Enantioselective Diels–Alder reactions catalyzed by hydrogen bonding

Avinash N. Thadani*, Ana R. Stankovic, and Viresh H. Rawal†

Department of Chemistry, University of Chicago, 5735 South Ellis Avenue, Chicago, IL 60637

Edited by Barry M. Trost, Stanford University, Stanford, CA, and approved March 5, 2004 (received for review December 21, 2003)

Like molecules of life (e.g., proteins and DNA), many pharmaceutical drugs are also asymmetric (chiral); they are not superimposable on their mirror images. One mirror image form (enantiomer) of a drug can have desirable activity, the other not. Consequently, the development of methods for the selective synthesis of one enantiomer is of great scientific and economic importance. We report here that a simple, commercially available chiral alcohol, \( \alpha,\alpha,\alpha',\alpha'-\text{tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)} \), catalyzes the all-carbon Diels–Alder reactions of aminosiloxydienes and substituted alkenes to afford the products in good yields and high enantioselectivities (up to 92% enantiomeric excess). It is remarkable that the reactions are promoted by hydrogen bonding, the ubiquitous “glue” that helps to keep water molecules together and holds up the 3D structures of proteins. Hydrogen bond catalysis is little used in chemical synthesis, wherein most reactions are promoted by complexes of Lewis acidic metal salts coordinated to chiral ligands. As it does for enzymes, hydrogen bonding not only organizes TADDOL into a well defined conformation, but, functioning as a Bronsted acid catalyst, it also activates the dienophile toward reaction with the diene. The gross structure of the TADDOL has been found to have a profound influence on both the rate and the enantioselectivity of the cycloadditions. These structure–function effects are rationalized by evaluating the conformation adopted by the TADDOLs in the crystal state. It is suggested that \( \pi,\pi \)-stacking plays an central role in the overall catalytic cycle, in particular, the enantioselective step.

Most biomolecules are asymmetric (chiral), that is, they are not superimposable on their mirror image. Likewise, small molecules that might be used to modulate the response of the biomolecule are also frequently chiral. One mirror-image form (enantiomer) of the small molecule may elicit a desirable response, such as stimulation or inhibition of a particular function, whereas the other image might produce no response or a completely different response. It is, in part, for this reason that a tremendous effort has been put into the development of methods for the selective synthesis of one enantiomer. In 2002, single enantiomer drugs comprised 37% ($152 billion) of the total market of $400 billion. This number is projected to increase steadily, such that chiral drugs will constitute a market of $>200 billion by 2008. The growing economic importance of chiral compounds has spurred major research efforts from many laboratories, academic and industrial, directed at the selective preparation of chiral compounds. In this report, we describe our results on the hydrogen-bonding-mediated catalysis of the all-carbon Diels–Alder reaction.

The precursor process for forming functionalized cyclohexenes, with up to four new stereogenic centers (1), the Diels–Alder reaction plays a pivotal strategic role in the synthesis of numerous complex natural products (2). The steady evolution of this reaction has seen the use of chiral auxiliaries to promote diastereo selectivity (3) and chiral catalysts to induce enantioselectivity (4–8). The latter area has proven particularly fertile. Numerous Lewis acidic metal-based chiral catalysts have been shown to promote Diels–Alder reactions with excellent enantioselectivities (4–8). In addition to Lewis acid catalysis, two other catalytic methods have emerged for the promotion of enantioselective Diels–Alder reactions, both using metal-free, “organic” catalysts (9, 10). MacMillan and coworkers (11, 12) demonstrated a broadly useful and strategically novel approach for the asymmetric catalysis of Diels–Alder reactions. These authors showed that, in the presence of a chiral amine, \( \alpha,\beta \)-unsaturated aldehydes and ketones exist in equilibrium with the corresponding chiral iminium ions, which undergo diastereoselective Diels–Alder reactions. Subsequent hydrolysis of the iminium species liberates the Diels–Alder adduct in high enantioselectivity, along with the chiral amine catalyst. The second metal-free catalysis of Diels–Alder reactions is based on the activation of the dienophile by hydrogen bonding, a form of Brønsted acid catalysis, with a chiral catalyst. To date this approach has been reported to provide only modest successes [\( \approx 50% \) enantiomeric excess (ee)] (13). In this article, we report the highly enantioselective carbon Diels–Alder reactions (up to 92% ee) catalyzed through hydrogen bonding to an organic catalyst (14).

