ACCOUNTS
of chemical research

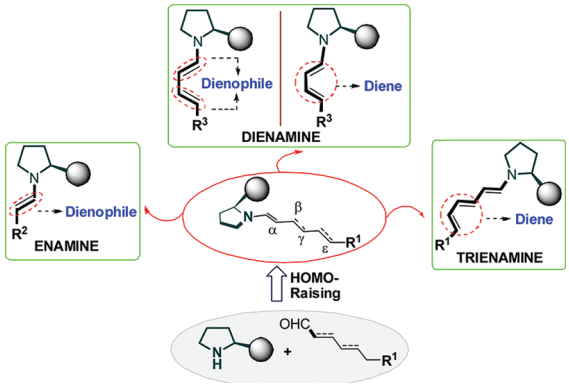
Aminocatalytic Asymmetric Diels–Alder Reactions via HOMO Activation

JUN-LONG LI,[‡] TIAN-YU LIU,[†] AND YING-CHUN CHEN*[,†,‡]

[†]*College of Pharmacy, Third Military Medical University, Chongqing 400038, China, and* [‡]*Key Laboratory of Drug-Targeting and Drug Delivery Systems of the Ministry of Education, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*

RECEIVED ON DECEMBER 30, 2011

CONSPECTUS



In the first successful catalytic asymmetric Diels–Alder reaction in 1979, Koga and colleagues used a chiral aluminum complex as a Lewis acid catalyst, but since then, researchers have developed numerous catalytic systems for these reactions. By 2000, several chiral organic compounds, such as the salts of imidazolidinones or TADDOLs, emerged as robust catalysts in the asymmetric Diels–Alder reactions. According to frontier molecular orbital theory, most of these catalysts employ a LUMO-lowering strategy as a means of activating electron-deficient dienophiles. Only rarely do chiral catalysts take advantage of the alternative strategy of activating the HOMO.

In this Account we will discuss the development of asymmetric Diels–Alder reactions based on the HOMO-raising effects of chiral amines. First, we show that enamine intermediates formed in situ between an amine catalyst and enolizable aliphatic aldehydes can act as electron-rich dienophiles in inverse-electron-demand Diels–Alder reactions. We describe the preparation of a variety of oxygen- or nitrogen-containing heterocycles with high optical purity. Then, we demonstrate that the dienamine species from α,β-unsaturated aldehydes can act either as electron-rich dienes in normal-electron-demand Diels–Alder reactions or as dienophiles in inverse-electron-demand Diels–Alder reactions. These reactions generally occur with high chemo-, regio-, and stereoselectivity. Finally, we introduce a new activation mode for Diels–Alder reactions, in which reactive trienamine intermediates derived from 2,4-dienals or even 2,4-dienones play a key role. Notably, we observe remarkable β,ε-regioselectivity and obtain excellent stereocontrol even at the very remote ε-reactive center—up to seven bonds away from the chiral center of the amine catalyst.

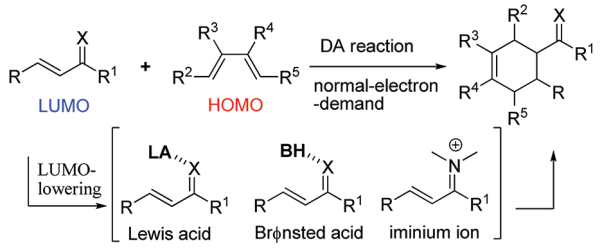
These results demonstrate that a HOMO-activation strategy via aminocatalysis could become a significant tool in asymmetric Diels–Alder reactions. In addition, these reactions using enamine, dienamine, or trienamine intermediates produce a diverse array of densely functionalized cyclic scaffolds, which may serve as valuable structures in drug discovery and natural product synthesis.

Introduction

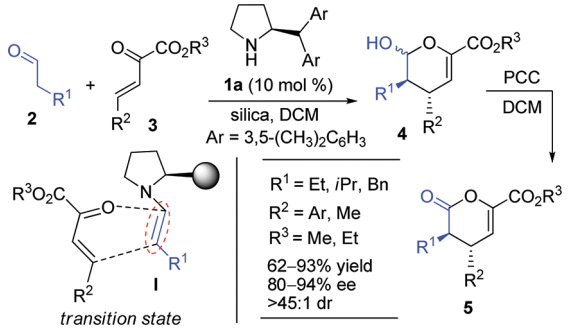
The Diels–Alder (DA) cycloaddition has proven to be one of the most powerful protocols for accessing six-membered carbo- or heterocycles, generally with high chemo-, regio-, and stereoselectivity in an atom-economic manner.[1] While chiral Lewis acid complexes have predominantly been used to catalyze asymmetric DA reactions in past decades,[2] MacMillan and co-workers reported in 2000 that chiral secondary amines, such as imidazolidinones, can catalyze asymmetric DA reactions via iminium activation of

Published on the Web 06/20/2012 www.pubs.acs.org/accounts
10.1021/ar3000822

SCHEME 1. Traditional Activation Modes for the Catalytic Diels–Alder Reactions



SCHEME 2. Organocatalytic Asymmetric IED Hetero-DA Reaction



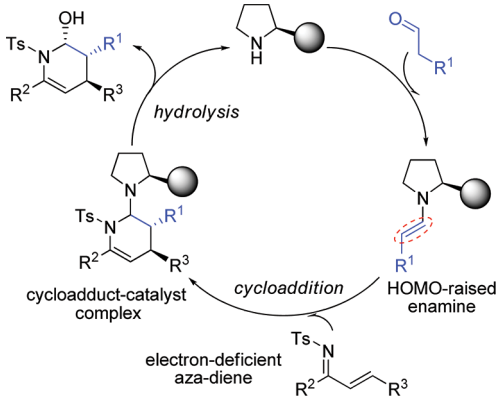
α,β-unsaturated aldehydes.[3] Later, Rawal used simple chiral TADDOLs as Brønsted acids to promote a highly enantioselective hetero-DA reaction via hydrogen-bonding interactions.[4] According to frontier molecular orbital (FMO) theory,[5] all of these catalysts work by lowering the lowest unoccupied molecular orbital (LUMO) in dienophiles (Scheme 1).

Theoretically, the concerted [4 + 2] process could be accelerated by either lowering the LUMO or raising the highest occupied molecular orbital (HOMO).[5] In practice, HOMO-activated electron-rich dienes have been extensively applied in DA cycloadditions,[6] while the asymmetric versions have been carried out using chiral auxiliaries.[7] Nevertheless, recent developments in chiral amine-catalyzed asymmetric DA reactions have confirmed the power of the alternative HOMO-raising strategy. The present account will highlight the efforts of our group to perform aminocatalytic asymmetric DA reactions using diverse carbonyl compounds, especially aldehydes. Closely related works by other groups will also be summarized.

