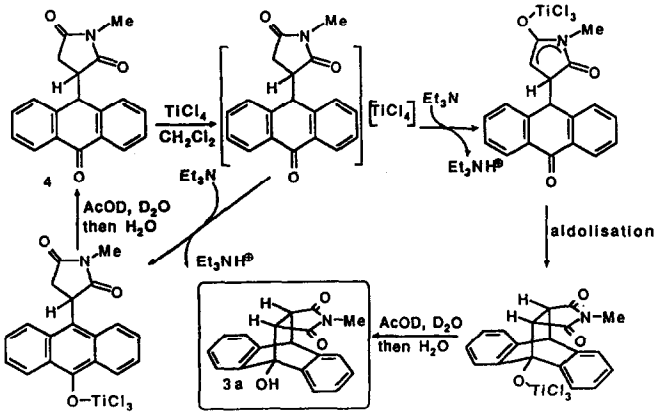

Fig. 6. Cyclisation of **4** into **3a** via a titanium enolate.

Since oxyanion **5** (Figure 1) is most probably involved in the cycloaddition process, it is necessary to discuss the origin of the asymmetric induction. A certain amount of organization between the reactant and the chiral catalyst is required in order to favor one of the two competing transition states. It is proposed that oxyanion **5** and N-methylmaleimide are both bound by hydrogen bonds to the conjugate acid of chiral β–aminoalcohols (**A**, Figure 7). **A** has ion-pair character. It is not unusual for some chiral recognition to also occur in ion-pairs in the organic phase during asymmetric catalysis,[29-35] especially if additional weak interactions (hydrogen bonds, charge transfers) are present. The species **A** is in agreement with the almost complete loss of enantioselectivity when chloroform is replaced by methanol (Table 2) or when the free OH of the β–aminoalcohol is protected (Table 1, entries 3 and 17, Table 4, entries 6 and 10). The temperature effect studied with quinidine as catalyst indicated a negative $\Delta\Delta S^{\neq}$ (- 3 eu). The species **A** (Figure 7) is entropy poor with respect to the three free components, but it is difficult for any given catalyst (such as quinidine) to decide which transition state will be lower in negative entropy content. Aggregation of **A** in an aprotic solvent such as chloroform is possible, giving rise to diastereomeric entities. One can then suspect a nonlinear effect in the asymmetric synthesis.[43] For that purpose (S)-prolinol of varying enantiomeric excess (100%, 70% and 50%) was used as a catalyst (0.1 equiv.) Ee's of the cycloadduct **3a** prepared at -20°C were 43.8%, 27.9% and 20.4% respectively, showing a good linear correlation and affording no special mechanistic information. Some correlations exist between the stereochemistry of the catalyst and the absolute configuration of product. For example, quinine and quinidine are diastereomers with pseudo-enantiomeric relationships at C_8 and C_9, and indeed they afford (-)-(R)-**3** and (+)-(S)-**3** respectively. Similarly, cinchonidine and cinchonine which have the same type of relationship, give enantiomeric products. Quinine and cinchonidine, or quinidine and cinchonine, which differ only by the presence or absence of a methoxy group at C_6 (Figure 4) catalyze the production of cycloadducts of *opposite absolute configuration*. Such observations are unusual in asymmeric catalysis, although Prelog and Wilhelm observed that the formation of some nitriles from aldehydes and HCN catalyzed by quinine or cinchonidine sometimes gave products of opposite absolute configurations.[44] Such a situation reflects the formation of diastereomeric transition states where the methoxy group at C_6 plays a steric or electronic role. In order to realize the molecular assembly **A** (Figure 7) we propose to select a conformation

around C_8-C_9 by putting the bridged nitrogen and OH at C_9 in a syn relationship (sp conformation) in order to achieve a doubly hydrogen bonded system. The conformation of the cinchona alkaloids have been discussed[45] but we are not sure that the results obtained can be applied to the present case. It is also difficult to discuss the steric course of the reaction with most of the catalysts used, because of the poor enantiomeric excesses of **3a**. Only (S)-prolinol gave an enantioselectivity close to that given by quinidine (with opposite absolute configuration for **3a**).

