Asymmetric Synthesis

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Bifunctional Organocatalytic Strategy for Inverse-Electron-Demand Diels–Alder Reactions: Highly Efficient In Situ Substrate Generation and Activation to Construct Azaspirocyclic Skeletons**

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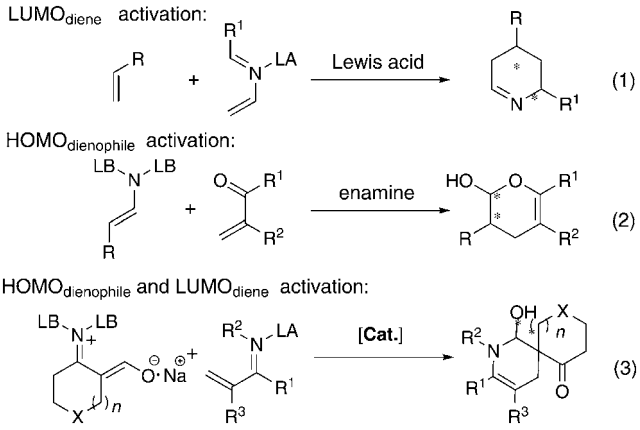
The catalytic asymmetric Diels–Alder reaction (DAR)[1] is among the most powerful protocols for the stereoselective construction of six-membered functionalized cyclic frameworks. Its versatility in the synthesis of diverse natural products provides organic chemists with a prodigious starting point to discover new reaction modes for this cycloaddition. In the wake of the emergence of the first metal complexes for the Lewis acid catalyzed asymmetric inverse-electron-demand Diels–Alder reactions (IEDDAR) through the LUMO-lowering strategy reported by the group of Kobayashi,[2] several remarkable studies have been presented involving the activation of dienes through lowering of the LUMO energy by Lewis acidic metal complexes[3] or organic molecules[4] [Eq. (1), Scheme 1]. Recently, amine organocatalysis has been attracting considerable interest since the development of the highly enantioselective organocatalytic DAR by MacMillan and co-workers.[5] Alternatively, Jørgensen and co-workers[6] reported the first organocatalytic asymmetric IEDDAR with dienophiles whose HOMO energy has been raised by an enamine activation [Eq. (2)], and considerable advances in this field have recently been achieved by the Chen group.[7] Bifunctional organocatalysis has emerged as a potentially powerful tool in catalytic asymmetric synthesis.[8] This concept aims to efficiently achieve asymmetric transformations that cannot be approached by using either a Lewis acid or base catalyst alone. To the best of our knowledge, there is no report to date of an asymmetric IEDDAR that is controlled with a single reactive catalyst through a bifunctional activation strategy; that is simultaneous activation of the HOMO of the dienophile and the LUMO of the diene [Eq. (3)]. There is a report on the use of a combination of an enamine with metal Lewis acid activation that proved to have potential for this transformation.[9] Herein, we introduce a bifunctional catalyst for an in situ substrate generation/activation strategy as a new platform for the design of organocatalytic intermolecular cycoaddition processes. In this context, we document the first highly enantioselective bifunctional catalytic IEDDAR that involves dual control of the $HOMO_{dienophiles}$ and $LUMO_{dienes}$ energies of the substrates.



Scheme 1. Different activation strategies for the IEDDAR. LA = Lewis acid, LB = Lewis base.

The spirocyclic core is a privileged structural element that is featured in a large number of naturally occurring bioactive alkaloids. Although the significant bioactivity and preparation methods of such motifs attract the interest of chemists, as reported in some elegant works including intramolecular alkylation, metal-based cyclization, intermolecular cycloaddition, rearrangements, and other reactions,[10] the enantioselective catalytic approach to access chiral spiro architectures containing all-carbon quaternary stereocenters still remains challenging. As an important skeleton in the larger spirocycle family, the spirolactam scaffold not only often shows interesting biological activities, but it can also act as an intermediate in the synthesis of more sophisticated spirocyclic frameworks (Figure 1).[11] However, it is worth noting that the enantioselective catalytic synthesis of this kind of skeleton has not yet been established. Given the demand for new catalytic asymmetric methodology for the construction of spirocyclic scaffolds, we present a highly efficient in situ generation/activation catalytic system that allows rapid construction of highly functionalized chiral spirocyclic skeletons with all-carbon quaternary stereocenters using the above-mentioned bifunctional strategy for catalytic asymmetric IEDDAR of cyclic keto/enolate salts.