The general concept of using hydrogen bonding to promote a reaction while controlling its regio-, stereo-, and enantioselectivities has been little used in organic synthesis. In a seminal article, Kelly et al. (15) showed that the Diels–Alder reaction of cyclopentadiene with various acroleins and acrylates is accelerated significantly in the presence of an achiral biphenylenediol at 40–50 mol% catalyst loading (16, 17). The increased rate results from activation of the carbonyl group through complexation with the diol by two hydrogen bonds. Etter and others (18–24) have developed ureas that are capable of forming hydrogen bonds to Lewis basic oxygen atoms. Hydrogen bonding has also been exploited as a force for enantioselective catalysis of reactions. Jacobsen and coworkers (25–28) have developed chiral urea-based catalysts that are highly effective for the hydrocyanation of aldimines and ketimines. The same group has recently reported highly enantioselective Mannich reactions catalyzed by a similar thiourea catalyst (29, 30). In the area of cycloadditions, Göbel and coworkers (13) showed that enantioselective catalysis of Diels–Alder reactions could be achieved through hydrogen-bond-mediated association of a dienophile to an axially chiral ammidion ion. Other recent examples of the use of hydrogen bonding are enantioselective Morita–Bayliss–Hilman reactions of cyclic enones catalyzed by chiral BINOL derivatives (31), and Michael additions of malonates to nitroolefins catalyzed by functionalized thioureas (32).

**Typical Experimental Procedure for the Synthesis of 8b**

To a solution of \( \alpha,\alpha',\alpha'-\text{tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)} \) 4c (66.7 mg, 0.1 mmol) and methacryl...
lein (41.5 μl, 0.5 nmol) in toluene (0.75 ml) cooled to −80°C was added aminosiloxydiene 1 (260 μl, 1.00 mmol). The reaction mixture was stirred for 48 h and then treated with LiAlH₄ (1.0 M in Et₂O, 2.00 ml, 2.00 mmol) at −80°C. The mixture was stirred for 0.5 h at −80°C and another 1.5 h at room temperature. After cooling to 0°C, the excess LiAlH₄ was quenched with water (0.5 ml) and the solids were removed by filtration. The solids were washed extensively with Et₂O (5 × 3 ml), and the filtrate was concentrated in vacuo. The resulting oil was taken up in CH₂CN (2.0 ml), cooled in an ice bath, and treated with HF (5% in CH₂CN, 5.0 ml). After stirring for 0.5 h at room temperature, the volatiles were removed in vacuo and the residue was subjected to silica gel chromatography (3:7 hexanes/EtOAc) to afford 8b as a clear, colorless oil (116 mg, 83%).

**Results and Discussion**

As part of our ongoing investigation of the unique reactivity profile of 1-amino-3-siloxy-1,3-butadienes (33–36), we observed that the parent aminosiloxydiene, 1, reacts smoothly at room temperature with aldehydes, in the absence of any Lewis acids, to afford, after elimination of the amine, dihydropyranones in good yields (37). Further examination of this hetero-Diels–Alder reaction revealed that solvents capable of hydrogen bonding greatly accelerate the reaction of diene 1 with aldehydes. In 2-butanol, for example, even unactivated ketones participate as good yields (37). Further examination of this hetero-Diels–Alder reaction (38) catalyzed through hydrogen bonding.

![Diagram](https://example.com/diagram.png)

**Table 1. Effect of TADDOL on the Diels–Alder reaction of aminosiloxydiene 1 and methacrolein**

<table>
<thead>
<tr>
<th>Entry</th>
<th>TADDOL</th>
<th>Yield, %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>83</td>
<td>91</td>
</tr>
</tbody>
</table>