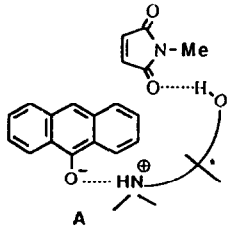

Fig. 7.

N-methylmaleimide has been replaced by other dienophiles. N-Phenylmaleimide and anthrone **1** react in the presence of quinidine under standard conditions at room temperature. The cycloadduct is formed in good yield but with a poor ee (20%). Methyl acrylate also leads to the corresponding cycloadduct **8** (0%ee); methyl fumarate gave cycloadduct **9** (30%ee). These two reactions are quite slow, in agreement with the known inertness of acrylate and fumarate compounds with respect to N-methyl maleimide.[18] Methyl maleate was unreactive. It is of interest to mention that titanium dienolate **10** (Figure 8) reacts with methyl acrylate to give cycloadduct **8** without formation of the Michael adduct.

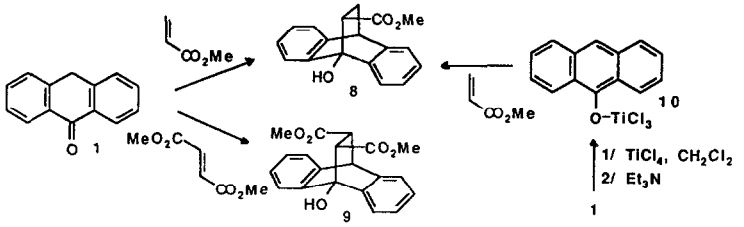

Fig. 8. Cycloaddition between anthrone and some conjugated esters.

Conclusion

It has been established for the first time that chiral bases are able to act as asymmetric catalysts in some Diels-Alder reactions. The best enantiomeric excess reach 61 % ee in the asymmetric synthesis of cycloadduct **3a**. Quinidine appears to be the best enantioselective catalyst although unfortunately it has not yet been able to design a chiral catalyst able to reach useful level of enantioselectivities for synthetic applications.[46] The absolute configurations of **3a** and **4** were safely assigned by X-ray crystallography and chemical correlations. Only dienophiles as reactive as N-methylmaleimide seem promising for this class of asymmetric reactions. The extension of this unique asymmetric reactions to other systems such as dienolates obtained from enones under catalytic conditions is currently under investigation.

Acknowledgment

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EXPERIMENTAL

General

^{1}H NMR spectra were recorded on Bruker AM 250 MHz and Bruker AM 200 MHz spectrometers in deuteriochloroform using tetramethylsilane as internal standard. Optical rotations were measured on a Perkin-

Elmer 241 polarimeter. Microanalysis was performed at the Service de Microanalyse du CNRS (Gif sur Yvette). HPLC were recorded using two different chiral columns :

1/ SOA-2000 ; 4 mm Ø x 25 cm x 2; l = 230 nm; rate flow : 1 mL/ min.

2/ Chiralpak OT(+); 4 mm Ø x 25 cm , l = 254 nm.

Chemicals

Quibec (N-benzyl-cinchonidium chloride), the cinchona alkaloids as well as the other amines of Figure 6, N-methylmaleimide and anthrone were purchased from Aldrich. Amines **11** and **12** were obtained from Merck.

Asymmetric catalysis of the Diels-Alder reaction : general procedure for the preparation of 3a.

The aminoalcohol (0.5 mmol, 0.1 equiv) was added at room temperature to a solution of anthrone **1** (970 mg, 5 mmol) and N-methylmaleimide **2** (555 mg, 5 mmol) in 50 mL of the appropriate solvent. After 15 min the reaction was quenched by addition of 1 N HCl and the organic phase was diluted with dichloromethane. The organic phase was separated and washed several times with aqueous 1N HCl. The solution was dried over $MgSO_4$, filtered and concentrated to give the crude adduct as a white to slightly yellow solid (1.45 g, 95 % yield). The crude product was analyzed by chiral HPLC (Sumipax OA-2000, hexane/1,2-dichloroethane/EtOH : 450/50/2 (v/v/v) as a mobile phase). Results are given in Tables 1-4.

In most of the examples the ^1H NMR spectrum of **3a**[18] showed it to be chemically pure. Further purification could be achieved by flash chromatography on silica gel (cyclohexane / EtOAc = 1:1).

