Brønsted-acid and Brønsted-base catalyzed Diels–Alder reactions†

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The enantioselective Diels–Alder reaction is one of the most important reactions for the synthesis of complex molecules. It provides access to chiral six-membered carbocyclic compounds containing up to four stereogenic centers in a single step. Asymmetric catalysis in the Diels–Alder reaction has mainly been realized using chiral Lewis acids. In this perspective, we describe several cases of chiral Brønsted-acid and Brønsted-base catalyzed Diels–Alder reactions, providing an overview of this rapidly growing field.

1 Introduction

The Diels–Alder reaction provides important access to complex carbocycles, and represents arguably one of the most powerful approaches in organic chemistry. In particular, the asymmetric variants have received unprecedented attention.[1,2] They have proven to be a versatile means of synthesizing a large number of important chiral building blocks, *e.g.* intermediates in the total synthesis of natural products.[3] Many groups have conducted extensive research on chiral Lewis-acid catalyzed asymmetric Diels–Alder reactions. This state of the art of asymmetric Lewis-acid catalyzed Diels–Alder reactions has been reviewed.[1c]

Organocatalysts have been shown in recent years to promote a large range of reactions including most C–C bond formation reactions.[4] Organocatalysts are less toxic, easy to handle, generally air and moisture tolerable, and can been applied to large-scale synthesis. Organic Brønsted acids or Brønsted bases can be used to catalyze Diels–Alder reactions and recent developments in this area are described in this perspective.

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† We would like to dedicate this paper to Professor Andrew B. Holmes on the occasion of his 65th birthday.

2 Brønsted-acid catalyzed Diels–Alder reactions

Chiral Brønsted acids are classified into two categories: (1) neutral Brønsted acids, such as thiourea[5,6] and TADDOL derivatives,[7] which are also known as hydrogen-bonding catalysts, and (2) stronger Brønsted acids, such as amidinium salts[8] and phosphoric acids with a BINOL backbone.[9,10] However, it is often difficult to make a distinction between the two types of catalyst without further mechanistic studies.

2.1 Thioureas

Schreiner and Wittkopp have demonstrated that diarylthioureas can catalyze the Diels–Alder reaction between cyclopentadiene and α,β-unsaturated carbonyl compounds.[6] To avoid solubility problems often associated with the use of diarylureas, more soluble thiourea analogues were investigated. From experiments using thioureas **1a–f**, it was identified that thiourea **1f**, bearing two trifluoromethyl groups at the 3,5-positions of the aromatic rings, is the most efficient catalyst (Scheme 1).[6b] Electron-withdrawing substituents at the *meta*- or *para*-positions aid in reducing the flexibility of the catalyst, thereby minimizing the entropy loss upon complexation with carbonyl compounds.[6b] The hydrogen atoms in the *ortho* position are more positively polarized because of the

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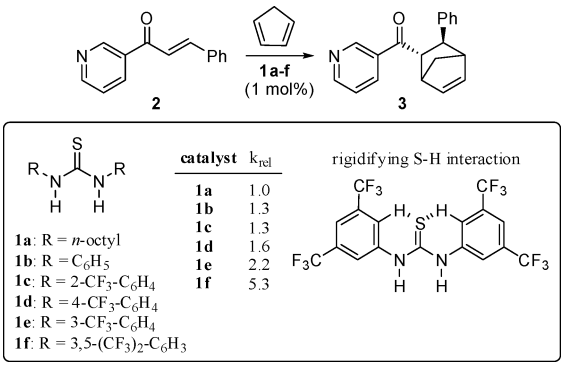
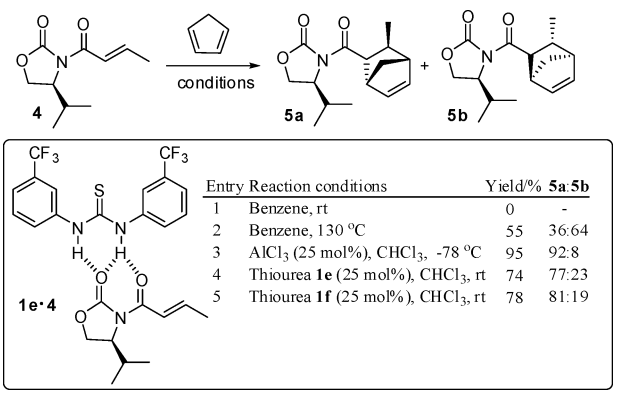
electron-withdrawing groups. The hydrogen-bond donor ability of these C–H bonds leads to internal interactions between the Lewis-basic sulfur and the *ortho* hydrogen atoms, which hinder the rotation of the phenyl groups (Scheme 1). It is likely that enthalpic factors also contribute to the high activity of **1f**. The 3,5-$(CF_3)_2$ substituents would significantly increase the acidity of the N-H protons relative to those in **1a**.



Scheme 1 Thiourea catalyzed Diels–Alder reaction.

