Organocatalysis

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Chiral Brønsted Acid Catalyzed Enantioselective Aza-Diels–Alder Reaction of Brassard's Diene with Imines**

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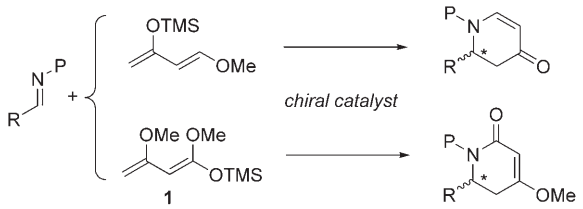
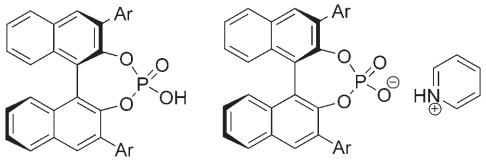
Piperidine derivatives are precursors of the biologically important piperidine alkaloids,[1] peptides, and aza sugars, and are therefore important synthetic targets. Development of novel efficient methods for the synthesis of piperidine derivatives in optically pure form is important from the standpoint of the pharmaceutical sciences as well as synthetic organic chemistry. The enantioselective aza-Diels–Alder reaction of electron-rich dienes with aldimines provides an efficient protocol for the preparation of piperidine derivatives in scalemic form.[2] Thus, the aza-Diels–Alder reaction of an imine with 1-alkoxy-3-siloxy-1,3-butadienes and its derivatives (Danishefsky's diene)[3] furnishes functionalized piperidinones. A catalytic asymmetric version of the aza-Diels–Alder reaction was investigated recently, and high enantioselectivity was attained.[4] Another potential candidate as an electron-rich diene is 1,3-dimethoxy-1-(trimethylsiloxy)butadiene **1** (Brassard's diene),[5] the reaction of which provides piperidinone derivatives (Scheme 1).[6] In contrast to Danishefsky's diene, Brassard's diene has been less extensively studied. Although diastereoselective versions of aza-Diels–Alder reactions with chiral imines that lead to optically active piperidinone derivatives have been reported by Waldmann et al.,[7] Midland and Koops,[8] and Kawecki,[9] the catalytic enantioselective reaction of Brassard's diene with imines has, to the best of our knowledge, not been reported.[10] The high reactivity and lability of Brassard's diene is associated with the paucity of its hetero-Diels–Alder reaction.



Scheme 1. The aza-Diels–Alder reaction. TMS = trimethylsilyl.

Recently, chiral Brønsted acid catalysis,[11,12] a variant of metal-free organocatalysis, has become a rapidly growing area.[13] We have already developed chiral phosphoric acid **2**,



2a: Ar= 9-anthryl **3**: Ar= 9-anthryl

derived from (*R*)-BINOL, as a chiral Brønsted acid catalyst.[14,15] One of the potential problems associated with **2** lies in its strong acidity,[16] in particular when applied to labile substrates. We have found that its pyridinium salt **3** also exhibits efficient catalytic activity as a chiral Brønsted acid catalyst but is more compatible than **2** with labile substrates such as Brassard's diene. Herein, we report the chiral Brønsted acid catalyzed aza-Diels–Alder reaction of aldimines with Brassard's diene **1** to afford piperidinone derivatives in high yields and with excellent enantioselectivities (up to 99% *ee*). To our knowledge, this is the first report of an enantioselective aza-Diels–Alder reaction of Brassard's diene with aldimines.[17]

Screening of substituents at the 3,3′-positions of phosphoric acid **2** revealed that 9-anthryl groups as in **2a**[15c] were the most effective for the aza-Diels–Alder reaction. Thus, aldimine **4a** (R = Ph), derived from benzaldehyde and 2-amino-4-methylphenol, and Brassard's diene **1** were treated with **2a** (3 mol%) in mesitylene at −40 °C for 24 h. Treatment of the reaction mixture with $PhCO_2H$ (1 equiv) with heating for 12 h afforded cycloadduct **5a** in 72% yield and with 92% *ee* (Table 1, entry 1). Note that as little as 3 mol% of the catalyst suffices for the reaction to proceed efficiently. Interestingly, use of the equivalent amount (3 mol%) of its pyridinium salt **3** improved the yield significantly with comparable enantioselectivity (Table 1, entry 2). A range of aldimines derived from aromatic and heteroaromatic aldehydes underwent the aza-Diels–Alder reaction to afford cyclization products with excellent enantioselectivities (Table 1, entries 3–14). Aliphatic aldimines, which were generated in situ, also gave corresponding cycloadducts with excellent *ee* values (Table 1, entries 15, 16). The absolute stereochemistry of **5** (R = *p*-BrC_6H_4; Table 1, entry 3) was unambiguously determined by X-ray crystallographic analysis,[18] and those of the other cycloadducts were assigned by analogy.

To demonstrate the utility of the present aza-Diels–Alder reaction, the experiment was performed on a gram scale. Thus, when 1.01 g of aldimine **4a** was treated with **3** (3 mol%), 1.40 g of the corresponding cyclization product **5a** was obtained without any loss in the enantioselectivity or yield (Scheme 2).