^1H NMR d 2.50 (3H, s), 3.12 (1H, d, J = 8.1 Hz), 3.32 (1H, dd, J = 8.1 & 3.8 Hz), 4.46 (1H, s), 4.72 (1H, d, J = 3.8 Hz), 7.0-7.80 (8H, m).

$[\alpha]_D$= 71.3 (c 0.5, chloroform) calculated for **3a** 100 % ee (see Fig. 4 for stereochemical correlations).

Analysis $C_{19}H_{15}NO_3$ Calc C 74.67; H 4.91; O 15.72. Found C 75.17; H 5.29; O 15.61.

Asymmetric phase transfer catalysis

Anthrone **1** (970 mg, 5 mmol) and N-methylmaleimide **2** (555 mg, 5 mmol) were dissolved in 50 mL of dry toluene under an argon atmosphere. The Schlenk tube was opened quickly under a flow of argon, and 290 mg anhydrous potassium fluoride followed by Quibec (22.5 mg, 0.05 mol) were added. The bright orange suspension was kept overnight under vigorous stirring before quenching with aqueous 1 N HCl. The yellow toluene solution was recovered and washed twice with a saturated sodium chloride solution. After standard treatment, the crude adduct was purified by flash chromatography on silica gel (cyclohexane / EtOAc : 50/50). The enantiomeric excess of the purified adduct **4** was shown to be 16.5 % by HPLC analysis on a chiral stationary phase (Chiralpak OT(+), hexane/ *i*- PrOH : 9/1 (v/v) as a mobile phase).

$[\alpha]_D$= +26.3 (c 0.55, chloroform); ^1H NMR d 1.87 (1H, dd, J = 18.5 & 5 Hz), 2.22 (1H, dd, J = 18.5 & 9 Hz), 2.88 (3H, s), 3.45 (1H, ddd, J = 9.0, 5.0 & 3.5 Hz), 5.18 (1H, d, J = 3.5 Hz), 7.30-7.70 (6H, m), 8.20-8.40 (2H, m).

Racemic **4** has been described.[18]

Synthesis of enantiomerically pure Michael adduct (S)-(-)-4.

To a chloroform (750 mL) solution of anthrone **1** (14.56 g, 75 mmol) and **2** (8.6 g, 75 mmol) was added 760 mg of (S)-(+) prolinol (0.757 g, 7.5 mmol) and the resulting bright yellow solution was stirred at room temperature overnight. The solution was diluted with 1 L dichloromethane and washed three times with aqueous 1 N HCl solution and dried over magnesium sulfate. After filtration and evaporation of solvent under reduced pressure, the crude reaction mixture (23 g) was taken up in 800 mL of boiling ethanol and the resulting solution was refluxed for one hour. After cooling, crystallization is induced by seeding with crystals of the racemic adduct and the solution was kept at room temperature for 24 h. The racemic crystals (5 g) were isolated by filtration and the filtrate was evaporated under reduced pressure. The resulting yellow solid was purified by flash chromatography on silica (cyclohexane/EtOAc = 50:50) and then recrystallized from cyclohexane/EtOAc (60/40) mixture. A second crystallization did not modify the $[\alpha]_D$ of the compound and chiral HPLC analysis showed a single peak establishing the product to be enantiomerically pure.

$[\alpha]_D$= -160 (c 0.55, chloroform).

Analysis $C_{19}H_{15}NO_3$ Calc (%) C 74.73; H 4.95; N 4.59; O 15.73. Found C 74.66; H 4.86; N 4.52; O 15.95.

Synthesis of bromide (R)-(-)-7

To a solution of Michael adduct (-)-**4** (100% ee, 900 mg , 3 mmol) in 20 mL of dichloromethane was added 7.2 mL of a 0.5 M bromine solution in dichloromethane (3.6 mmol, 1.2 equiv), followed by acetic acid (0.5 mL). The resulting orange solution was protected from light and allowed to stand at room temperature for 24 h. The solution was washed once with 0.1 M sodium thiosulfate solution and twice with saturated sodium bicarbonate solution. After drying over magnesium sulfate, filtration and evaporation of the solvent under reduced pressure,

the crude bromide was obtained as a light yellow solid (quantitative yield). Suitable crystals for X-ray analysis were obtained by recrystallization from dichloromethane / hexane.