Enamine Pathway

The electron-rich C=C bond in enamine has been used in DA-type reactions, and the first such pyrrolidine-catalyzed DA cycloaddition was reported by Boger in 1982.[8,9] However, the catalytic asymmetric variation was not reported until 2003. Jørgensen and co-workers found that the chiral

SCHEME 3. Catalytic Cycle of the Asymmetric IED aza-DA Reaction

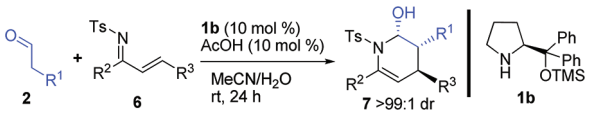


enamine species **I** generated in situ between amine **1a** and aliphatic aldehydes **2** could act as HOMO-raised dienophiles in the inverse-electron-demand (IED) hetero-DA reaction with β,γ-unsaturated α-ketoesters **3** (Scheme 2).[10] Pyran-2-one derivatives **5** were obtained with high stereoselectivity after PCC (pyridinium chlorochromate) oxidation of hemiacetals **4**. Silica gel played a key role in the catalytic cycle, causing the hydrolysis of *N*,*O*-acetal cycloadducts to give hemiacetals **4**. This reaction was an important breakthrough that clearly demonstrated that asymmetric DA-type cycloaddition could be efficiently catalyzed by a simple chiral amine via a HOMO-activation pathway.

Despite this initial success, this promising catalytic protocol has not received much attention.[11] In our continuing studies of asymmetric organocatalysis,[12] we recognized the contributions from Boger, who introduced the IED aza-DA reaction of *N*-sulfonyl-1-azadienes and electron-rich olefins as a way to access valuable tetrahydropyridines.[13] These reactions generally exhibit the characteristics of a concerted [4 + 2] mechanism with high regiospecificity and diastereoselectivity. Although the utility of this aza-DA reaction has been fruitfully explored in recent decades, including the introduction of a highly diastereoselective variation with chiral dienophiles,[14] only limited progress has been made toward developing catalytic asymmetric variations.[15] We found that enamine intermediates were applicable to Boger's IED aza-DA reaction, as outlined in Scheme 3. Interestingly, similar to Jørgensen's catalytic conditions,[10] the addition of a small amount of water turned out to be crucial for the conversion, perhaps because it facilitates release of the catalyst from the cycloadducts, which leads to the completion of the catalytic cycle.

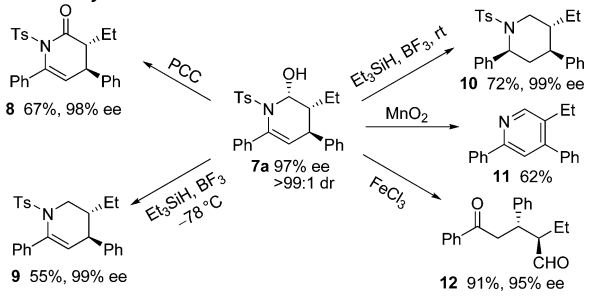
As summarized in Table 1, the readily available Jørgensen–Hayashi catalyst[16] α,α-diphenylprolinol *O*-TMS

TABLE 1. Asymmetric IED aza-DA Reaction of *N*-Ts-1-Azadienes **6** and Aldehydes **2**

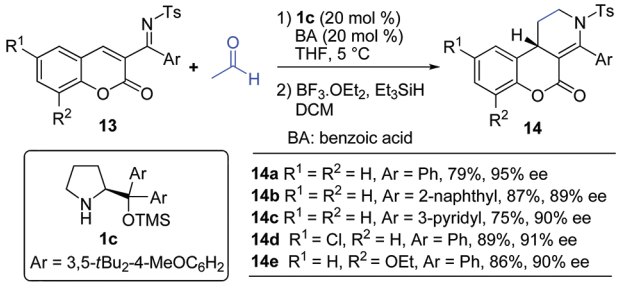


entry	**7**	R^1	R^2	R^3	yield (%)	ee (%)
1	**7a**	Et	Ph	Ph	88	97
2	**7b**	Et	Ph	2-thienyl	87	98
3	**7c**	Et	Ph	Me	83	93
4	**7d**	Et	Ph	CO_2Et	95	99
5	**7e**	Et	*o*-ClC_6H_4	Ph	74	99
6	**7f**	Me	Ph	Ph	92	98
7	**7g**	$BnO(CH_2)_2$	Ph	Ph	72	99

SCHEME 4. Synthetic Transformations of Hemiaminal **7a**



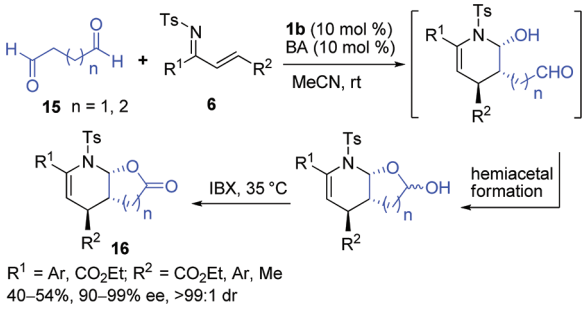
SCHEME 5. Asymmetric aza-DA Reaction of 1-Azadienes Based on Coumarin Cores



ether **1b** effectively promoted the cycloaddition of *N*-Ts-1-azadienes **6** and aldehydes **2** to afford the hemiaminals **7**, which bear three contiguous chiral centers, with outstanding diastereo- (>99:1) and enantioselectivity. In general, a wide range of 1-azadienes with aryl, heteroaryl, alkyl, and ester groups were well tolerated for combination with linear aldehydes (Table 1). However, both branched isovaleraldehyde and aqueous acetaldehyde failed to participate in this reaction.[17]

A series of useful molecules, such as chiral lactam **8**, piperidine derivatives **9** and **10**, trisubstituted pyridine **11**, or 1,5-dicarbonyl compound **12**, have been readily prepared in a single step from the chiral hemiaminal **7a** (Scheme 4).

SCHEME 6. Synthesis of Lactone[2,3-*b*]tetrahydropyridines



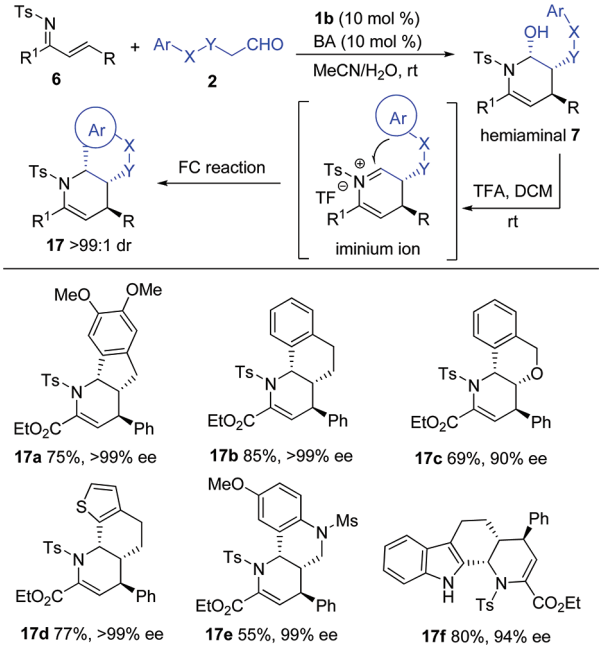
Subsequently, aqueous acetaldehyde was used in reactions involving a special type of 1-azadienes **13** derived from 3-argiocarbonylcoumarins, which bear a 2,3,4-trisubstituted pattern and which have been used to synthesize the core structure of Streptonigrone by Boger.[18] Catalyst **1b** gave a quite disappointing ee value (36%), but a bulkier analogue **1c** developed in our group gave the chiral chroman-2-ones **14** with dramatically improved enantioselectivity after dehydroxylation (Scheme 5).[19]