We postulated that cyclic keto/enolates could serve as the perfect dienophiles because of their high reactivity as well as unique structural characteristics for the construction of spirocycles. However, enolates require harsh conditions and

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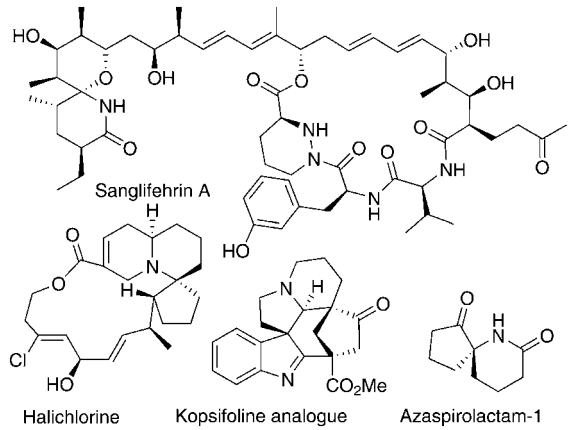
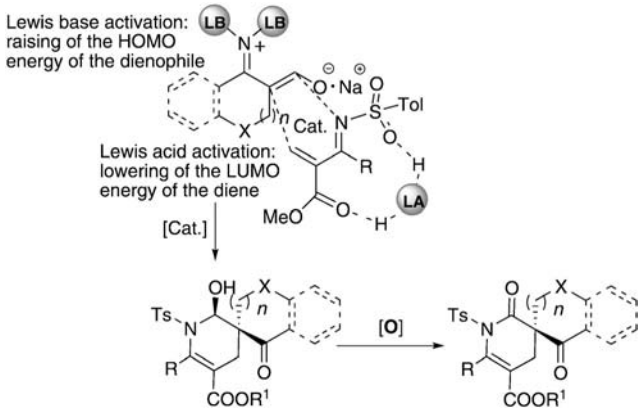


Figure 1. Natural products and bioactive compounds containing spirolactams scaffolds.

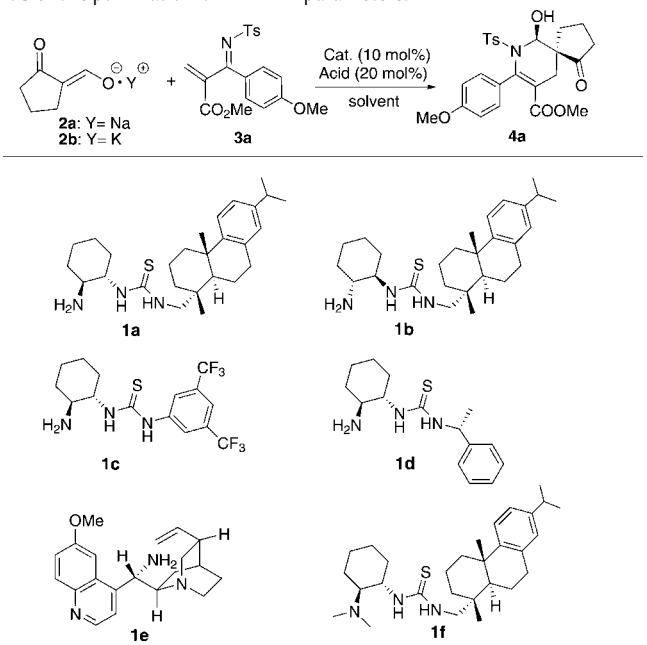
their purification and storage are rather troublesome. Therefore, in this study, we established an efficient in situ generation/activation catalysis, wherein a salt was directly used as a reactant in the asymmetric catalysis. Subsequently, an attempt was made in the asymmetric process to obtain the enolates from easily available and more stable enolate salts by employing an in situ generation/activation strategy. The generation of a ketiminium ion by the interaction between primary amine salts as iminium catalysts and ketones has been explored recently.[12] Herein, we found that the activation of cyclic keto/enolates through the formation of a ketimine cation would be more feasible. The *N*-tosyl-2-methylenebut-3-enoates, activated by lowering of the $LUMO_{dienes}$ through the Lewis acid, would be expected undergo nucleophilic attack by the cyclic keto/enolates, which are activated by raising of the $HOMO_{dienophiles}$ energy through the Lewis base, to lead to the generation of spirohemiaminals, which can then be oxidized into the spirolactams in a single transformation (Scheme 2). We recently embarked upon the development of a bifunctional strategy for organocatalytic processes based upon design features of a rosin-derived bifunctional amine/thiourea catalysts.[13] We surmised that this kind of primary amine/thiourea would be suitable for catalyzing the asymmetric IEDDAR through in situ generation/activation. In addition, this in situ enolate generation strategy using a salt opened up a promising way for the wide application of an enolate as an important nucleophile in organic synthesis.



