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Chiral Bicyclic Guanidine-Catalyzed Enantioselective Reactions of Anthrones

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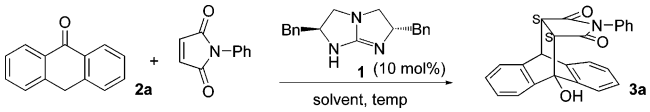
The catalytic enantioselective Diels−Alder reaction is a powerful method to construct complex molecular structures.[1] Recently, small organic molecules[2] have been applied successfully in several Diels−Alder and hetero-Diels−Alder reactions. The use of Brønsted bases to catalyze the Diels−Alder reaction is a less established approach.[3] For example, the active diene in the anthrone Diels−Alder reaction can be generated using a catalytic amount of a Brønsted base. Mechanistic investigations, conducted by Rickborn and Koerner, are in agreement with a concerted [4 + 2] process.[4] Riant and Kagan further postulated that the oxyanion intermediate, in association with a chiral conjugate acid, could lead to high enantioselectivity.[5] The Diels−Alder adducts obtained could be useful as chiral templates to prepare α,β-unsaturated lactams.[6] Dithranol derivatives have been shown to possess antipsoriatic and antiproliferative activity.[7]

The guanidinium group has a specific pattern of hydrogen bonding which enables it to play key roles in molecular recognition and catalysis in biological systems.[8] Polycyclic C_2-symmetrical guanidiniums have been shown to be excellent phase transfer catalysts in alkylation[9] and epoxidation.[10] The potential of chiral guanidines as catalytic Brønsted bases has been demonstrated in several reactions, including the Strecker reaction, epoxidation, and conjugate addition reactions.[11] We have previously shown that chiral bicyclic guanidines can be prepared efficiently via an aziridine-based synthesis.[11k] In this communication, we report the use of one of such guanidines as a highly enantioselective catalyst for the base-catalyzed Diels−Alder reaction.

We found that the reaction of anthrone **2a** and phenylmaleimide can be efficiently catalyzed by 10 mol % of the bicyclic guanidine **1** (Table 1). While the reaction worked well in common solvents, such as THF and toluene, only chlorinated solvents, such as CH_2Cl_2, $CHCl_3$, and $ClCH_2CH_2Cl$, gave significant levels of enantioselectivity. In CH_2Cl_2 and at a decreased temperature of −20 °C, we found that the enantiomeric excess increased to 81% (Table 1, entry 7). This reaction was particularly useful, with enantiomeric excesses of up to 98%, if substituted phenylmaleimides were the dienophiles (Table 2, entries 1 and 2).

A series of substituted anthrones **2b**−**e** (Table 2) were prepared from the reduction of their corresponding anthracenediones.[12] It was found that the reaction between 1,8-dichloro-9-anthrone **2b** (Table 2, entries 3−7) went well with benzylmaleimides and alkylmaleimides. We were initially concerned that the presence of two Cl substituents next to the oxyanion would prevent close interaction with the chiral guanidinium and result in low enantioselectivity. However, high yields and enantiomeric excesses were observed. Subsequently, both 4,5-dichloro-9-anthrone **2c** (entries 8−10) and 1,5-dichloro-9-anthrone **2d** (entries 11 and 12) were found to give high yields and excellent enantiomeric excess of Diels−Alder adducts with arylmaleimides. Excellent regioselectivity was also observed when 1,5-dichloro-9-anthrone **2d** was used as the diene. For example, Diels−Alder adduct **3l-1**[13] (Figure 1) was obtained in a 8:1 ratio with its regioisomer **3l-2**. 4-(*N*-Methylamino)-9-anthrone **2e** (entries 13 and 14) was also found to give good yields and enantiomeric excess with alkylmaleimides. In the reaction with ethylmaleimide, only a small amount of the regioisomer, most likely **3n-2**, was detected.

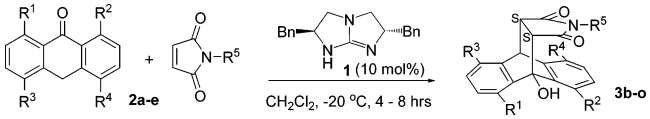
Table 1. Chiral Bicyclic Guanidine-Catalyzed Diels−Alder Reaction between Anthrone and Phenylmaleimide



entry	solvent	temp/°C	time/h	yield/%[a]	ee/%[b]
1	THF	rt	1	92	7
2	toluene	rt	1	88	12
3	CH_2Cl_2	rt	1	91	52
4	$CHCl_3$	rt	1	95	52
5	$ClCH_2CH_2Cl$	rt	1	90	44
6	CH_2Cl_2	0	1.5	90	68
7	CH_2Cl_2	−20	3	90	81[c]
8	CH_2Cl_2	−40	6	91	75

[a] Isolated yield. [b] Chiral HPLC. [c] Absolute configuration of **3a** was determined by comparing with literature reports.[5a,13a]