The cycloadducts **7** possess a relatively stable hemiaminal functionality, which can be useful for designing domino or tandem processes to construct highly complex fused tetrahydropyridines. For example, we developed a domino aza-DA–hemiacetal formation sequence involving aqueous glutaraldehyde **15** and 1-azadienes **6**; after subsequent IBX oxidation, the corresponding chiral lactone[2,3-*b*]-tetrahydropyridines **16** were efficiently obtained in an enantiomerically enriched form. Nevertheless, overall yields were low to moderate due to side reactions in the final step (Scheme 6).[20]

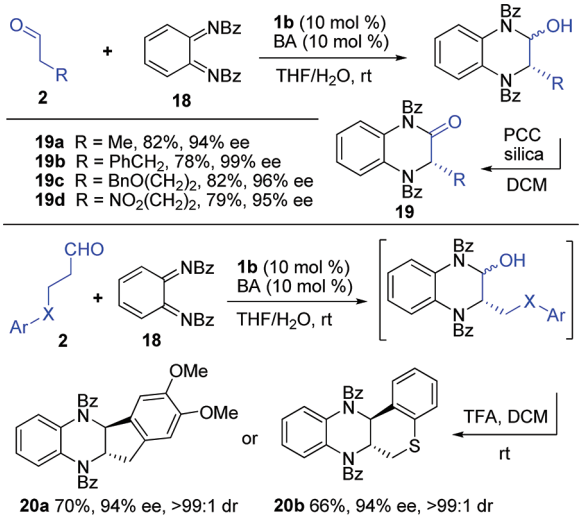
In further work we used this aminocatalysis to construct versatile fused heterocycles with diverse skeletons. As illustrated in Scheme 7, aldehydes **2** tethered to an arene motif have been used in the IEDDA reaction with 1-azadienes **6**. The corresponding hemiaminals **7** were subsequently converted to electrophilic iminium ions under strongly acidic conditions, and these underwent intramolecular Friedel–Crafts (FC) cyclization with the tethered arene motif to give fused tetrahydropyridine frameworks. Using this approach, a spectrum of highly enantioenriched heterocycles **17** have been produced in a straightforward manner. Since fused piperidine structures are ubiquitous in natural alkaloids and biologically important compounds, these polycyclic architectures may be of interest in medicinal chemistry.[21]

In addition to the aza-DA reaction of activated 1-azadienes, we have also applied enamine species to the construction of other types of chiral heterocycles.

SCHEME 7. Assembly of Fused Heterocycles via Sequential aza-DA–FC Reactions

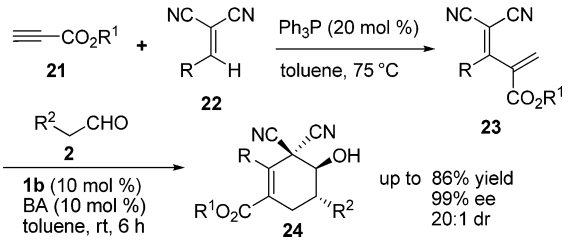


SCHEME 8. Synthesis of Chiral Quinoxaline Derivatives



Quinoxalines and related scaffolds exist in a number of pharmaceutical agents. Lectka developed an elegant IEDDA reaction of *o*-benzoquinone diimides with ketene enolates formed in situ from acyl chlorides; this reaction was catalyzed by cinchona alkaloids, also via a HOMO-activation strategy. Notably, low temperature (−78 °C) was necessary to ensure high stereocontrol.[22] We demonstrated that the IED hetero-DA reaction of *o*-benzoquinone diimide **18** with aldehydes **2** proceeded smoothly via the catalysis of **1b** at ambient temperature. An array of chiral quinoxalinones **19**

SCHEME 9. Asymmetric All-Carbon-Based IEDDA Reaction



was obtained with excellent enantioselectivity after PCC oxidation of the hemiaminals.[23] A hetero-DA–FC reaction sequence has also been used to construct fused tetrahydroquinoxalines **20** in excellent stereoselectivity, while a different *trans*-selectivity was observed in the later FC step (Scheme 8).[21]

An asymmetric, all-carbon-based IEDDA reaction has been reported by Wang and co-workers. They disclosed that a novel type of electron-poor dienes **23** could be generated via a PPh_3-catalyzed cascade reaction of propiolates **21** and α,α-dicyanoolefins **22**, which could then undergo asymmetric cycloaddition with enamine species. This approach has been used to generate a broad spectrum of highly substituted cyclohexenols **24** in good yield and with high stereoselectivity (Scheme 9).[24]

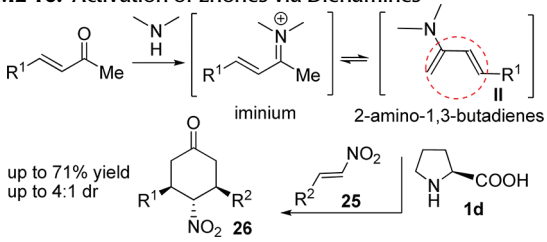
Dienamine Pathway

Chiral dienamine species derived from α,β-unsaturated ketones have been used in a diastereoselective DA-type reaction involving nitroolefins.[7b] Barbas was the first to report in 2002 that in situ-formed 2-amino-1,3-butadienes **II** could act as electron-rich dienes in a normal-electron-demand (NED) DA reaction with nitroolefins **25**, but poor enantioselectivity was observed when the reaction was catalyzed by L-proline **1d** (Scheme 10).[25] Subsequently, this approach was improved to allow synthesis of useful compounds.[26] It is possible that these reactions proceed via a stepwise cascade sequence;[27] such catalysis will not be depicted in detail here in consideration of space limitations.[28]

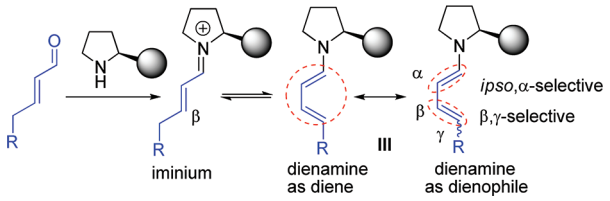
The electrophilic iminium ions derived from α,β-unsaturated aldehydes in the presence of amine catalyst can isomerize to electron-rich 1-amino-1,3-butadiene species. The HOMO-raised dienamines **III** may react either with electron-deficient olefins in a NEDDA reaction manner or with electron-poor dienes as regioselective dienophiles in an IEDDA reaction (Scheme 11).

Dienamine as Diene. The first asymmetric NEDDA reaction with dienamine species was reported by Serebryakov in 1998, and the reaction was inefficient.[29] In 2006, the

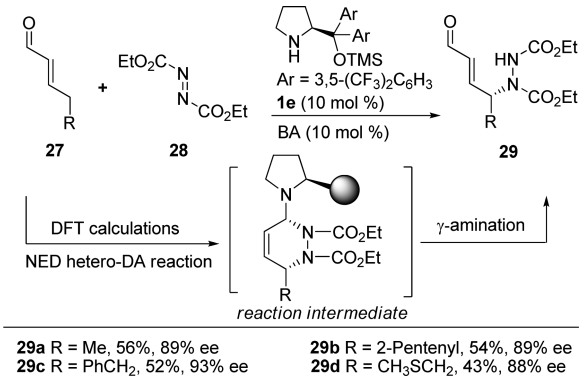
SCHEME 10. Activation of Enones via Dienamines