The methoxy group in **5a** could be transformed into other functionalities. As an example, acid hydrolysis of the methyl

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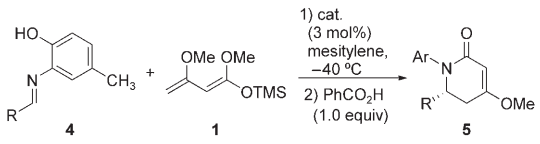
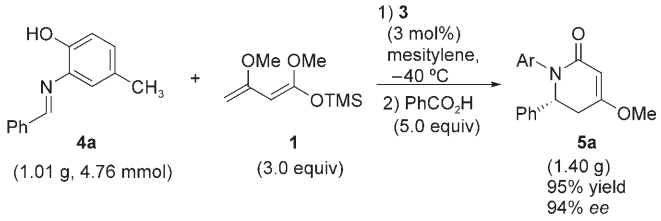
Table 1: Results of the aza-Diels–Alder reaction.[a]



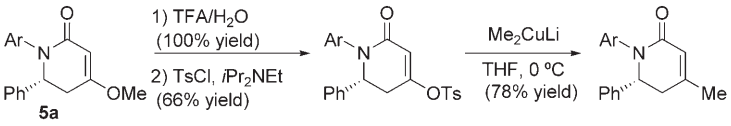
Entry	Catalyst	R	Yield [%]	*ee* [%]
1[b]	**2a**	C_6H_5	72	92
2[b]	**3**	C_6H_5	87	94
3	**3**	*p*-BrC_6H_4	86	96
4	**3**	*p*-ClC_6H_4	90	97
5[b]	**3**	*p*-FC_6H_4	76	98
6	**3**	*p*-$CH_3C_6H_4$	90	95
7	**3**	*p*-$CH_3OC_6H_4$	84	99
8[b]	**3**	*o*-BrC_6H_4	83	98
9[b]	**3**	*o*-ClC_6H_4	86	98
10	**3**	*o*-$CH_3C_6H_4$	76	96
11	**3**	1-naphthyl	79	98
12[b]	**3**	2-naphthyl	91	97
13[b,c,d]	**3**	2-furyl	63	97
14[b,c]	**3**	PhCH=CH	76	98
15	**3**	cyclohexyl	69	99
16	**3**	*i*Pr	65	93

[a] 3.0 equiv of **1** was employed. [b] 5 equiv of $PhCO_2H$ was employed. [c] 4.0 equiv of **1** was employed. [d] **1** was added in one portion.



Scheme 2. Scaled-up version of the aza-Diels–Alder reaction.

ether and a subsequent addition–elimination reaction of the tosylate with Me_2CuLi introduced a methyl group (Scheme 3).



Scheme 3. Transformation of the cycloadduct **5a**. Ar = 2-hydroxy-5-methylphenyl; TFA = trifluoroacetic acid; Ts = *p*-toluenesulfonyl.

The stability of Brassard's diene **1** toward acid **2a** and toward **3** in the presence of phosphoric acid was studied in wet [D_8]toluene at room temperature. The amount of **1** was monitored by ^{1}H NMR specroscopy.[19] In the presence of **2a** only 12% of Brassard's diene was detected after 1 h, whereas in the presence of **3** 75% of the starting amount of diene was measured. This result clearly shows that the weaker acidity of **3** is responsible for the increased yields of the cycloadduct **5**, as compared to those with **2a**.

As the presence of the hydroxy moiety on the *N*-aryl group is essential for attaining high enantioselectivity,[20] we surmised that the present aza-Diels–Alder reaction proceeds via a nine-membered cyclic transition state, wherein the phosphoryl oxygen atom forms a hydrogen bond with the hydrogen atom of the imine OH moiety, with the nucleophile attacking the *Re* face of the aldimine preferentially (Figure 1).[21,22]

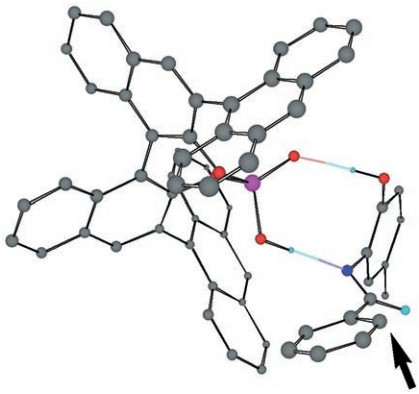


Figure 1. Chem3D representation of a minimized structure of the complex derived from **2a** and **4a**. Most of the hydrogen atoms are omitted for clarity. Hydrogen bonds are shown. P pink, O red, N blue, C gray, H turqoise. The arrow indicates *Re* facial attack.

In summary, we have developed the aza-Diels–Alder reaction of Brassard's diene with imines, catalyzed by a chiral Brønsted acid derived from (*R*)-BINOL, to give dihydropyridone derivatives with excellent enantioselectivities. The application of the present chiral Brønsted acid catalysis system to other asymmetric reactions is underway.

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[18] CCDC-280243 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] See Supporting Information for details.

[20] An aldimine derived from *p*-methoxyaniline exhibited lower enantioselectivity.

[21] The nine-membered cyclic structure was observed as one of the energy minima of the complex derived from **2a** and **4a** by quantum chemical calculations (PM3, Spartan'02, Wavefunction, Inc.).

[22] We suppose pyridine would not participate in the transition state but may stabilize Brassard's diene in the reaction.