Table 2. Chiral Bicyclic Guanidine-Catalyzed Diels−Alder Reactions between Substituted Anthrones and Maleimides



entry	**2** [R^1, R^2, R^3, R^4]	R^5	**3**	yield/%[a]	ee/%[b]
1	**2a** [H, H, H, H]	2-$NO_2C_6H_4$	**3b**	87	98
2	**2a**	2,5-$Cl_2C_6H_3$	**3c**	88	95
3	**2b** [Cl, Cl, H, H]	Bn	**3d**	92	95
4	**2b**	*c*-hexyl	**3e**	88	98
5	**2b**	*t*-butyl	**3f**	87	93
6	**2b**	*i*-butyl	**3g**	92	91
7	**2b**	4-$ClC_6H_5CH_2$	**3h**	85	98[c]
8	**2c** [H, H, Cl, Cl]	Ph	**3i**	92	99
9	**2c**	2,6-$F_2C_6H_3$	**3j**	92	99
10	**2c**	2-$MeOC_6H_4$	**3k**	90	98
11	**2d** [H, Cl, Cl, H]	Ph	**3l-1**	87	99
12	**2d**	2,4,6-$Me_3C_6H_2$	**3m-1**	85	99
13	**2e** [H, H, NHMe, H]	Et	**3n-1**	95	98
14	**2e**	*c*-hexyl	**3o-1**	96	85

[a] Isolated yield. [b] Chiral HPLC. [c] Reaction performed at −40 °C.

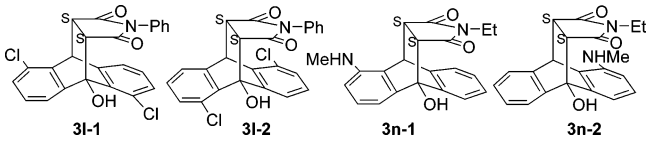


Figure 1. Possible regioisomers of Diels−Alder adducts **3l** and **3n**.

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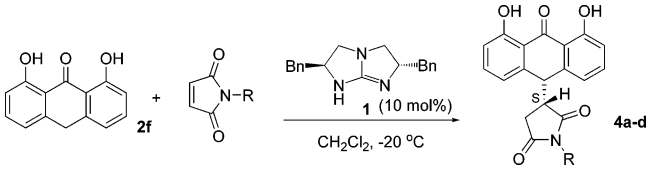
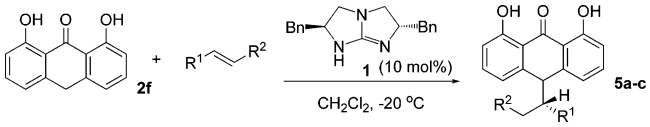
Table 3. Chiral Bicyclic Guanidine-Catalyzed Reaction between Dithranol and Various Maleimides



entry	R	adduct	time/h	yield/%[a]	ee/%[b]
1	Ph	**4a**	7	80	99
2	2-$NO_2C_6H_4$	**4b**	8	87	97
3	3,4-$Cl_2C_6H_3$	**4c**	8	89	98
4	Bn	**4d**	8	86	93

[a] Isolated yield. [b] Chiral HPLC.

Table 4. Chiral Bicyclic Guanidine-Catalyzed Reaction between Dithranol and Various Olefins



entry	R^1	R^2	adduct	time/h	yield/%[a]	ee/%[b]
1	CO_2Me	CH_3CO	**5a**	6	92	98
2	CO_2Et	PhCO	**5b**	7	92	95
3	CN	CN	**5c**	7	90	94

[a] Isolated yield. [c] Chiral HPLC.

Catalyst **1** can tolerate a range of substituents and substitution pattern on the anthrone, and careful optimization should result in high enantioselectivity when suitable maleimides are used. The choice of maleimides also depends on finding suitable resolution conditions.

Prolonged reaction time or the treatment of the isolated Diels−Alder adducts under basic conditions causes a retro-Aldol ring-opening reaction. Significant racemization was observed for these ring-opening products. We were unable to convert these ring-opening products back to the Diels−Alder adducts.

For certain anthrone derivatives, such as dithranol, 1,8-dihydroxy-9-anthrone **2f**, reactions with dienophiles almost always lead to the exclusive formation of the Michael adducts. No Diels−Alder adducts were observed during the reaction. When dithranol was screened against a series of maleimides, including phenylmaleimide and benzylmaleimide, it was found that high enantiomeric excess and yields can be obtained for the Michael adducts (Table 3).

Dithranol **2f** also worked well with olefins, such as methyl *trans*-4-oxo-2-pentenoate and ethyl *trans*-3-benzoylacrylate (Table 4, entries 1 and 2). We had previously shown that these olefins are excellent substrates for Michael reaction, and high regioselectivity was observed when 1,3-dicarbonyl compounds were used in the presence of chiral bicyclic guanidines.[14] These olefins gave Michael adducts **5a** and **5b**[13] with high regioselectivity, and both were obtained in high yields and enantiomeric excess. Fumaronitrile (entry 3) was also observed to be an excellent substrate for this reaction, giving high yield and enantiomeric excess. Other anthrones were also able to work well with these olefins, and highly enantiopure Diels−Alder adducts were obtained. However, attempts to use diethyl fumarate and diethyl maleates as the dienophiles were not as successful.

In summary, chiral bicyclic guanidine **1** was found to be an excellent catalyst for Brønsted base-catalyzed reactions between anthrones and various dienophiles. The catalyst can tolerate a range of substituents and substitution patterns, making several anthrone derivatives suitable for this reaction. Both Diels−Alder and Michael adducts were obtained in excellent yields, high regioselectivities, and high enantioselectivities. This is the first case of a highly enantioselective base-catalyzed anthrone Diels−Alder reaction. The chiral bicyclic guanidines are currently being used to investigate other base-catalyzed reactions.

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Supporting Information Available: Experimental procedures, characterization, and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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