We have extended these investigations and report that hydrogen-bonding catalysis can also be used to promote high enantioselectivity in the all-carbon Diels–Alder reaction. In preliminary studies, we focused our attention on the examination of the previously established TADDOL class of chiral 1,4-diols as potential catalysts for the reaction of 1-amino-3-siloxybutadiene (1) with methacrolein in toluene at −80°C (Table 1). The initial Diels–Alder cycloadduct (7b) from the catalyzed reaction was reduced with lithium aluminum hydride and then subjected to HF in acetonitrile to effect desilylation and subsequent amine elimination. The enantiopurity of the resulting cyclohexenone (8b) was determined by Mosher ester analysis (40). The three commercially available TADDOLS (4a–c) were screened in the reaction above at 20 mol% catalyst loading (Table 1). The results indicate that the structure of the TADDOL has a profound effect on both the yield and, more importantly, the enantioselectivity of the reaction. Thus, substitution of the aryl groups of phenyl TADDOL catalyst (4a) with a 2-naphthyl group (compare catalyst 4b) increased the ee of the resulting cycloadduct slightly from 31% to 33% and had a beneficial effect on the isolated yield (from 30% to 45%; Table 1, entries 1 and 2). The 1-naphthyl TADDOL (4c) proved to be the best catalyst, providing the product in increased yield (83%) and dramatically higher enantioselectivity (91%). These initial results were rationalized through a combination of structural information on TADDOLS and examination of molecular models. The solid-state structures of TADDOLS 4a and 4b and the cyclohexyldiene derivative of 4c were determined by means of integration of the CH₂OR protons of the corresponding Mosher ester. This result was confirmed by chiral HPLC analysis (Chiralcel OD-H, PrOH/hexanes = 1:9, 0.2 ml/min, λ = 254 nm, tᵣ (major) = 48.4 min, tᵣ (minor) = 51.1 min).

**Table 1. Effect of TADDOL on the Diels–Alder reaction of aminosiloxydiene 1 and methacrolein**

<table>
<thead>
<tr>
<th>Entry</th>
<th>TADDOL</th>
<th>Yield, %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>83</td>
<td>91</td>
</tr>
</tbody>
</table>
have been determined. All three compounds exhibit near-perfect $C_2$-symmetry with a gross propeller-type arrangement of the aryl groups (Fig. 1) (41, 42). This well defined 3D arrangement appears to be cemented by an intramolecular hydrogen bond between the two hydroxyl groups, resulting in the formation of a seven-membered ring. The unique structural and reactivity properties of TADDOLs renders them capable of forming strong complexes with Lewis basic groups, a capability that has been exploited for the resolution of racemic compounds possessing one or more hydrogen bond acceptors (39). Analysis of the crystal structures of the phenyl ($4a$) and 2-naphthyl ($4b$) TADDOL derivatives shows that both have similar orientations of the pseudoaxial and equatorial aryl groups. The aryl groups in the 1-naphthyl variant ($4c$), on the other hand, are not only arranged differently but have more restricted rotation about the carbon–naphthyl bonds (Fig. 1). The intramolecular hydrogen bond in TADDOL $4c$ is expected to render the remaining hydroxyl proton more acidic, hence better able to participate in an intermolecular hydrogen bond with the carbonyl group of the dienophile.

To further probe this form of organic catalysis, we sought to investigate the effect of temperature variation on the yield and the enantioselectivity of the cycloaddition (Table 2). The results show that, as the temperature of the reaction was decreased from room temperature ($21^\circ C$) to $-80^\circ C$, the enantiopurity of the cycloadduct increased steadily. Provided the reaction times were increased appropriately for the low-temperature reactions, the yields remained uniformly good. A plot of the ee of the product versus temperature shows an almost linear relationship (Fig. 2). We attribute the steady increase in enantioselectivity to the formation of a more persistent hydrogen bond and a better organized TADDOL–methacrolein hydrogen bond complex as the available thermal energy is decreased.

The scope of the Diels–Alder reaction was then investigated in more detail. A variety of acroleins was examined in the presence of 20 mol% of catalyst $4c$ (Table 3). The intermediate adduct ($7$) of the cycloaddition was subjected to either of two workup protocols. Treatment with excess HF in acetonitrile afforded aldehyde $9$, which was easily isolated by silica gel chromatography. Alternatively, reduction with an excess of LiAlH$_4$, followed by acidic hydrolysis provided alcohol $8$. The reactions with $\alpha$-substituted aldehydes proceeded smoothly under the conditions shown in Table 3. Uniformly high yields of both alcohols $8$ and aldehydes $9$ were obtained. More impor-

---

**Table 2. Effect of temperature on the enantioselectivity of Diels–Alder cycloadditions catalyzed by TADDOL**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature, °C</th>
<th>Time, h</th>
<th>Yield, %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>15 min</td>
<td>75</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>6</td>
<td>75</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>-20</td>
<td>24</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>-40</td>
<td>24</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>-80</td>
<td>48</td>
<td>83</td>
<td>91</td>
</tr>
</tbody>
</table>

