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Axially Chiral Amidinium Ions as Inducers of Enantioselectivity in Diels–Alder Reactions

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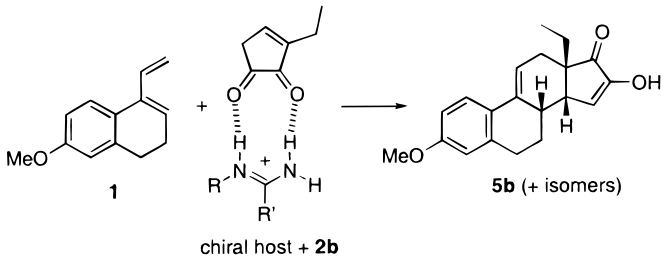
ABSTRACT



Enantioselective catalysis of Diels–Alder reactions is mostly achieved by coordinating the dienophile to relatively strong chiral Lewis acids. Here we report on a novel approach employing the hydrogen-bond-mediated association of dienophiles to chiral host molecules. In a reaction forming the steroid skeleton of norgestrel, chiral amidinium ions induce 5:ent-5 ratios of up to 2.5:1. Improved and simplified amidinium catalysts may become interesting candidates to perform stereoselective transformations.

About 60 years ago, the Diels−Alder reaction of diene **1** and diketone **2a** (Scheme 1) was investigated in the hope of finding, via the intermediate *rac*-**5a**, the first synthetic route toward estrone.[1] The noncatalyzed cycloaddition, however, has a strong preference for the constitutional isomer *rac*-**6a**, thus preventing successful synthesis in those days.[2] It has been shown more recently by Quinkert and co-workers that Lewis acids may completely reverse the ratio of *rac*-**5a** and *rac*-**6a**.[3] Using TADDOL-derived chiral Lewis acids, enantioselectivities of adduct **5a** of up to 93% were obtained in the chirogenic cycloaddition step. The same conditions could be applied to the reaction of diene **1** with the ethyl diketone **2b**. Here the product **5b** is formed (89% ee), a central intermediate in a synthesis of (−)-norgestrel.[3]

We have observed that the diketone **2a** forms hydrogen bonds with lipophilic amidinium ions (e.g., **7**). The increased electrophilicity of bound **2a** leads to a pronounced acceleration of the cycloaddition with diene **1**. Moreover, in the amidinium-catalyzed reaction compound *rac*-**5a** becomes the dominating product. The effect of amidinium ions, therefore, is comparable with the influence of mild Lewis acids.[4] In this communication we report on enantioselective Diels−Alder reactions of diketones **2a** and **2b** in the presence of chiral amidinium salts.

The same experimental conditions have been used as in our previous studies:[4] a CH_2Cl_2 solution of diene **1** (45 mM) and diketone **2a** or **2b** (30 mM) in the presence of the internal standard 2-methoxy-6-methylnaphthalene (10 mM) was kept at 4−5 °C for 2 days. Reaction rates, based on the disappearance of diene **1**, were obtained from repeated HPLC analyses of this mixture. When the Diels−Alder reaction was complete, addition of water and acetonitrile accelerated the tautomerization of the unstable diketones **3** and **4**. Semi-

(1) (a) Dane, E.; Schmitt, J. *Justus Liebigs Ann. Chem.* **1938**, *536*, 197. (b) Dane, E.; Schmitt, J. *Justus Liebigs Ann. Chem.* **1939**, *537*, 207.
(2) Singh, G. *J. Am. Chem. Soc.* **1956**, *78*, 6109.
(3) Quinkert, G.; Del Grosso, M.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, *78*, 1345 and references cited therein.

(4) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.*, submitted for publication.

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Table 1. Diels−Alder Experiments with Diketone **5a**

catalyst (amt (equiv))	conditions	yield (%)[a]	(**5a** + *ent*-**5a**): (**6a** + *ent*-**6a**)[a]	ee (%)[b] **5a** and *ent*-**5a**	ee (%)[b] **6a** and *ent*-**6a**	k ($mM^{-1}\,s^{-1}$)[c]
no catalyst	CH_2Cl_2/7−8 °C	<3[d]	<0.1:1[d]	0	0	$<4 \times 10^{-8}$
7 (1)	CH_2Cl_2/4−5 °C	46	2.4:1	0	0	4.6×10^{-6}
8 (1)	CH_2Cl_2/4−5 °C	70	2.5:1	−11	+15	6.1×10^{-6}
9a (1)	CH_2Cl_2/4−5 °C	83	2.8:1	+22	−28	5.3×10^{-6}
9a (1)	CH_2Cl_2/−27 °C	73	2.8:1	+26	−33	1.1×10^{-6}
9b (1)	CH_2Cl_2/4−5 °C	35[e]	1.0:1[e]	+1[e]	−2[e]	very slow

[a] Yields after tautomerization with H_2O in MeCN, determined by reverse-phase HPLC (Merck Purospher 100 RP-18 ec, 125 × 4). [b] All enantiomeric excesses were determined by HPLC on a chiral phase column (Daicel OJ-R 150 × 4). A positive ee stands for an excess of enantiomer **5** (faster running enantiomer); in the case of **6** and *ent*-**6** it means an excess of the enantiomer with the shortest retention time (the absolute configuration of these compounds has not been confirmed by chemical correlation). [c] Second-order rate constants are based on the decrease of the diene concentration. [d] After 1 week. [e] After 3 weeks.