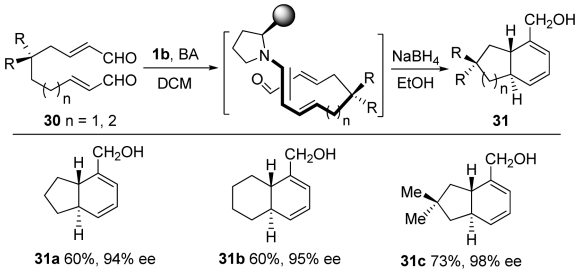
SCHEME 11. Activation Modes of α,β-Unsaturated Aldehydes



SCHEME 12. γ-Amination of Enals via Dienamine Pathway

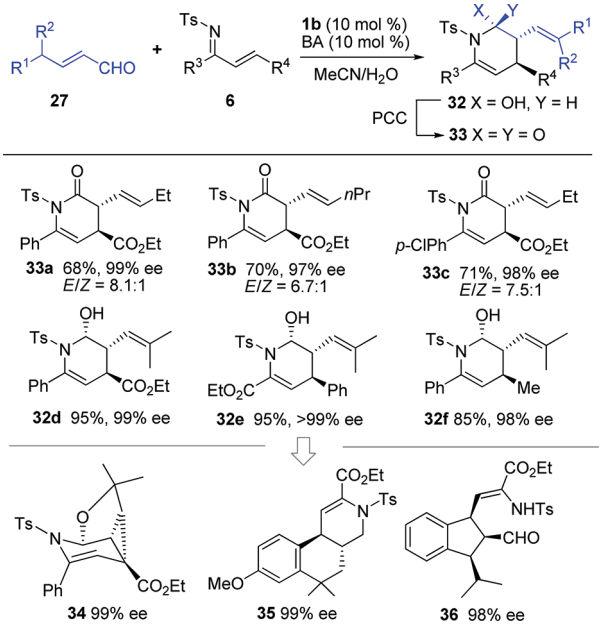


SCHEME 13. Intramolecular Asymmetric NEDDA Reaction



Jørgensen group achieved direct asymmetric γ-amination of α,β-unsaturated aldehydes **27** with diethyl azodicarboxylate (DEAD) **28** catalyzed by chiral amine **1e**. The high enantioselective outcome (up to 93% ee) was rationalized by DFT calculations, suggesting a concerted [4 + 2] cycloaddition pathway involving a dienamine intermediate and DEAD (Scheme 12).[30]

SCHEME 14. Asymmetric *ipso*,α-Regioselective IED aza-DA Reaction[a]



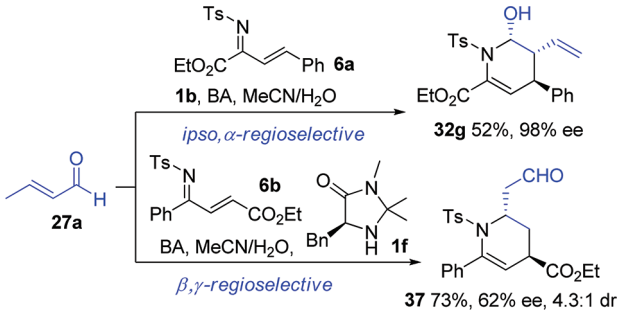
[a]For **32**–**36**, >99:1 dr; yields of **33** referred to pure *E*-isomer.

An asymmetric intramolecular NEDDA reaction was later developed by Christmann.[31] Amine **1b** was employed to promote the cycloaddition of tethered α,β-unsaturated dialdehydes **30** in *endo*-selectivity. The unsaturated bicyclic systems **31** were produced with good yield and excellent optical purity, as amine **1b** was removed eliminatively after the cycloaddition step (Scheme 13).

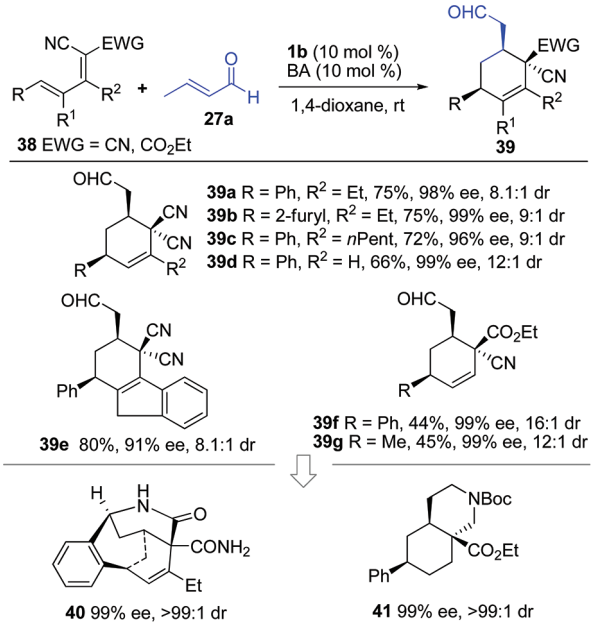
Dienamine as Dienophile. In addition to participating in the NEDDA reaction, HOMO-activated 1-amino-1,3-butadienes play a role as dienophiles in the IEDDA reaction. We discovered that dienamine species of α,β-unsaturated aldehydes and amine **1b** exhibited high reactivity in the aza-DA reaction with *N*-Ts-1-azadienes **6**. Moreover, this process showed remarkable *ipso*,α-regioselectivity, delivering hemiaminals **32** containing an alkene moiety. After oxidation to lactams **33**, the major *E*-isomers were easily separated with outstanding diastereo- (>99:1) and enantioselectivity. Reactivity was even greater for γ,γ-disubstituted 4-methyl-2-pentenal (products **32d**–**f**). Notably, the newly generated C=C bond in the hemiaminals allowed some simple intramolecular transformations, yielding a diversity of complex frameworks **34**–**36** (Scheme 14).[32]

Interestingly, different regioselectivity was observed when crotonaldehyde **27a** was used. While 1-azadiene **6a** gave the normal *ipso*,α-regioselective adduct **32g**, the differently substituted 1-azadiene **6b** exclusively showed unexpected β,γ-regioselectivity.[33] MacMillan's catalyst **1f**

SCHEME 15. Regioselective IEDDA Reaction of Crotonaldehyde



SCHEME 16. Asymmetric All-Carbon-Based IEDDA Reaction of Crotonaldehyde

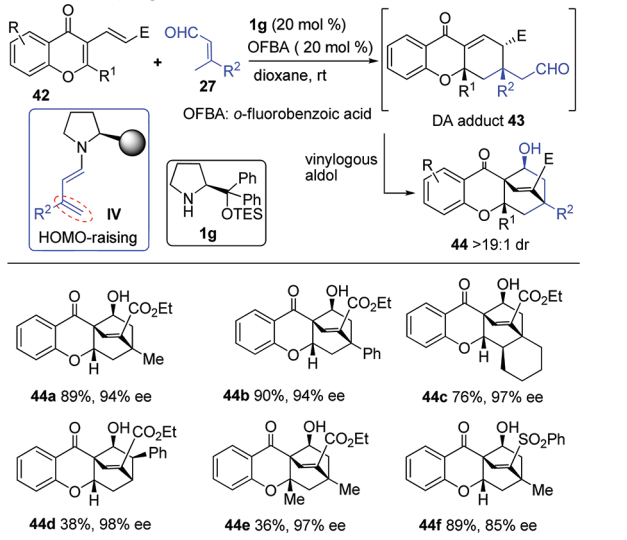


provided better stereocontrol, but the ee value was still modest (Scheme 15).