Scheme 2. Bifunctional catalyst for the asymmetric IEDDAR.

To explore the possibility of the proposed cyclization process, a model reaction of cyclopentyl keto/enolate sodium salt (**2a**) with *N*-tosyl-2-methylenebut-3-enoate (**3a**) was performed at room temperature (Table 1). The rosin-derived bifunctional primary amine/thiourea **1a** (10 mol%) in combination with different acids (20 mol%) smoothly catalyzed the reactions to give the desired product with excellent yields and diastereoselectivity (95–99% yields, d.r. > 99:1, entries 1–3). The compound **4a** having a 75% *ee* was obtained in the presence of 20 mol% of acetic acid (entry 2). A survey of the solvents indicated that a substantial change in the solvent has a significant effect on the enantioselective outcome (entries 2 and 4–7); the biphasic solvent mixture of toluene and water is the most suitable reaction media. Notably, although **1b**–

Table 1: Optimization of IEDDAR parameters.[a]



Entry	Cat.	Acid	Solvent[b]	Yield [%][c]	*ee* [%][d]
1	**1a**	BzOH	toluene/H_2O	98	71
2	**1a**	AcOH	toluene/H_2O	99	75
3	**1a**	TFA	toluene/H_2O	95	58
4	**1a**	AcOH	CH_2Cl_2/H_2O	99	55
5	**1a**	AcOH	$CHCl_3$/H_2O	90	31
6	**1a**	AcOH	Et_2O/H_2O	93	22
7	**1a**	AcOH	THF/H_2O	89	18
8	**1b**	AcOH	toluene/H_2O	96	−55
9	**1c**	AcOH	toluene/H_2O	92	29
10	**1d**	AcOH	toluene/H_2O	83	25
11	**1e**	AcOH	toluene/H_2O	90	61
12	**1f**	AcOH	toluene/H_2O	86	3
13[e]	**1a**	AcOH	toluene/H_2O	99	83
14[f]	**1a**	AcOH	toluene/H_2O	99	90
15[g]	**1a**	AcOH	toluene/H_2O	58	80
16[f,h]	**1a**	AcOH	toluene/H_2O	99	56