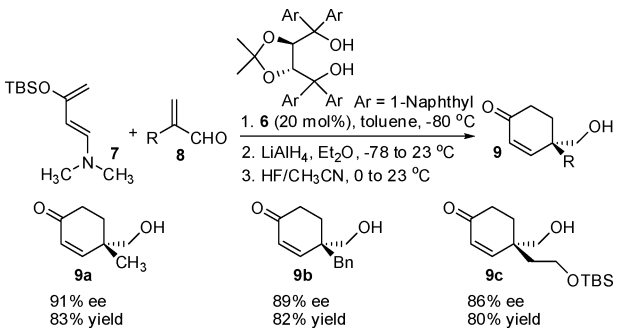
The complexation between thiourea **1e** and **4** was studied using a combination of dynamic NMR, low-temperature IR and density functional theory (DFT).[6a] A comparison of the measured and calculated C=O IR absorptions for the complex **1e**·**4**, implicated the binding of the catalyst to both carbonyl moieties of the oxazolidinone (Scheme 2). These findings were further supported by the Diels–Alder reaction of **4** and cyclopentadiene (Scheme 2). Since the uncatalyzed reaction did not occur at 23 °C (Scheme 2, entry 1), prolonged heating was carried out to obtain the cycloadducts **5a** and **5b** in a ratio of 36 : 64 (entry 2). In marked contrast, catalytic amounts of Lewis acids such as $AlCl_3$ accelerated the reaction greatly to give **5a** and **5b** in good yield with high diastereoselectivity (entry 3). Similarly, thioureas **1e** and **1f** catalyzed the reaction well enough so that it could be carried out at 23 °C with appreciable yields (entries 4 and 5). In the thiourea-catalyzed reactions, the de's were also enhanced and adduct **5a** was obtained as the major product.



Scheme 2 Diels–Alder reaction between **4** and cyclopentadiene.

2.2 TADDOL

TADDOL derivative **6** was first introduced as a chiral hydrogen-bond donor catalyst in the enantioselective hetero-Diels–Alder reaction of amino-dienes with aldehydes.[7a] Rawal *et al*. extended the investigations of the chiral diol catalyst **6** to the Diels–Alder reaction between amino-siloxydienes and α,β-unsaturated aldehydes.[7b] Catalyst **6** was identified as optimal for reactions between 1-amino-3-siloxybutadiene **7** and α-substituted aldehydes **8** (Scheme 3). Consistently high enantioselectivities were observed with alkyl α-substituted aldehydes **8** to afford functionalized cyclohexenone products **9**. Modifications to the chiral diol backbone structure have been investigated by both Yamamoto and Rawal.[7c] Axially chiral 1,1′-biaryl-2,2′-dimethanol **10** (Fig. 1, BAMOL) provides high yields and selectivities for the hetero-Diels–Alder reactions of a wide range of aldehydes with amino-siloxydienes.[7c]



Scheme 3 TADDOL-catalyzed Diels–Alder reaction.

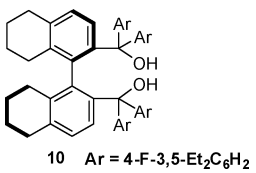


Fig. 1 Axially chiral diol-1,1′-biaryl-2,2′-dimethanol (BAMOL).

X-Ray crystallographic analysis has been useful in elucidating the structural features of TADDOL that enable it to function effectively as a chiral catalyst. Yamamoto and Rawal have succeeded in obtaining an X-ray structure of a complex of 2,2′-bis-(diphenylhydroxymethyl) binaphthylene (a simple member of the BAMOL family of catalysts) and benzaldehyde (Fig. 2).[7c] This structure reveals the presence of an intramolecular hydrogen-bond between the two hydroxy groups and an intermolecular hydrogen-bond to the carbonyl oxygen of benzaldehyde. As a result of the intramolecular interaction, the proton not enagaged in hydrogen-bonding is both acidified and orientationally defined. The complex

Fig. 2 Crystal structure of a BAMOL–benzaldehyde complex.

suggests that the carbonyl activation is through a single H-bond, as was postulated for TADDOL catalysis (Fig. 3).

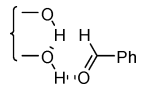
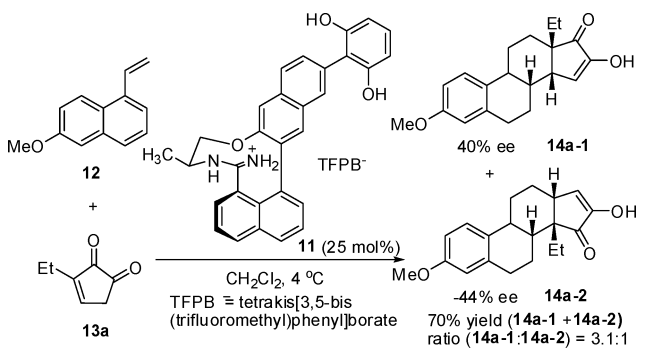


Fig. 3 Proposed single H-bond between TADDOL and benzaldehyde.