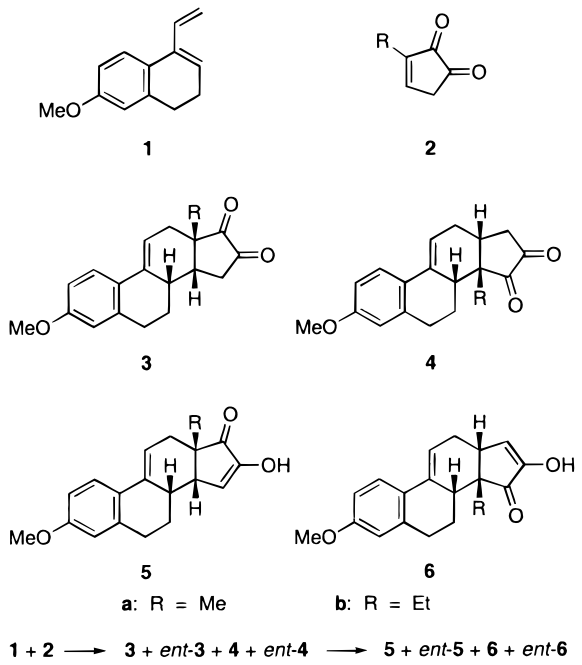
Table 2. Diels-Alder Experiments with Diketone **5b**

catalyst (amt (equiv))	conditions	yield (%)[a]	(**5b** + *ent*-**5b**): (**6b** + *ent*-**6b**)[a]	ee (%)[b] **5b** and *ent*−**5b**	ee (%)[b] **6b** and *ent*−**6**	k ($mM^{-1}\,s^{-1}$)[c]
7 (1)	CH_2Cl_2/4−5 °C	33	2.8:1	0	0	3.2×10^{-6}
9a (0.1)	CH_2Cl_2/4−5 °C	20	3.1:1	+39	−42	$<4 \times 10^{-7}$
9a (0.25)	CH_2Cl_2/4−5 °C	70	3.1:1	+40	−44	$\sim 5 \times 10^{-7}$
9a (0.5)	CH_2Cl_2/4−5 °C	89	3.0:1	+40	−45	8×10^{-7}
9a (1)	CH_2Cl_2/4−5 °C	83	2.9:1	+40	−46	1.6×10^{-6}
9a (1)	CH_2Cl_2/−27 °C	94	3.2:1	+43	−50	$\sim 5 \times 10^{-7}$
9a (1)	CH_2Cl_2/CCl_4/4−5 °C	87	3.8:1	+30	−40	2.5×10^{-6}
9a (1)	CH_2Cl_2/toluene/4−5 °C	86	2.4:1	+35	−40	2.0×10^{-6}

[a−c] See footnotes *a*−*c* in Table 1.

preparative HPLC then allowed us to separate the products **5** and **6**. Finally, the **5**:*ent*-**5** and **6**:*ent*-**6** ratios were determined on a chiral column (Tables 1 and 2). The absolute configuration of **5a** has been established by chemical correlation with (+)-estrone.[3]

Scheme 1



In the uncatalyzed cycloaddition of methyl diketone **2a**, the upper limit of k_2 was estimated to be 4×10^{-8} $mM^{-1}\,s^{-1}$.[4] One equivalent of the achiral amidinium salt **7a** caused a 100-fold rate increase and, as expected, no detectable enantioselectivity. The same ratio of constitutional isomers **5a** and **6a** (2.5:1) and a somewhat higher rate increase (150-fold) was obtained in the presence of the axially chiral amidinium salt **8a** (Figure 1).[5] This catalyst induced a slight selectivity in favor of the nonnatural stereoisomer *ent*-**5a** (−11% ee), resulting from an addition of **1** to the *Re* face of diketone **2a**. In the preferred transition state, therefore, the methyl group of the bound diketone is directed toward the phenyl ring of the cation. Since the noncovalent interactions between these functional groups are weak, the low enantioselectivity induced by **8a** was not unexpected.

More recently, we have synthesized amidinium salt **9a**, a receptor molecule with converging NH and OH groups.[6,7] If one assumes the hydrogen bond pattern shown in Figure 2

(5) Preparation of compound **8**: Lehr, S.; Schütz, K.; Bauch, M.; Göbel, M. W. *Angew. Chem.* **1994**, *106*, 1041; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 984.