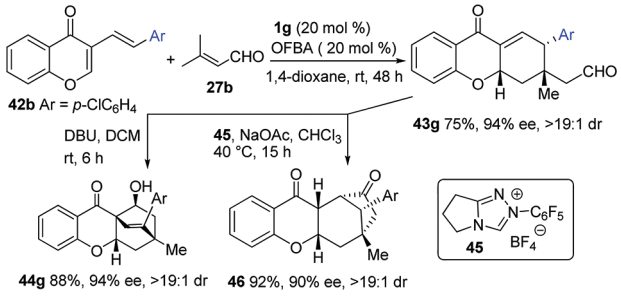
Inspired by these findings, we developed the first asymmetric, all-carbon based IEDDA reaction of electron-deficient dienes and crotonaldehyde via dienamine activation. Using **1b** as catalyst, crotonaldehyde reacted with a diversity of dienes **38** with exclusive β,γ-regioselectivity, affording multifunctional cyclohexenes **39** with excellent enantioselectivity and good diastereocontrol (Scheme 16). In addition, this approach has been used to synthesize a caged polycyclic compound **40** and a decahydroiso-quinoline **41** after some simple derivations (Scheme 16).[34]

Unfortunately, crotonaldehyde was the only enal substrate found to undergo the above DA reaction. Expanding on the IEDDA reaction of chromone-fused dienes and electron-rich ethenes described by Bodwell,[35] we discovered that

SCHEME 17. Asymmetric IEDDA Reaction of β,β-Disubstituted Enals and Domino Vinylogous Aldol Reaction



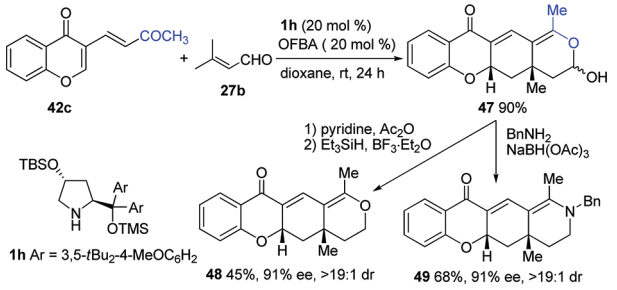
SCHEME 18. Reaction of a 3-Styryl-Substituted Chromone



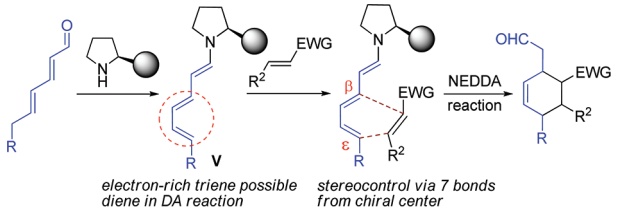
these dienes were highly reactive with the dienamine species of β,β-disubstituted α,β-unsaturated aldehydes. This reactivity may be because, although a quaternary center must be formed in the cycloadducts, the electron-donating effects of another β-substituent further raise the HOMO energy of the dienamine system **IV**, as outlined in Scheme 17, and this helps to overcome the reaction barrier. A domino vinylogous aldol reaction occurred after the desired IEDDA reaction, affording an array of natural product mimics **44** with caged tetrahydroxanthone skeletons from chromone-fused dienes **42** bearing an ethoxycarbonyl or sulfonyl group. Most of these reactions occurred with excellent stereoselectivity.

The domino vinylogous aldol reaction did not occur when a 3-styryl-substituted chromone **42b** was used because of the decreased acidity of vinylogous C–H in **43g**, but a similar caged compound **44g** could be generated after treating **43g** with DBU. An intramolecular Stetter reaction furnished a diverse bicyclo[3.2.1]octane system **46** in the presence of carbene precursor **45** and NaOAc (Scheme 18).

SCHEME 19. Construction of Chiral Tetracyclic Frameworks



SCHEME 20. HOMO-Activation Mode for 2,4-Dienals



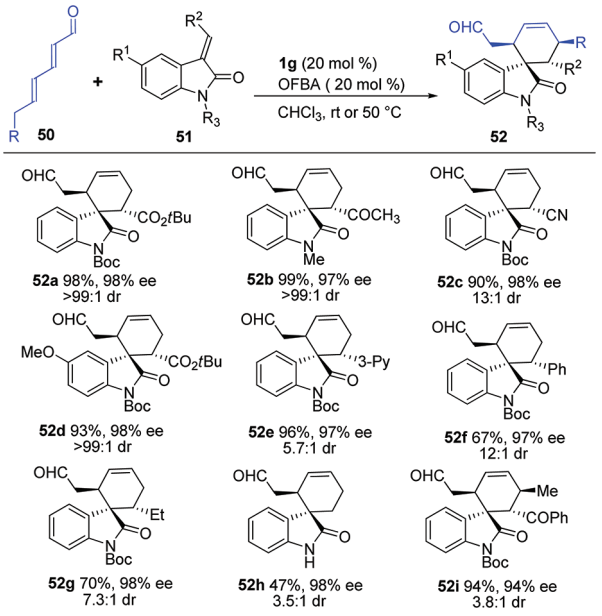
A tetracyclic hemiacetal **47**, rather than the vinylogous aldol adduct, was obtained for diene **42c** containing an acetyl group. Using a bulky amine **1h** gave dihydropyran **48** or tetrahydro-pyridine **49** with high stereoselectivity after dehydroxylation or reductive amination, respectively (Scheme 19).[36]

Trienamine Pathway

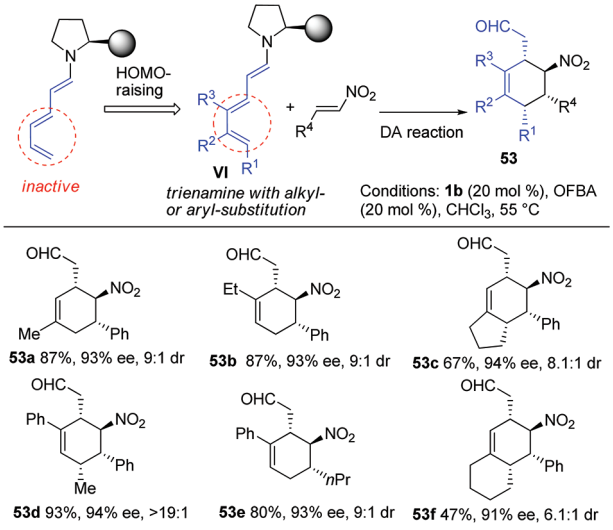
A longstanding goal in organic synthesis is the discovery and development of novel catalytic modes. In our continuing efforts to explore asymmetric DA reactions via HOMO-activation, we wondered whether the dienamine pathway could be taken further. We reasoned that a polyconjugated 2,4-dienal might form an analogous trienamine intermediate **V** with an amine catalyst (Scheme 20). Since its electron-rich property should raise the HOMO-energy of the triene system, a NED-type DA reaction with a suitable activated olefin would be facilitated.