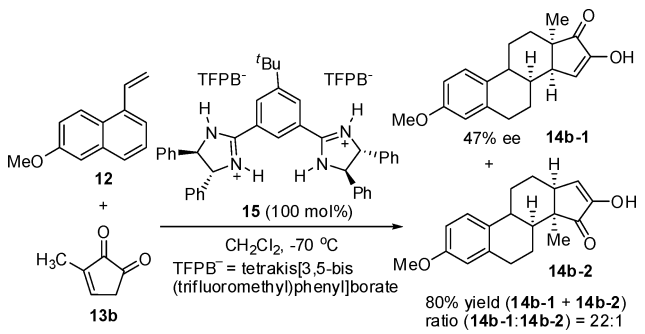
2.3 Amidinium salts

Göbel *et al.* first designed an axially chiral mono-amidinium ion **11** for the Diels–Alder reaction of vinyl dihydronaphthalene derivatives with cyclopentene-1,2-dione derivatives (Scheme 4).[8a,b] A stoichiometric amount of the amidinium salt was required and only modest enantioselectivities were obtained. A drawback of these organocatalysts is the long and tedious synthetic route to their preparation.



Scheme 4 Diels–Alder reaction catalyzed by mono-amidinium cation **11**.

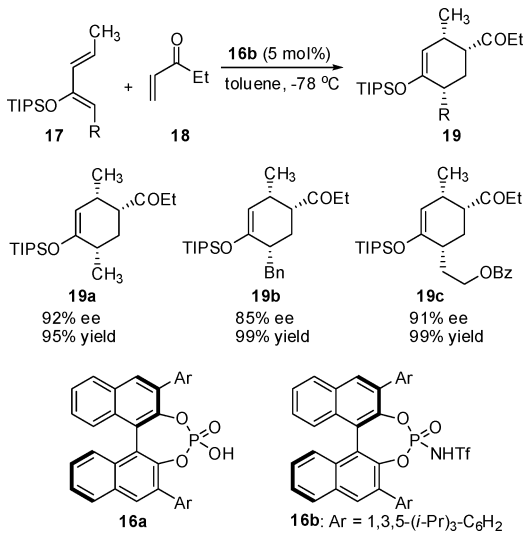
A more accessible C_2-symmetrical bis-amidinium salt **15** was developed by the same group and it can be synthesized *via* a shorter synthetic route.[8c] Bis-amidinium **15** was used to promote the reaction between diene **12** and dienophile **13b**. With one equivalent of **15**, the adduct **14b-1** was formed with enantioselectivity up to 47% ee (Scheme 5).[8c] A lower ee was obtained when a catalytic amount of **15** was used. The rate of reaction is much higher than that with the mono-amidinium salt **11**. Substitution of the phenyl group in the catalyst structure by bulkier groups is regarded as a strategy for further optimization of the catalyst.



Scheme 5 Diels–Alder reaction catalyzed by bis-amidinium cation **15**.

2.4 Phosphoric acids

Chiral phosphoric acids have been conventionally employed as chiral ligands and as chiral shift reagents. More recently, they have emerged as an important class of chiral Brønsted acids catalysts for Diels–Alder reactions.[9] The majority of effective chiral phosphoric-acid catalysts possess the general structure shown in Scheme 6. They are derived from (*R*)-BINOL with varying aryl substitutions at the 3,3′-positions.[9] Application of chiral phosphoric-acid catalysts has been limited primarily to the activation of relatively Brønsted-basic imine substrates. However, Yamamoto found that the more acidic *N*-triflyl phosphoramide variant **16b** catalyzed the Diels–Alder reaction of electron-rich dienes **17** with α,β-unsaturated ketone **18** with high enantioselectivities, while phosphoric acid **16a** is inactive (Scheme 6).[10] An appropriate choice of substituents at the 3,3′-positions is crucial for the realization of high enantioselectivity. These promising results suggest that the phophoramide class of catalysts might find considerable application in the reactions of carbonyl electrophiles.



Scheme 6 Chiral phosphoramide catalyzed Diels–Alder reaction.