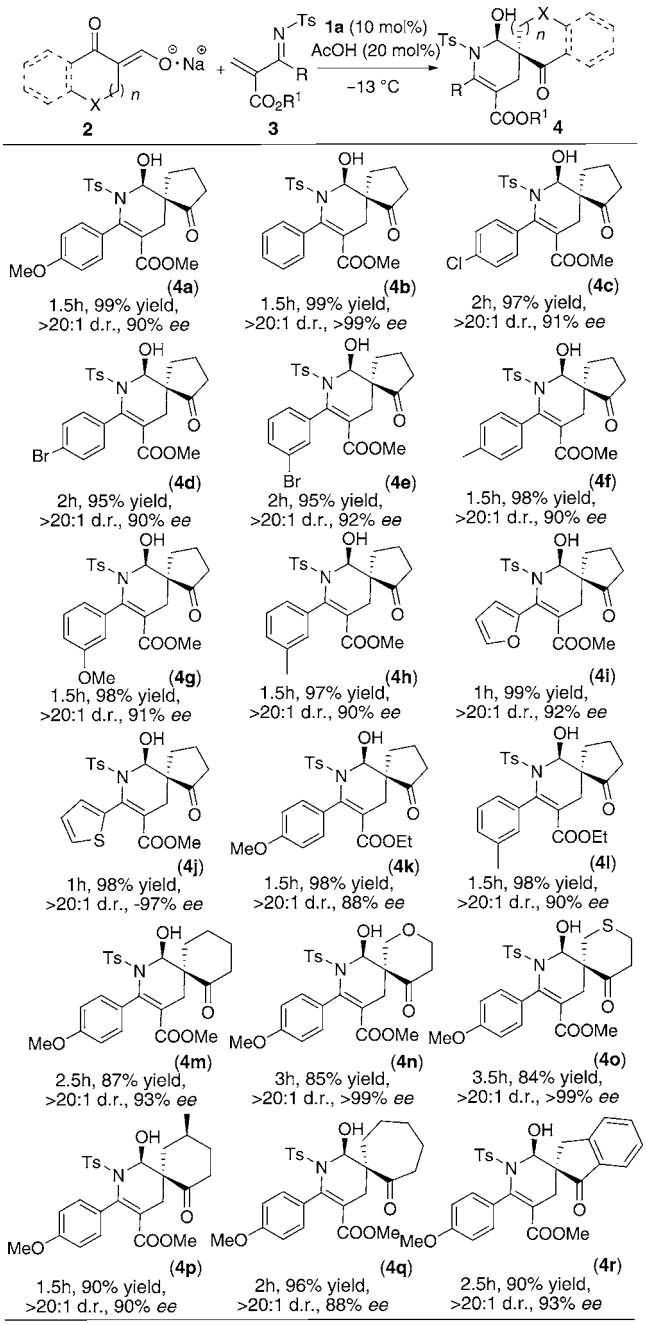
[a] The reaction was performed on 0.1 mmol scale with **2a** (2.0 equiv), **3a** (1.0 equiv), and acid (20 mol%). [b] Organic solvent/H_2O (1.0 mL, 1:1). [c] Yield of isolated product. [d] Determined by HPLC analysis on a chiral stationary phase, and products were observed with d.r. > 20:1 (^{1}H NMR spectroscopic analysis). [e] The reaction was performed at 0°C. [f] At −13°C. [g] At −40°C. [h] Using **2b**. THF = tetrahydrofuran, TFA = trifluoroacetic acid, Ts = 4-toluenesulfonyl.

e could provide excellent product yields and diastereoselectivities, poor enantioselectivities were observed in all reactions (entries 8–11). To gain a better understanding of this catalytic system, the tertiary amine/thiourea **1f** was also tested under the same reaction conditions. The result showed that **1f** afforded an almost racemic product (entry 12), and the asymmetric reaction was indeed promoted by the acetic acid salt of the bifunctional primary amine/thiourea. Gratifyingly, the more favorable outcome of 90% *ee* was observed without a decrease in yield when the reaction was performed at −13 °C (entry 14). In addition, the keto/enolate potassium salt **2b** was tested, and a 99% yield was still obtained, but with a low *ee* value of 56% (entry 16).

Having established optimal reaction conditions, the new method for the synthesis of chiral spirohemiaminals was explored with a variety of substituted *N*-tosyl-2-methylenebut-3-enoates and cyclic keto/enolate salts. As summarized in Scheme 3, various substituted *N*-tosyl-2-methylenebut-3-enoates including those bearing electron-withdrawing and electron-donating substituents at different positions on the aromatic ring, as well as heterocyclic groups could be tolerated, and gave the corresponding compounds **4a–l** in excellent yield (95–99%), diastereoselectivity (> 20:1 d.r.), and high to excellent enantioselectivity (88–> 99% *ee*). Gratifyingly, the diversely structured spirohemiaminals **4m–q** were obtained in high to excellent yield (84–96%), enantioselectivity (88–> 99% *ee*), and excellent diastereoselectivity (> 20:1 d.r.). Additionally, as expected, the catalytic system also proved to be efficient for aromatic dienophiles, again leading to **4r** with 90% yield, 93% *ee*, and a greater than 20:1 d.r. The configurations of the products were determined by X-ray crystal structure analysis of **4k** and **4j**.