We subsequently showed that the reaction of 2,4-dienals **50** and 3-olefinic oxindoles **51** proceeded smoothly with amine **1g** as catalyst. The cycloaddition exhibited exclusive β,ε-regioselectivity and excellent stereoselectivity, affording a spectrum of spirocyclic oxindoles **52** featuring a cyclohexene motif (Scheme 21).[37] Notably, excellent stereocontrol was maintained even when a C–C bond was formed at the remote ε-position of the 2,4-dienal skeleton, seven bonds away from the chiral center of the amine catalyst. This can be attributed to the concerted bond-forming reaction at the β-site of the trienamine intermediate, as proposed in Scheme 20.[38]

SCHEME 21. NEDDA Reaction of 2,4-Dienals and 3-Olefinic Oxindoles

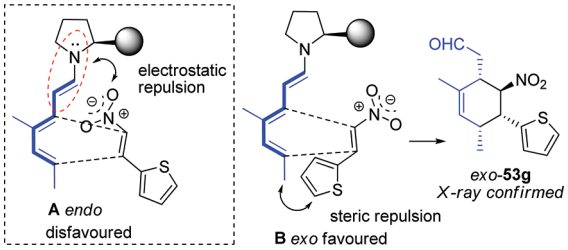


SCHEME 22. HOMO-Raising Strategy in Asymmetric NEDDA Reaction of 2,4-Dienals and Nitroolefins

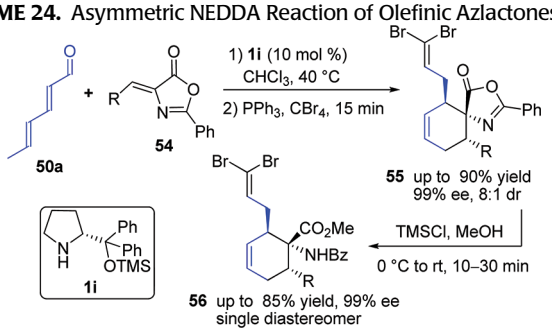


Highly active alkylidenecyanoacetates also exhibited good reactivity with simple 2,4-hexadienal via the trienamine pathway.[37] However, β-nitrostyrene remained inert even at much higher temperature (80 °C), though this and similar dienophiles have been widely employed in DA reactions. By introducing an alkyl or aryl group into the skeleton of 2,4-dienals, which may raise the HOMO-energy of the resulting trienamine intermediates **VI** (Scheme 22), we successfully carried out the NEDDA reaction with nitroolefins. The scope for both substrates is substantial, and a

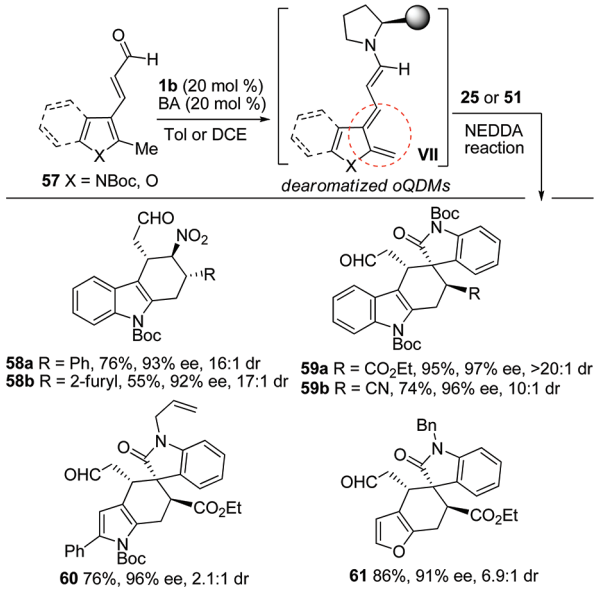
SCHEME 23. Rationalization for *exo*-Selective DA Reaction of Nitroolefins



SCHEME 24. Asymmetric NEDDA Reaction of Olefinic Azlactones



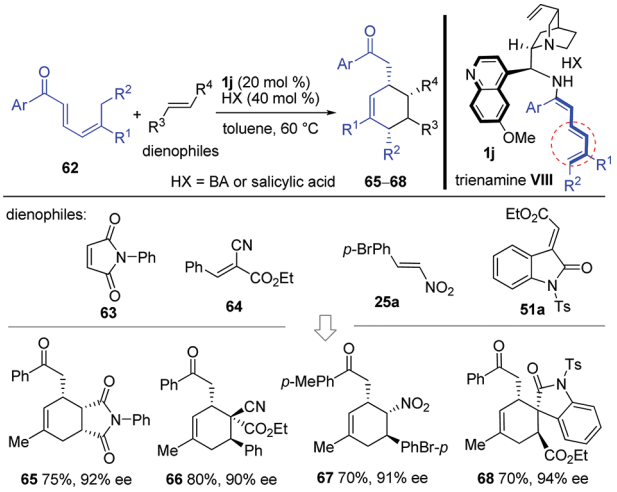
SCHEME 25. Asymmetric DA Reaction with in Situ Generated *o*QDMs



number of densely substituted cyclohexenes **53**, including bicyclic ring frameworks **53c** and **53f**, have been constructed with excellent enantioselectivity and good diastereocontrol.

Unexpectedly, this NEDDA reaction of nitroolefins exhibited abnormal *exo*-selectivity, though the same trienamine pathway was involved.[37] We proposed that the unique

SCHEME 26. NEDDA Reaction of 2,4-Dienones[a]



[a]For cycloadducts **65**–**68**, >19:1 dr.

exo-selectivity might be due to electrostatic repulsion between the π electrons of the trienamine motif and the nitro group, as depicted in model A in Scheme 23.[39]

Trienamines of 2,4-dienals have also been explored by the Jørgensen group.[40] Olefinic azlactones **54** were utilized as a new type of dienophiles, and outstanding regio- and stereoselectivity (dr >5:1, >96% ee) were obtained in the reaction with simple 2,4-hexadienal **50a**. The optically pure products **55** can be transformed to more useful building blocks in protein chemistry, such as chiral, *N*-protected amino acid esters **56** (Scheme 24).

Melchiorre and co-workers have made important advances in developing the trienamine concept.[41] They used α,β-unsaturated aldehydes **57** tethered to a 2-methylindole motif as precursors of trienamines. Catalyzed by amine **1b**, the heterocyclic *ortho*-quinodimethanes **VII** (*o*QDMs), which can be considered a special type of HOMO-raised trienamine species, were generated in situ from the enals, thereby overcoming the high energy barrier of dearomatization. Highly stereoselective DA cycloadditions have been realized with nitroolefins **25** or 3-olefinic oxindoles **51**, affording a wide range of structurally complex chiral indole derivatives **58** and **59**. It should be noted that *exo*-selectivity was also observed for cycloadducts **58**.[39] Such a catalytic system is compatible with 2-methylpyrrole- or furan-based enals, which yield fused heterocycles **60** or **61**, respectively (Scheme 25).

Very recently, we expanded trienamine chemistry to include 2,4-dienone substrates using quinine-derived primary amine **1j** as catalyst. A special type of 2,4-dienones with a δ,δ-disubstitution must be used; otherwise, the 2,4-dienones act directly as diene counterparts in a noncatalyzed

DA reaction. Several types of electron-deficient dienophiles, such as *N*-phenyl maleimide **63**, benzylidenecyanoacetate **64**, nitroolefin **25a**, and 3-olefinic oxindole **51a**, have been successfully used to react with trienamine species **VIII**, giving multifunctional cyclohexenes **65**–**68** with excellent diastereo- (>19:1) and enantioselectivity (Scheme 26).[42,43]

Conclusion

A series of HOMO-activated species, including enamines, dienamines, and trienamines, have been efficiently applied to asymmetric Diels–Alder reactions. A variety of simple starting materials, such as aliphatic aldehydes, α,β-unsaturated aldehydes, and even 2,4-dienals or 2,4-dienones, have been used in elegant combinations with diverse electron-deficient dienes or dienophiles by the catalysis of a chiral amine, providing versatile protocols to access a broad spectrum of highly diastereo- and enantioenriched, structurally complex six-membered carbo- and heterocycles. The amine-based HOMO-activation strategy is compatible with a variety of Diels–Alder reaction patterns, including inverse-electron-demand, normal-electron-demand, and hetero- or all-carbon-based processes. Thus, this strategy has broad utility and power in asymmetric catalysis. We believe that the future will bring more exciting results.