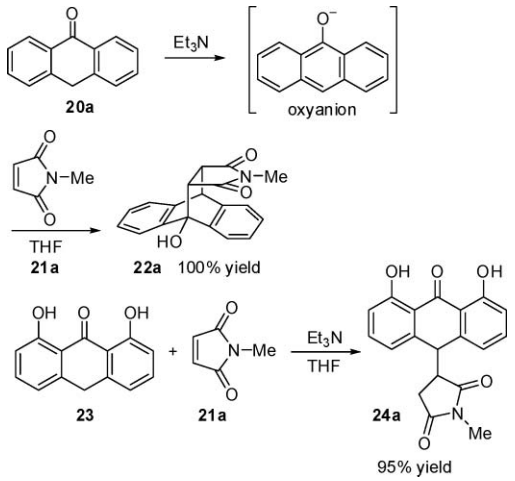
3 Brønsted-base catalyzed Diels–Alder reactions

It is common for catalytic Diels–Alder reactions to proceed by using a Lewis acid catalyst to lower the LUMO of the dienophile. However, base-catalyzed Diels–Alder reaction works in a different manner; the base catalytically activates the diene to give a higher HOMO level.[11,12]

3.1 Brønsted-base catalyzed reactions of anthrones

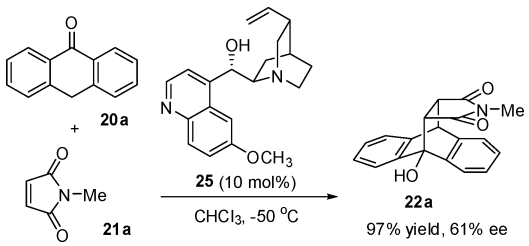
Rickborn and Koerner were the first to report the base catalyzed reaction between anthrone and various dienophiles (Scheme 7).[11] The reactions were believed to follow a concerted mechanism *via* an intermediate oxyanion to give Diels–Alder adducts. Dithranol (1,8-dihydroxy-9-anthrone) **23** was observed to favour Michael adducts instead (Scheme 7).

The first asymmetric catalytic Diels–Alder reaction of anthrones was reported by Kagan and Riant in 1989.[13a] Alkaloid bases, prolinol and *N*-methylephedrine were investigated as



Scheme 7 Base catalyzed reactions of anthrones.

organocatalysts. In the presence of 1–10 mol% of these chiral catalysts, anthrone **20a** reacted as a masked diene with *N*-methyl maleimide **21a**. The best result was obtained with 10 mol% quinidine **25** in chloroform at −50 °C; the desired product **22a** was obtained in 97% yield and 61% ee (Scheme 8). During their study, Kagan and Riant also observed that the free hydroxyl group in the alkaloid organocatalyst was essential if high enantioselectivity was to be achieved.

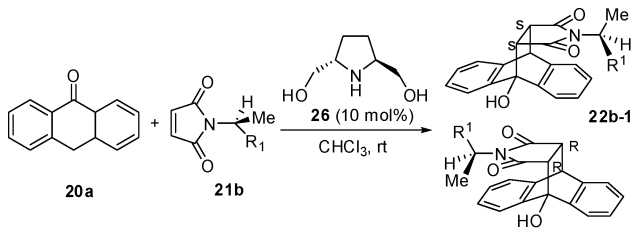


Scheme 8 Alkaloid catalyzed Diels–Alder reaction of anthrone.

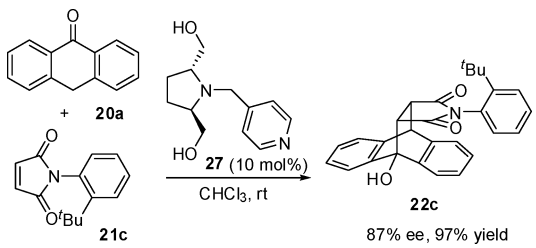
A detailed study of the reaction conditions was subsequently conducted using different *Cinchona* alkaloids as catalysts.[13b] Lower temperatures and less polar solvents would result in better enantioselectivities. The range of dienophile substrates was also studied. Much slower reaction rates were observed when methyl acrylate (0% ee) and methyl fumarate (30% ee) were used. When methyl maleate was used as the dienophile, no reaction was observed. The results of the mechanistic studies were in agreement with a concerted [4 + 2] cycloaddition process. Hydrogen bonding during the transition state was proposed to be essential for chiral recognition.

The enantioselectivities of anthrone reactions have been improved with other catalysts such as the C_2-symmetrical chiral pyrrolidine **26**.[14] Yamamoto *et al.* reported a double asymmetric synthetic approach using chiral *N*-substituted maleimides **21b** with C_2-chiral pyrrolidine **26** as the catalyst. In this reaction, **22b-2** was isolated as the major isomer, and a maximum de of 80% was obtained (Scheme 9).[14a]

Various pyrrolidine derivatives were examined for the reaction between anthrone and maleimides. The best asymmetric induction of 87% ee was attained when *N*-4-pyridylmethyl-2,5-bis(hydroxymethyl) pyrrolidine **27** was used in the reaction of anthrone **20a** with 2-*tert*-butyl-phenylmaleimide **21c** (Scheme 10).[14b] The high selectivity is partly due to its conformation, in which the aromatic ring is perpendicular to the maleimide ring with one face of the latter being shielded by the ^{t}Bu group.



Scheme 9 Double asymmetric synthesis with chiral *N*-substituted maleimides and a C_2-pyrrolidine.



Scheme 10 Hydroxy-pyrrolidine catalyzed Diels-Alder reaction between anthrone and phenylmaleimide.