$[\alpha]_D$= -54.5 (c 1, chloroform).

^{1}H NMR d 2.44 (1H, d, J = 5 Hz), 2.49 (1H, d, J=8 Hz), 2.65 (3H, s), 3.94 (1H, m), 7.40-7.70 (4H, m, Ar), 7.90-8.05 (2H, m, Ar), 8.15-8.30 (2H, m, Ar). MS (CI, NH_3) m/e 403 (3.33 %), 401 (4.15), 386 (M+2, 2.65), 384 (M, 2.22), 324 (12), 323 (62.5), 307 (21), 306 (100), 304 (26), 209 (26), 208 (55.5), 206 (46), 194 (15.5), 193 (87.5), 165 (18), 127 (11.5).

Crystal structure: data collected at 23 ±1°C on an Enraf Nonius CAD4 diffractometer. Space group $P2_1$, a=8.646(1)Å, b=6.645(1)Å, c=29.112(3)Å, b=96.70(1)Å; V=1661.19(64)Å^3; Z=4; d calc = 1.540 g mL^{-3}. Mo-Kα radiation (l=0.71073Å) graphite monochromator. A total of 5223 unique reflexions were recorded in the range $2° \leq 2q \leq 60.0°$ of which 3154 were considered as unobserved ($F^2 < 3.0s(F^2)$), leaving 2069 for solution and refinement. The structure was solved by direct methods, yielding a solution for the whole molecule. R = 0.043, Rw = 0.053, G. O. F. = 1.10. For the enantiomeric structure the agreement factors are R = 0.046, Rw = 0. 058, G. O. F.= 1.18, thus indicating that the absolute configuration is (R), as shown in Figure 3.

Conversion of 4 to 3a by $TiCl_4$/Et_3N

To a solution of (±)-4 (305 mg, 1 mmol) in dichloromethane (5 mL) was added 1 mL of a 1 M $TiCl_4$ solution in dichloromethane (1 mmol) at 0°C under argon. A bright yellow precipitate formed immediately and the mixture was stirred for 10 min at this temperature. Upon dropwise addition of triethylamine (140 µL, 1 mmol), a deep blue color developed and the resulting mixture was stirred at 0°C for 1 h. One mililiter of CD_3CO_2D in D_2O (1mL of CD_3CO_2D in 10 mL D_2O) were added under argon and the solution was stirred until complete loss of the blue color. The solution was diluted with dichloromethane and the organic phase was washed once with a 1 N HCl solution. After drying over magnesium sulfate, filtration and evaporation of the solvents under reduced pressure, the composition of the crude mixture (3a and 4) was analysed by ^{1}H NMR.

Diels-Alder reaction with titanium anthrolate 10.

To a solution of 1 (580 mg, 3 mmol) in dichloromethane (12 mL) was added a 1 M $TiCl_4$ solution (3 mL) in dichloromethane (3 mmol) at 0°C under argon. A bright yellow precipitate formed immediately and the mixture was stirred for 10 min at this temperature. Upon dropwise addition of triethylamine (420 µL, 3 mmol), a deep blue color developed and the resulting mixture was stirred at 0°C for 15 min. Methyl acrylate (840 µL≈7 mmol) was injected and the deep blue solution was stirred at room temperature until discoloration (≈ 24 h). The pale green solution was hydrolysed with aqueous acetic acid and extracted with dichloromethane. After standard work-up, the adduct 8[18] was recovered quantitatively.

N-benzyl quininium anthrolate

This salt was prepared *in situ* from lithium anthrolate (obtained in THF through deprotonation of anthrone by one equivalent of LDA). Then THF and diisopropylamine were removed under vacuum, one equivalent of Quibec in dichloromethane was added, giving the desired salt and precipitation of LiCl. This mixture was used as a catalyst (5 % mol equiv) for the reaction between 1 and N-methylmaleimide at -78°C in dichloromethane for 24 h. The exclusive formation of cycloadduct (+)-4a (5 % ee) was observed (40 % conversion)

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