On the basis of our experimental results and recent studies,[8h,14] we have proposed a possible model to explain the stereochemistry of the IEDDAR employing a bifunctional in situ generation/activation strategy (Figure 2). The *N*-tosyl-2-methylenebut-3-enoate is fixed activated (lowering of the LUMO energy) by the two thiourea hydrogen atoms through weak hydrogen bonds, while the cyclic keto/enolate salt is activated (raising of the HOMO energy) by the simultaneous formation of ketiminium cation and protonation (the Brønsted acid not only involves in the formation of ketiminium intermediates, but also promotes the protonation of enolate salt). In recent studies,[15] we also tried to investigate the role of the structural features of the rosin-derived thiourea catalysts in obtaining high enantioselectivity by carrying out reactions with catalysts bearing different configurations of the chiral scaffold moiety as well as in comparison with other thiourea catalysts. As a result of the main stereochemical control from the 1,2-diaminocyclohexane moiety and steric hindrance from the dehydroabietic amine moiety of the thiourea, high *Re* face and *endo* selectivity would be enforced to give the desired chiral product, which is consistent with the experimental results.

With the successful construction of chiral azaspirocyclic skeletons as described above, the transformation of the spirocycloaddition product to a number of valuable compounds was performed. As an illustration in Scheme 4, **4b** could be converted smoothly into the spiropyridine **5b**, in 61% yield



Scheme 3. The reaction time required for each substrate is given. The reported yields are of the isolated products. The *ee* and d.r. values were determined by HPLC analysis.

without any loss of enantioselectivity, by reduction with $Et_3SiH/BF_3{\cdot}Et_2O$ at −78 °C. Furthermore, because of the significant bioactivity of spirolactams and the versatility in organic synthesis, the transformation into this scaffold was also performed. Upon oxidation with PCC, the spirolactam **5a** resulted in 82% yield and 94% *ee*. Compound **5a** was first subjected to DIBAL reduction and subsequent oxidation using DMP to give **6a** in 68% yield in two steps. Exposure of **6a** to vinyl magnesium bromide afforded allylic alcohol **7a** as a single isomer in 55% yield (we found that **7a** exhibited the significant antiproliferative activity, see the Supporting Infor-

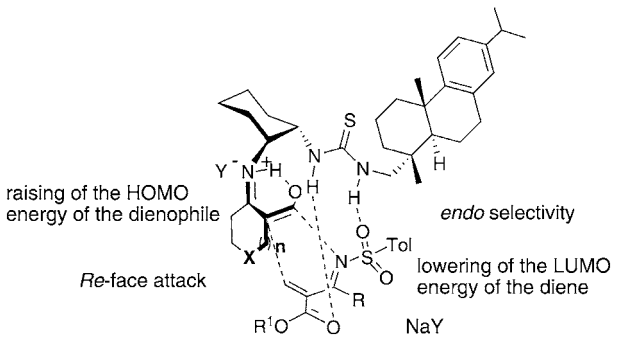
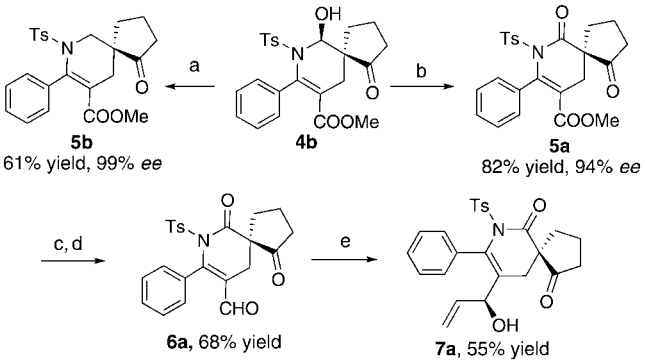


Figure 2. Proposed transition state for the reaction.



Scheme 4. Synthetic transformations of the chiral azaspirocyclic ketone **4b**. Reagents and conditions: a) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 5 h; b) PCC, CH_2Cl_2, 36 °C, 7 h; c) DIBAL, CH_2Cl_2, −78 °C, 5 h; d) DMP, $NaHCO_3$, CH_2Cl_2, RT, 2 h; e) vinylmagnesium bromide, THF, −40–−10 °C. DIBAL = diisobutylaluminum hydride, DMP = Dess–Martin periodinate, PCC = pyridinium chlorochromate.

mation). This representative example demonstrates the inherent synthetic potential of this kind of azaspirocycles.

In summary, we have disclosed a highly efficient in situ generation/activation strategy that has enabled the development of the first highly enantioselective inverse-electron-demand Diels–Alder reaction using a bifunctional organocatalyst. Furthermore, this process provides a promising method for the enantioselective construction of densely functionalized azaspirocyclic skeletons (up to 99% yield, >20:1 d.r., and >99% *ee*).

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