Yamamoto *et al.* presented a tentative transition state model which affords the (*S,S*)-product (Fig. 4).[14b] The protonated pyrrolidine catalyst interacts with the activated diene through ionic interactions and hydrogen bonds.[13b] The transition state should also be stabilized by the hydrogen bond between a carbonyl group of the maleimide and a hydroxy group of the catalyst.

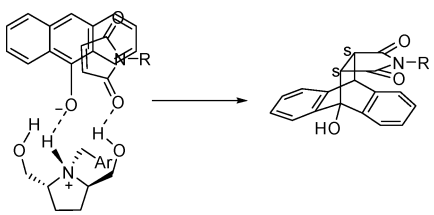
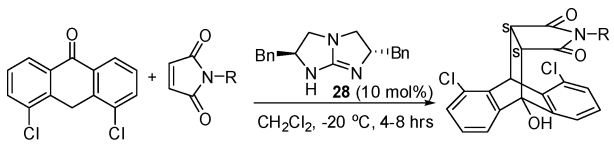


Fig. 4 Transition state model for the pyrrolidine catalyzed Diels–Alder reaction of anthrones.

The Brønsted-basic bicyclic guanidine **28** has been reported by our group to be an efficient catalyst for the enantioselective Diels–Alder reaction between various anthrones and dienes.[15] A typical example is shown in Scheme 11; the reactions allow the formation



Scheme 11 Bicyclic guanidine catalyst **28** for asymmetric Diels–Alder reactions.

of adducts in high yields and excellent enantiomeric excesses (up to 99% ee) under mild reaction conditions. Excellent regioselectivity was also observed when 1,5-dichloro-9-anthrone was used as the diene, leading to the products **22g**, whose regiochemistry was determined by X-ray crystallographic analysis (Fig. 5).

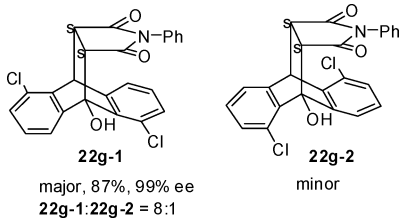
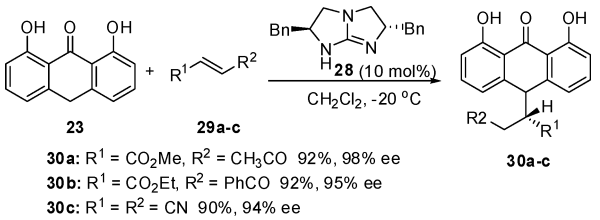


Fig. 5 Possible regioisomers of Diels–Alder adducts.

Guanidine catalyst **28** also promoted the related enantioselective conjugate additions of dithranol **23** with maleimides. Other activated olefins such as methyl *trans*-4-oxo-2-pentenoate **29a** and ethyl *trans*-3-benzoylacrylate **29b** also lead to the exclusive formation of Michael adducts (Scheme 12).[15] It was found that high enantiomeric excesses and yields could be obtained for the Michael adducts (up to 98% ee) under mild reaction conditions.

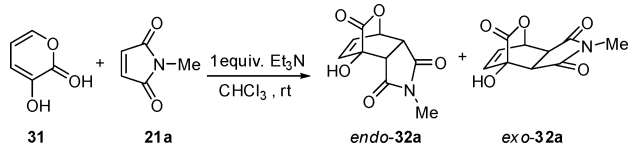


Scheme 12 Enantioselective Michael additions to olefins.

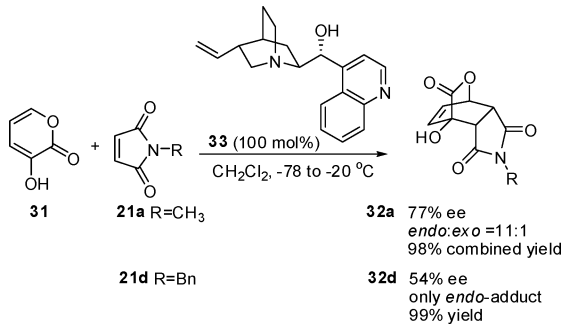
The guanidine catalyst was proposed to generate the active diene *in situ* through deprotonation. The role of the catalyst beyond its function as a Brønsted base is still under investigation. It is likely that hydrogen-bonding, ion-pairing, and π-interactions all contribute to the organization of a transition state that leads to high enantioselectivity.

3.2 Brønsted-base catalyzed reactions of pyrones

Okamura *et al.* were first to show that Brønsted bases such as Et_3N can promote the Diels–Alder reaction of 3-hydroxy-2-pyrone **31** and an electron-deficient dienophile, giving cycloadducts **32** in near quantitative yields (Scheme 13).[12a] When *N*-methylmaleimide **21a** was used as the dienophile, initial screening of different amino alcohols revealed that cinchonidine **33** was an effective promoter; *endo*-**32a** was always formed as the major diastereomer.[12b] Under optimized reaction conditions, this asymmetric reaction afforded *endo*-**32a** in 98% yield with 77% ee, and a diastereomeric ratio (*endo* : *exo*) of 11 : 1 (Scheme 14).[12b] Reducing the amount



Scheme 13 Base catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone.