We sincerely thank our collaborators, whose names are listed in the references. We are grateful for financial support from the NSFC (20972101, 21125206, and 21021001), the National Basic Research Program of China (973 Program, 2010CB833300), and Third Military Medical University.

BIOGRAPHICAL INFORMATION

Jun-Long Li was born in Sichuan, China, in 1986. He received his B.Sc. from Sichuan University in 2008. Then he joined Prof. Ying-Chun Chen's group at the same university as a Ph.D. student. His research interests are focused on asymmetric reactions catalyzed by organic amines.

Tian-Yu Liu was born in Chongqing, China, in 1977. He received his Ph.D. in medicinal chemistry from Sichuan University in 2007 under the direction of Prof. Ying-Chun Chen. Then he joined Prof. Matthew Gaunt's group at the University of Cambridge in 2008. In 2009, he moved to the Scripps Research Institute, where he worked as a postdoctoral researcher with Prof. Edward Roberts. He is currently an associate professor at the College of Pharmacy of Third Military Medical University.

Ying-Chun Chen was born in Chongqing, China, in 1972. He obtained his Ph.D. from the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, in 2001. Then he joined Prof. Dan Yang's group in the Department of Chemistry of The University of Hong Kong as a research assistant. In November 2003, he moved to West China School of Pharmacy, Sichuan University, and was appointed full professor in 2004. He is also a professor at the College of Pharmacy of Third Military Medical University. His interests are in the areas of asymmetric organocatalysis and medicinal chemistry.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: ycchenhuaxi@yahoo.com.cn.
The authors declare no competing financial interest.

REFERENCES

1 For selected reviews, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels–Alder Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Stocking, E. M.; Williams, R. M. Chemistry and Biology of Biosynthetic Diels–Alder Reactions. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115.

2 For selected reviews, see: (a) Kagan, H. B.; Riant, O. Catalytic Asymmetric Diels–Alder Reactions. *Chem. Rev.* **1992**, *92*, 1007–1019. (b) Corey, E. J. Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (c) Reymond, S.; Cossy, J. Copper-catalyzed Diels–Alder Reactions. *Chem. Rev.* **2008**, *108*, 5359–5406.

3 Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels–Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

4 Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. Hydrogen Bonding: Single Enantiomers from a Chiral-alcohol Catalyst. *Nature* **2003**, *424*, 146.

5 (a) Sustmann, R. Orbital Energy Control of Cycloaddition Reactivity. *Pure Appl. Chem.* **1974**, *40*, 569–593. (b) Houk, K. N. The Frontier Molecular Orbital Theory of Cycloaddition Reactions. *Acc. Chem. Res.* **1975**, *8*, 361–369.

6 (a) Snyder, H. R.; Hasbrouck, R. B.; Richardson, J. F. Reactions of Anils. III. A New Type of Diels–Alder Reaction. *J. Am. Chem. Soc.* **1939**, *61*, 3558–3560. (b) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. Diels–Alder Reactions between trans-1-N-Acylamino-1,3-dienes and Methyl Acrylate. A Correlation between Diene Photoelectron Ionization Potentials and Reactivity, Stereoselectivity, and Regioselectivity. *J. Am. Chem. Soc.* **1978**, *100*, 3182–3189. (c) Wu, T.-C.; Houk, K. N. Intramolecular Diels–Alder Reactions of Dienamines with Acrylates: Trends in Stereoselectivity upon Substitution. *Tetrahedron Lett.* **1985**, *26*, 2293–2296. (d) Kozmin, S. A.; Rawal, V. H. Preparation and Diels–Alder Reactivity of 1-Amino-3-siloxy-1,3-butadienes. *J. Org. Chem.* **1997**, *62*, 5252–5253.

7 (a) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. Diastereoselective Diels–Alder Reactions Using Furan Substituted with a Nonracemic Amine. *J. Org. Chem.* **1994**, *59*, 3246–3247. (b) Enders, D.; Meyer, O.; Raabe, G. Diastereo- and Enantioselective Synthesis of 4-Nitrocyclohexanones by [4 + 2] Cycloaddition of a Chiral 2-Aminobutadiene to Nitroalkenes. *Synthesis* **1992**, 1242–1244.

8 Boger, D. L.; Panek, J. S.; Meier, M. M. Diels–Alder Reaction of Heterocyclic Azadienes. 2. Catalytic Diels–Alder Reaction of in situ Generated Enamines with 1,2,4-Triazines: General Pyridine Annulation. *J. Org. Chem.* **1982**, *47*, 895–897.

9 For related reviews, see: (a) Boger, D. L. Diels–Alder Reactions of Aza Dienes. *Tetrahedron* **1983**, *39*, 2869–2939. (b) Boger, D. L. Diels–Alder Reactions of Heterocyclic Azadienes: Scope and Applications. *Chem. Rev.* **1986**, *86*, 781–793.

10 Juhl, K.; Jørgensen, K. A. The First Organocatalytic Enantioselective Inverse-electron-demand Hetero-Diels–Alder Reaction. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498–1501.

11 Samanta, S.; Krause, J.; Mandal, T.; Zhao, C.-G. Inverse-electron-demand Hetero-Diels–Alder Reaction of β,γ-Unsaturated α-Ketophosphonates Catalyzed by Prolinal Dithioacetals. *Org. Lett.* **2007**, *9*, 2745–2748.

12 (a) Chen, Y.-C. The Development of Asymmetric Primary Amine Catalysts Based on Cinchona Alkaloids. *Synlett* **2008**, 1919–1930. (b) Cui, H.-L.; Chen, Y.-C. α,α-Dicyanoalkenes: Versatile Vinylogous Nucleophiles for Organic Synthesis. *Chem. Commun.* **2009**, 4479–4486.

13 (a) Boger, D. L.; Kasper, A. M. A General Solution to Implementing the 4π Participation of 1-aza-1,3-butadienes in Diels–Alder Reactions: Inverse Electron Demand Diels–Alder Reactions of α,β-Unsaturated N-benzenesulfonyl Imines. *J. Am. Chem. Soc.* **1989**, *111*, 1517–1519. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. Inverse Electron Demand Diels–Alder Reactions of N-sulfonyl α,β-Unsaturated Imines: a General Approach to Implementation of the 4π Participation of 1-Aza-1,3-butadienes in Diels–Alder Reactions. *J. Am. Chem. Soc.* **1991**, *113*, 1713–1729.

14 Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. Diastereoselective Diels–Alder Reactions of N-Sulfonyl-1-aza-1,3-butadienes with Optically Active Enol Ethers: an Asymmetric Variant of the 1-Azadiene Diels–Alder Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 2587–2593.

15 (a) He, M.; Struble, J. R.; Bode, J. W. Highly Enantioselective Azadiene Diels–Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006**, *128*,

8418–8420. (b) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. Catalytic Asymmetric Inverse-electron-demand Diels–Alder Reaction of N-Sulfonyl-1-aza-1,3-dienes. *J. Am. Chem. Soc.* **2007**, *129*, 1480–1481.

16 (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Enantioselective Organocatalyzed α-Sulfenylation of Aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael Reaction of Aldehydes and Nitroalkenes. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

17 Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. Organocatalytic Asymmetric Inverse-electron-demand Aza-Diels–Alder Reaction of N-Sulfonyl-1-aza-1,3-butadienes and Aldehydes. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971–9974.