---

**Table 3. Enantioselective Diels–Alder reaction of aminosiloxydienes catalyzed by hydrogen bonding**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield of $9$, %</th>
<th>Yield of $8$, %</th>
<th>ee of $8$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>—</td>
<td>77 (8a)</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>85 (9b)</td>
<td>83 (8b)</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>80 (9c)</td>
<td>83 (8c)</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>77 (9d)</td>
<td>81 (8d)</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$Ph</td>
<td>84 (9e)</td>
<td>82 (8e)</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$CH$_2$OTBS</td>
<td>80 (9f)</td>
<td>80 (8f)</td>
<td>86</td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Plot of enantioselectivity (ee) versus temperature for the TADDOL-catalyzed Diels–Alder reaction of aminosiloxydienes $1$. Shown is the effect of temperature on enantioselectivity.
tantly, the Diels–Alder cycloadducts were formed with high enantioselectivities, ees in the range of 86–91% (Table 3, entries 2–6). As might be expected, the catalyst not only imparts asymmetry in the products, it also provides substantial acceleration in the rates of the reactions. The reaction shown in entry 3, when carried out in the absence of the catalyst, under otherwise identical conditions, yielded only a negligible amount (<2% isolated yield of 8) of the product.

The lower enantiomeric excess reported for compound 8f is a consequence of the fact that a mixed solvent system (PhCH3/CH2Cl2) was used in place of toluene to alleviate the excessive viscosity observed at low temperatures (Table 3, entry 6). The result from entry 6 also shows that the presence of another Lewis basic site in the acrolein does not interfere with catalyst function. It is also interesting to contrast the stabilities of the tert-butyldimethylsilyl-protecting groups in the resulting cycloadducts 8f and 9f (Fig. 3). Thus, the reaction conditions leading from 7f to 8f led to deprotection of the tert-butyldimethylsilyl-protecting group and subsequent Michael addition of the resulting hydroxyl group. Treatment of intermediate 7f with excess HF in acetonitrile, however, did not result in removal of the silyl group.

The TADDOL-catalyzed Diels–Alder reaction with acrolein itself was less enantioselective (Table 3, entry 1) than the analogous reaction with methacrolein (Table 3, entry 2). The lower enantioselectivity (73% vs. 91% ee) may be due to a less organized TADDOL–acrolein complex because of the greater conformational flexibility of acrolein. Several other dienophile (e.g., methyl acrylate, methyl vinyl ketone, and crotonaldehyde) were also examined in the TADDOL-catalyzed Diels–Alder reaction with diene 1. The outcomes of these reactions were not promising due to either the sluggish nature of the reactions at low temperatures or the low enantioptureity of the resulting cycloadducts. Overall, these preliminary results indicate that the reaction works best with tert-butylsubstituted acrolein and acrylonitrile, which provides the necessary lowering of the lowest unoccupied molecular orbital energy through a Lewis acid-like mechanism. Second, the complexed, electron-deficient carbonyl double bond is expected to be stabilized through a π–π donor–acceptor (possibly π–π*) interaction with the electron-rich π system of the proximal equatorial 1-naphthyl ring, which would selectively shield one face of the dienophile. For the TADDOL shown, our model indicates that the Si-face of the aldehyde is accessible to the aminosiloxydienes and correctly predicts the observed absolute configuration of the cycloadduct.

Conclusions

We have presented a highly enantioselective all-carbon Diels–Alder reaction catalyzed by hydrogen bonding to a chiral diol. The effective catalyst, TADDOL 4c, is a simple, commercially available compound that greatly accelerates the cycloaddition between aminosiloxydienes and acrolein dienophiles. Even through these initial studies, the enantioselectivities obtained for the cycloadducts are in a range that makes these reactions synthetically useful. It is expected that more effective catalysts can be developed by judicious structural and electronic tuning of the scaffold.

Although the catalyst used in the present method is metal-free, it promotes the reactions in much the same way as metal-based Lewis acids, by coordinating with the carbonyl oxygen and thereby lowering the lowest unoccupied molecular orbital energy of the dienophile. In this way, the present method is mechanistically different from the other form of organic catalysis, which uses a chiral secondary amine and involves the formation of a covalent bond to the dienophile in the catalytic cycle. Application of the general concepts described here to the catalysis of other reaction types needs further study.

This work was supported by the National Science Foundation. A.N.T. thanks the National Science and Engineering Research Council of Canada for a postdoctoral fellowship.