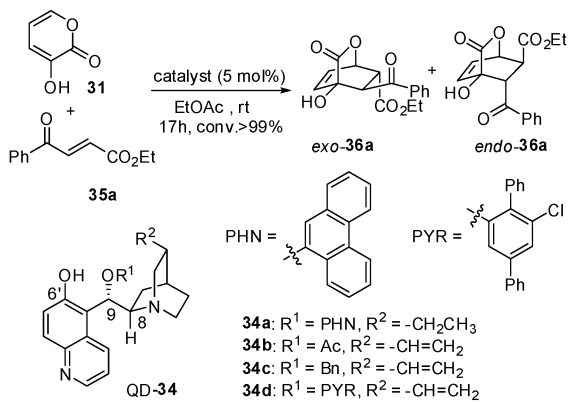


Scheme 14 Asymmetric Diels–Alder reaction of 3-hydroxy-2-pyrone.

of catalyst to 10 mol% still gave the desired product in high yield (100%) but with lower enantioselectivity (66% ee) and diastereoselectivity. When cinchonine was used as the catalyst, the opposite enantiomer was obtained in 95% yield and with 71% ee.

The reaction with *N*-benzylmaleimide **21d** afforded the *endo*-**32d** in 99% yield with 54% ee when cinchonidine **33** was used as the promoter (Scheme 14).[12c] No *exo*-adduct was observed in this reaction. The enantioselectivity was improved to 63% ee when quinine (1 equiv.) was used. When the catalyst loading was decreased to 30 mol%, a nearly comparable enantioselectivity of 59% ee was obtained, but the reaction was slower. The enantioselectivity afforded by natural *Cinchona* alkaloids was modest. Okamura proposed that the mode of action of natural *Cinchona* alkaloids was to activate and orientate **31** in the Diels–Alder reaction.

Deng *et al*. reported the first highly enantioselective and diastereoselective asymmetric Diels–Alder reactions of pyrones with various *Cinchona* alkaloid-based bifunctional catalysts.[16] It was found that 6′-OH *Cinchona* alkaloids **34a–d** afforded significantly better catalytic efficiency than natural *Cinchona* alkaloids (Scheme 15). The structure of the tunable 9-substituent is equally important for high enantioselectivities. The best result was obtained with 5 mol% of catalyst **34a**; the adduct *exo*-**36a** was obtained in 93 : 7 dr and 89% ee (Scheme 15, entry 8). It was



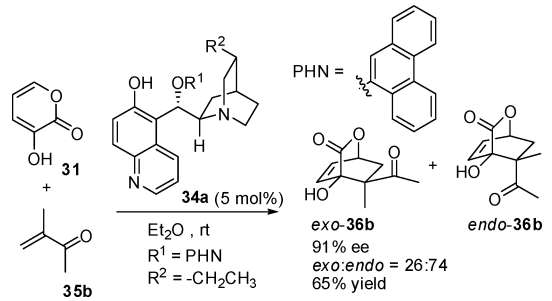
entry	catalyst	dr[a] *exo*:*endo*	ee (%)[a] of *exo*-**36a**	entry	catalyst	dr[a] *exo*:*endo*	ee (%)[a] of *exo*-**36a**
1	quinidine	66:34	5	5	QD-**34c**	87:13	80
2	cinchonine	62:38	-5	6	QD-**34d**	85:15	82
3	DHQD-PHN	66:34	33	7	QD-**34a**	88:12	88
4	QD-**34b**	90:10	57	8[b]	QD-**34a**	93:7	89

[a] In crude reaction mixture. [b] Reaction was run in Et_2O

Scheme 15 *Cinchona* alkaloid catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone.

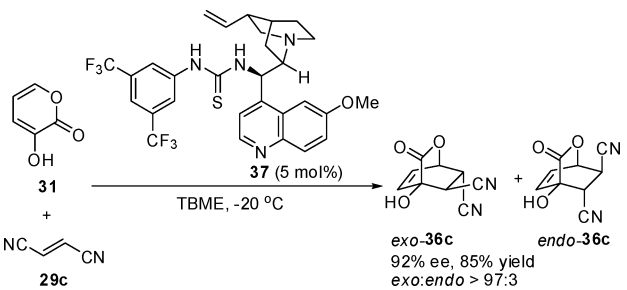
proposed that **34a** simultaneously raises the HOMO of the pyrone and lowers the LUMO of the dienophile while orienting the two reagents to exert stereochemical control.