18 (a) Boger, D. L.; Nakahara, S. Diels–Alder Reactions of N-Sulfonyl 1-aza-1,3-butadienes: Development of a Synthetic Approach to the Streptonigrone C ring. *J. Org. Chem.* **1991**, *56*, 880–884. (b) Boger, D. L.; Cassidy, K. C.; Nakahara, S. Total Synthesis of Streptonigrone. *J. Am. Chem. Soc.* **1993**, *115*, 10733–10741.

19 Li, J.-L.; Zhou, S.-L.; Han, B.; Wu, L.; Chen, Y.-C. Aminocatalytic Asymmetric Inverse-electron-demand Aza-Diels–Alder Reaction of N-Ts-1-aza-1,3-butadienes Based on Coumarin Cores. *Chem. Commun.* **2010**, *46*, 2665–2667.

20 He, Z.-Q.; Han, B.; Li, R.; Wu, L.; Chen, Y.-C. Enantioselective Construction of Lactone[2,3-b]piperidine Skeletons via Organocatalytic Tandem Reactions. *Org. Biomol. Chem.* **2010**, *8*, 755–757.

21 Zhou, S.-L.; Li, J.-L.; Dong, L.; Chen, Y.-C. Organocatalytic Sequential Hetero-Diels–Alder and Friedel–Crafts Reaction: Constructions of Fused Heterocycles with Scaffold Diversity. *Org. Lett.* **2011**, *13*, 5874–5877.

22 Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. Catalytic, Enantioselective Bifunctional Inverse Electron Demand Hetero-Diels–Alder Reactions of Ketene Enolates and o-Benzoquinone Diimides. *J. Am. Chem. Soc.* **2006**, *128*, 13370–13371.

23 Li, J.-L.; Han, B.; Jiang, K.; Du, W.; Chen, Y.-C. Organocatalytic Enantioselective Hetero-Diels–Alder Reaction of Aldehydes and o-Benzoquinone Diimide: Synthesis of Optically Active Hydroquinoxalines. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3952–3954.

24 Jiang, X.; Fu, D.; Shi, X.; Wang, S.; Wang, R. PPh_3-catalyzed Synthesis of Dicyano-2-methylenebut-3-enoates as Efficient Dienes in Catalytic Asymmetric Inverse-electron-demand Diels–Alder Reaction. *Chem. Commun.* **2011**, *47*, 8289–8291.

25 Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F., III. Amine-catalyzed Direct Diels–Alder Reactions of α,β-Unsaturated Ketones with Nitro Olefins. *Tetrahedron Lett.* **2002**, *43*, 3817–3820.

26 (a) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. Organocatalytic Asymmetric Domino Knoevenagel/Diels–Alder Reactions: A Bioorganic Approach to the Diastereospecific and Enantioselective Construction of Highly Substituted Spiro[5,5]undecane-1,5,9-triones. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233–4237. (b) Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. In Situ Enamine Activation in Aqueous Salt Solutions: Highly Efficient Asymmetric Organocatalytic Diels–Alder Reaction of Cyclohexenones with Nitroolefins. *Angew. Chem., Int. Ed.* **2009**, *48*, 3821–3824.

27 (a) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. Enantioselective Tandem O-Nitroso Aldol/Michael Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963. (b) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. Targeting Structural and Stereochemical Complexity by Organocascade Catalysis: Construction of Spirocyclic Oxindoles Having Multiple Stereocenters. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200–7203. (c) Westermann, B.; Ayaz, M.; van Berkel, S. S. Enantiodivergent Organocascade Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 846–849.

28 For a review on dienamine chemistry, see: Ramachary, D. B.; Reddy, Y. V. Dienamine Catalysis: An Emerging Technology in Organic Synthesis. *Eur. J. Org. Chem.* **2012**, 865–887.

29 Serebryakov, E. P.; Nigmatov, A. G.; Shcherbakov, M. A.; Struchkova, M. I. The Effects of the Nature of Catalyst and of the Solvent on the Stereoselectivity in Amine-catalyzed Asymmetric Synthesis of Substituted Cyclohexa-1,3-dienes from Prenal and Monoesters of Ylidenemalonic Acids. *Russ. Chem. Bull.* **1998**, *47*, 82–90.

30 Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. Dienamine Catalysis: Organocatalytic Asymmetric γ-Amination of α,β-Unsaturated Aldehydes. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

31 Figueiredo, R. M.; Fröhlich, R.; Christmann, M. Amine-Catalyzed Cyclizations of Tethered α,β-Unsaturated Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450–1453.

32 Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. Organocatalytic Regio- and Stereoselective Inverse-electron-demand Aza-Diels–Alder Reaction of α,β-Unsaturated Aldehydes and N-Tosyl-1-aza-1,3-butadienes. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474–5477.

33 For a recent example with β,γ-regioselectivity, see: Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. Asymmetric Organocatalytic Formal [2 + 2]-Cycloadditions via Bifunctional H-Bond Directing Dienamine Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 2543–2546.

34 Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. Organocatalytic Asymmetric Inverse-electron-demand Diels–Alder Reaction of Electron-deficient Dienes and Crotonaldehyde. *Angew. Chem., Int. Ed.* **2010**, *49*, 6418–6420.

35 Dang, A.-T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. Electron-Deficient Dienes. 5. An Inverse-electron-demand Diels–Alder Approach to 2-Substituted 4-Methoxyxanthones and 3,4-Dimethoxyxanthones. *Org. Lett.* **2008**, *10*, 233–236.

36 Li, J.-L.; Zhou, S.-L.; Chen, P.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. Asymmetric Diels–Alder Reaction of β,β-Disubstituted Enals and Chromone-fused Dienes: Construction of Collections with High Molecular Complexity and Skeletal Diversity. *Chem. Sci.* **2012**, *3*, 1879–1882.

37 Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. Trienamines in Asymmetric Organocatalysis: Diels–Alder and Tandem Reactions. *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061.

38 We collaborated with Prof. Jørgensen on the mechanistic studies of this first trienamine chemistry; for more details, see ref 37.

39 Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. Exo-Selective Asymmetric Diels–Alder Reaction of 2,4-Dienals and Nitroalkenes by Trienamine Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638–8641.

40 Jiang, H.; Gschwend, B.; Albrecht, Ł.; Hansen, S. G.; Jørgensen, K. A. Asymmetric Trienamine Catalysis for the Construction of Structurally Rigid Cyclic α,α-Disubstituted Amino Acid Derivatives. *Chem.—Eur. J.* **2011**, *17*, 9032–9036.

41 (a) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. Asymmetric Catalysis of Diels–Alder Reactions with in Situ Generated Heterocyclic ortho-Quinodimethanes. *J. Am. Chem. Soc.* **2011**, *133*, 15212–15218. (b) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. Multicatalytic Asymmetric Synthesis of Complex Tetrahydrocarbazoles via a Diels–Alder/Benzoin Reaction Sequence. *Org. Lett.* **2012**, *14*, 1310–1313.

42 Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. Trienamine Catalysis with 2,4-Dienones: Development and Application in Asymmetric Diels–Alder Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 4401–4404.

43 For a highlight on trienamine chemistry, see: Arceo, E.; Melchiorre, P. Extending the Aminocatalytic HOMO-Raising Activation Strategy: Where Is the Limit? *Angew. Chem., Int. Ed.* **2012**, *51*, 5290–5292.