(6) Schuster, T.; Göbel, M. W. *Synlett* **1999**, 966.

(7) For a description of preparative and analytical methods see ref 4. All new compounds have been characterized by the usual spectroscopic methods and gave satisfactory elemental analyses.

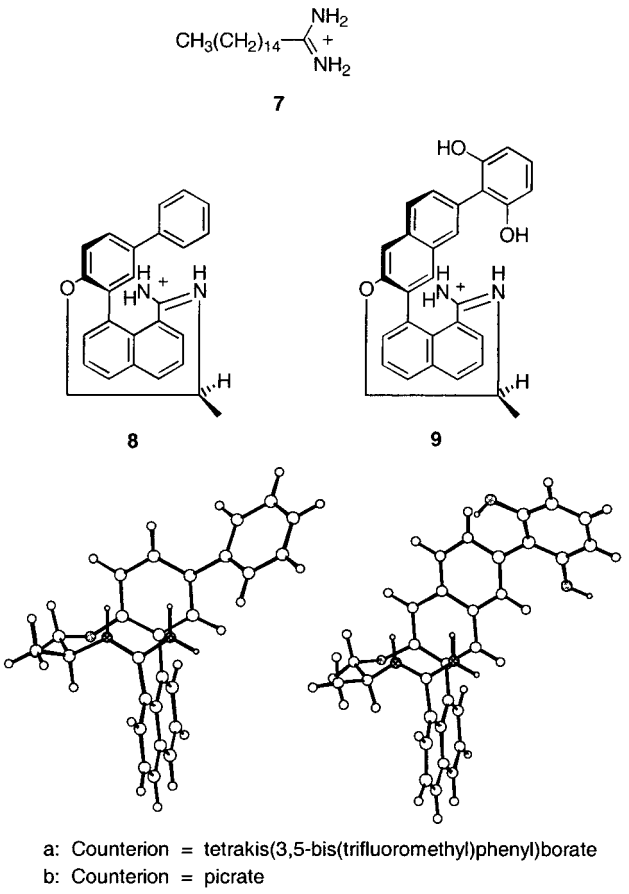


Figure 1. Molecular models of amidinium ions **8** and **9**.

for the amidinium diketone complex, an additional hydrogen bond with the alcohol should lead to a further rate increase as well as to improved enantioselectivity. In the sterically least hindered orientation of host versus guest, the best substrate activation by hydrogen bonds and the highest rates are expected. Shielding of the *Re* face of diketone **2a** by the chiral receptor, as shown in Figure 2, will then favor the natural enantiomer **5a** in the cycloaddition step. Catalysis by compound **9a** indeed favored product **5a** (Table 1). The stereoselectivity, however, remained small and the total rate compared to that for catalyst **8a** was even reduced. It is thus questionable that the additional OH···O hydrogen bond is formed in the complex **2a**·**9a**. Lowering the temperature slightly improved the ee. When tetrakis(3,5-bis(trifluoromethyl)phenyl)borate was substituted by the more strongly

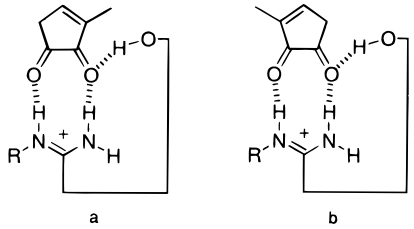


Figure 2. Schematic view of possible host−guest complexes formed from **2a** and **9a**: (a) unfavorable orientation due to the repulsion OH···CH_3; (b) Favorable orientation leading to optimal guest activation. When the backside (*Re*,*Re*) of **2a** is shielded by the phenylnaphthalene moiety of the host, cycloaddition should occur at the *Si*,*Si* face of the diketone.

coordinating counterion picrate (**9b**), rate effects and stereoselectivity both disappeared.

In the presence of catalyst **9a**, the sterically more demanding diketone **2b** reacted considerably slower with diene **1**. The ee of product **5b**, on the other hand, rose to 40%. The same ee was induced by substoichiometric amounts of catalyst down to 0.1 equiv (see Table 2). While lowering the temperature slightly improved the results (**5b**, 43% ee; **6b**, 50% ee), the addition of nonpolar cosolvents had no beneficial effects.

According to these experiments, the weak intermolecular forces between dienophile and catalyst are sufficient to gain significant control over the constitutional and stereochemical outcome of the Diels−Alder reaction. For synthetic applications the selectivities are still too low. It is remarkable, however, that, although the total rate increase is moderate, the intrinsic enantioselectivity of catalyst **9a** is completely conserved under substoichiometric conditions. Chiral amidinium compounds with improved selectivity, therefore, could be promising catalysts for cycloadditions.

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Supporting Information Available: Chemical correlation of compound **5a** with (+)-estrone. This material is available free of charge via the Internet at http://pubs.acs.org.

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