Catalyst **34a** was found to tolerate a significant degree of variation in both the pyrones and the dienophiles. The reactions between pyrone **31** and dienophiles with different substitution patterns proceeded very well. It is noteworthy that even the relatively unreactive dienophile **35b** could be employed in this reaction, thereby generating optically active chiral building blocks containing two adjacent tetra-substituted stereocenters (Scheme 16).[16] Moreover, catalyst **34a** was able to furnish useful levels of enantioselectivity and diastereoselectivity for reactions between dienophile **35a** and pyrone **31** bearing various substituents.



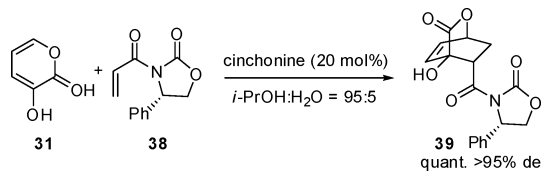
Scheme 16 Diels–Alder reaction between 3-hydroxy-2-pyrone with an unreactive dienophile catalyzed by **34a**.

However, catalyst **34a** was not useful for the reaction of **31** with fumaronitrile **29c**. Although the 9-thiourea *Cinchona* alkaloid **37** was found to be ineffective for the reaction between **31** and **35a**, it greatly improved the enantioselectivity and diastereoselectivity of the reaction between pyrone **31** and fumaronitrile **29c**. The adduct *exo*-**36c** was obtained in 85% yield with 92% ee and >97 : 3 dr (Scheme 17).[16] The reaction also worked well with maleonitrile, which illustrated the ability of **37** to tolerate dienophiles with either an *E*- or a *Z*-double bond. It is remarkable that these reactions are stereospecific with respect to the geometry of the double bond. These results are consistent with a concerted cycloaddition mechanism.[12a]



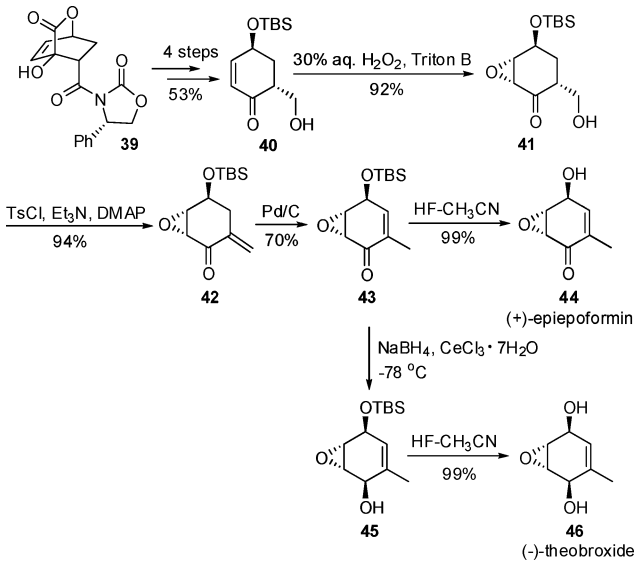
Scheme 17 Diels–Alder reaction of 3-hydroxy-2-pyrone catalyzed by **37**.

Okamura *et al.* reported an asymmetric Diels–Alder reaction between 3-hydroxy-2-pyrone **31** and an optically active acrylate **38**, which afforded a highly functionalized adduct **39** in almost quantitative yield with >95% de (Scheme 18).[17a] The adduct **39** is a useful starting material for the synthesis of various cyclohexene oxides[17b,c] such as (+)-epiepoformin **44**[18] and (−)-theobroxide **46**[19] (Scheme 19). The two compounds were reported to be metabolites of phytotoxic pathogens. (+)-Epiepoformin **44** is an



Scheme 18 Asymmetric base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone with a chiral acrylate derivative.

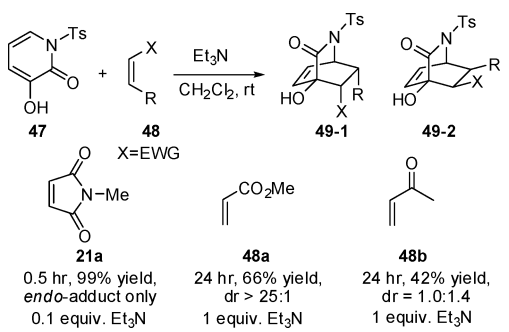
inhibitor of lettuce seed germination[18] and (−)-theobroxide **46** can induce potato micro-tubers and morning-glory flower buds.[19] The synthesis of both natural products started from the adduct **39** following the procedures as described below (Scheme 19).[17b,c]



Scheme 19 Synthesis of (+)-epiepoformin and (−)-theobroxide.

3.3 Brønsted-base catalyzed reactions of *N*-substituted-3-hydroxy-2-pyridone

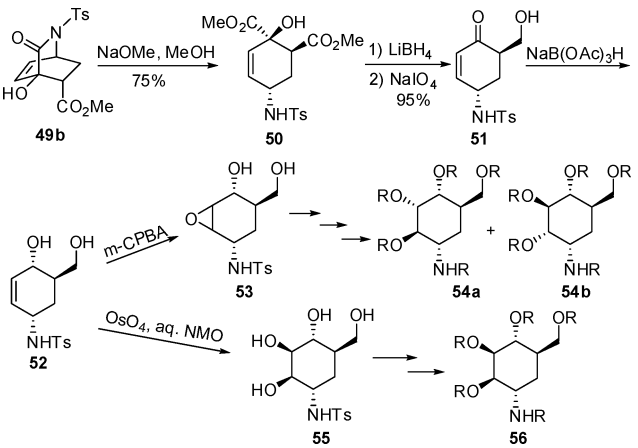
In a similar fashion, Diels–Alder reactions between *N*-tosyl-3-hydroxy-2-pyridone **47** and an electron-deficient dienophile can also be catalyzed by a base.[20] When Et_3N was used as catalyst, the reaction of **47** and *N*-methylmaleimide **21a** afforded an almost quantitative amount of the *endo*-adduct within 0.5 h (Scheme 20). The catalyst was also effective for reactions with less reactive dienophiles, such as methyl acrylate **48a** and 3-buten-2-one **48b**.



Scheme 20 Base-catalyzed reactions of *N*-tosyl-3-hydroxy-2-pyridone.

The *endo* selectivity of these reactions was very high, because the sterically bulky substituent led to an unfavorable interaction with the dienophile during its *exo* approach.[20] The bulkiness of the base catalyst also sterically influenced the approaching dienophile. In fact, a slightly lower *endo* selectivity was observed for the reaction using the less sterically hindered *t*-BuNH$_2$. Stronger inorganic bases such as *n*-BuLi were more effective than the amine catalysts. Using *n*-BuLi as the catalyst, the reaction was faster and gave a higher yield of product. However, *n*-BuLi was not effective for the reactions with olefins such as methyl acrylate **48a** and 3-buten-2-one **48b**. Direct addition of *n*-BuLi to these olefins may occur. Finally, it was proposed that the reaction proceeded *via* a concerted Diels–Alder reaction mechanism.[20]

The resulting product of this reaction is a highly functionalized bicyclic lactam, which is a useful building block for synthesizing *pseudo*-aminosugars. (±)-Validamine is a biologically active *pseudo*-aminosugar, first isolated as a degradation product of the strong antibiotic validamycin A in 1971.[21] The synthesis of a key intermediate **52** is shown in Scheme 21.[22] It was easily obtained as an exclusive product in good yield from the bicyclic lactam **49b** that resulted from a Diels–Alder reaction between pyridone **47** with methyl acrylate **48a** (Scheme 20). Three validamine type compounds were synthesized *via* this key intermediate **52**.



Scheme 21 Synthetic route to three validamine type compounds.

Tamiflu **57** (Fig. 6) is a potent neuraminidase inhibitor and the most widely used anti-influenza drug. Influenza viruses with reduced sensitivity to neuraminidase inhibitors have been reported recently.[23] The synthesis of modified Tamiflu is thus of high interest. Okamura *et al.* reported a short and efficient synthesis of Corey's intermediate **58**[24] (Scheme 22).[25] The Diels–Alder adduct **60** was easily obtained from an aqueous "green" Diels–Alder reaction that was able to be scaled-up to multigram quantities without significant loss of yield. Only four steps are required to prepare **58** and inexpensive reagents are used (Scheme 22).[25]

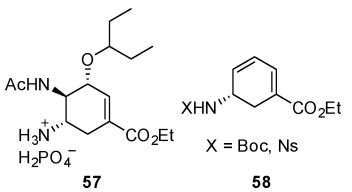
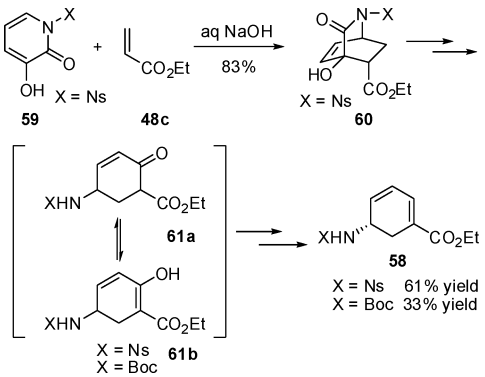


Fig. 6 Tamiflu and Corey's intermediate.



Scheme 22 Synthesis of Tamiflu intermediates.

Conclusions

Recent developments in the area of both acid- and base-catalyzed Diels–Alder reactions have been summarized. The use of Brønsted bases to catalyze the Diels–Alder reaction is a less established approach. Despite several important achievements in this field, our knowledge about the underlying mechanistic details is fairly limited and the role of individual active sites in catalytic processes is not clearly established. The successful design of a general chiral organocatalyst for the Diels–Alder reactions is still a challenging task. The design of suitable substrates for Brønsted-acid and Brønsted-base catalyzed Diels–Alder reactions also requires further innovation and creativity.

Acknowledgements

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