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# Catalytic Enantioselective Aza-Diels-Alder Reactions of Unactivated Acyclic 1,3-Dienes with Aryl-, Alkenyl-, and Alkyl-Substituted Imines†

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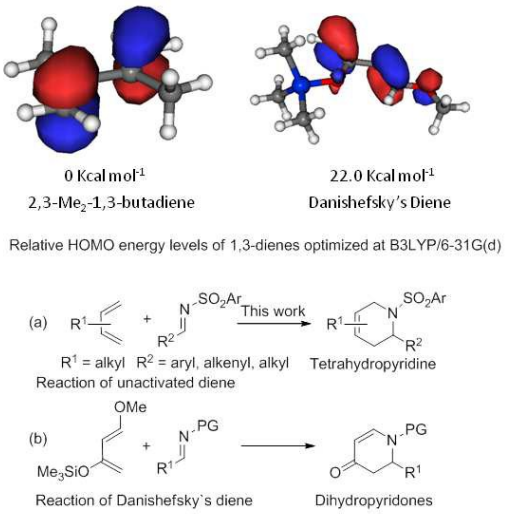
**Catalytic enantioselective aza-Diels-Alder reaction of unactivated acyclic dienes with aryl-, alkenyl-, and alkyl-substituted imines is described. With 5-10 mol % loadings of new Brønsted acid catalyst, the aza-Diels-Alder reaction of unactivated acyclic dienes proceeded to give the corresponding aza-Diels-Alder adducts in high yields (up to 98%) with excellent enantioselectivity (up to 98% ee). Preliminary DFT calculations suggest that the reaction proceeds through a chiral ion pair intermediate.**

The synthesis of chiral tetrahydropyridines and tetrahydropyridine-derived piperidines has been in the focus of the research for new pharmaceuticals, synthetic building blocks, and natural product synthesis.[1] The catalytic asymmetric aza-Diels-Alder reaction (ADA reaction) is the most powerful and convergent strategies for the enantioselective synthesis of tetrahydropyridine derivatives.[2] The ADA reactions are classified into two types: (a) the normal-electron demand ADA reaction of 1,3-butadienes with imine dienophiles, and (b) inverse-electron demand ADA reaction of aza-1,3-butadienes with dienophiles (Scheme 1a and 1b).[2e] In contrast to the recent great progress in the enantioselective inverse-electron demand ADA reaction catalyzed by chiral Lewis acids and organocatalysts,[3] there remains a critical problem with the catalytic asymmetric normal-electron demand ADA reaction. Thus, the highly enantioselective normal-electron demand ADA reactions that have been reported so far are mostly limited to the reaction of electron-rich dienes such as Brassard's diene and Danishefsky-type dienes activated by electron-donating substituents, significantly limiting the scope of the reaction.[2,4] Although the catalytic asymmetric normal-electron demand ADA reaction of cyclic dienes and unactivated acyclic dienes with strongly electron-deficient dienophiles such as 2-arylindol-3-ones and *N*-tosyl-$\alpha$-iminoesters have been reported,[5] the extension to more general ADA reaction of unactivated acyclic dienes with aryl-, alkenyl- and alkyl-substituted imine dienophiles seems to be difficult.[2e] The low reactivity of unactivated acyclic dienes such as 1,3-dimethylbutadiene in catalytic asymmetric ADA reaction is attributable to the lower HOMO energy level than that of activated electron-rich dienes such as Danishefsky's diene (Scheme 1).[6] The low HOMO energy level of the unactivated acyclic dienes leads to a large energy gap between the HOMO of dienes and the LUMO of imine dienophiles.

Herein, we describe an enantioselective normal-electron demand ADA reaction of unactivated acyclic dienes with aryl-, alkenyl- and alkyl-substituted imines catalyzed by chiral Brønsted acids to furnish tetrahydropyridines in good yields with high enantioselectivities (Scheme 1a), whereas the reaction of Danishefsky-type dienes with imine dienophiles gives dihydropyridones as the products (Scheme 1b).[4]




**Scheme 1**. Normal-electron demand aza-Diels-Alder reactions

With the purpose of evaluating the catalytic activity of a series of (*R*)-BINOL-derived *N*-triflylphosphoramides and (*R*)-BINOL-derived phosphoric acids,[7] the catalytic asymmetric ADA reaction of 2,3-dimethyl-1,3-butadiene **1a** with *N*-tosyl

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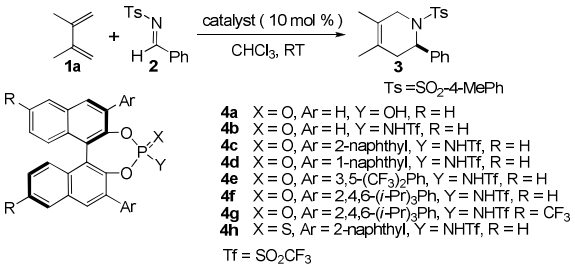
phenylimine **2** was examined at 10 mol % loading of Brønsted acid catalysts at room temperature. As shown in Table 1, (*R*)-BINOL-derived phophoric acid **4a** failed to catalyze the reaction, giving the corresponding Diels-Alder adduct (*R*)-**3** in very low yield (9%) with moderate enantiomeric excess (*ee*) (47% ee) (entry 1). The absolute configuration of the product **3** was assigned by analogy with compound **3ai** (Table 2, entry 13).[8]

**Table1.** Catalytic aza-Diels-Alder Reaction between **1a** and **2**.[a,b]




| Entry | Catalyst | Reaction time (h) | Yield [%][c] | Ee [%][d] |
|---|---|---|---|---|
| 1 | **4a** | 48 | 9 | 47 |
| 2 | **4b** | 16 | 89 | 9 |
| 3 | **4c** | 34 | 99 | 17 |
| 4 | **4d** | 48 | 75 | 39 |
| 5[e] | **4d** | 48 | 63 | 28 |
| 6 | **4e** | 10 | 75 | 19 |
| 7 | **4f** | 48 | 67 | 87 |
| 8[e] | **4f** | 96 | 27 | 56 |
| 9 | **4g** | 24 | 78 | 73 |
| 10[f] | **4g** | 24 | 75 | 85 |
| 11 | **4h** | 12 | 0 | - |

[a]Absolute configuration of **3** was assigned by analogy with compound **3ai** (Table 2, entry 13). [b]Reaction of 0.75 mmol of butadiene **1a** and 0.25 mmol of *N*-tosylphenylimine **2** with 10 mol % loading of catalyst **4** was carried out in $CHCl_3$ at room temperature unless otherwise noted. [c]Isolated yield. [d]Obtained by chiral HPLC analysis. [e]Reaction was conducted in the presence of 4 Å MS (50 mg). [f]The reaction was conducted with 5 mol % loading of **4g**

The low catalytic activity of **4a** can be ascribed to the weak acidity of **4a** (p*K*a = 12-14 in MeCN),[9] indicating the role of **4a** as a chiral Brønsted acid reagent in this reaction.[10]

We have found that stronger Brønsted acids, (*R*)-BINOL-derived *N*-triflylphosphoramide catalysts **4b-4g** (p*K*a = 6-7 in MeCN),[9] are capable of promoting the asymmetric ADA reaction between **1a** and **2** to afford aza-Diels-Alder adduct (*R*)-**3** in moderate-to-high yields (entries 2-10). Solvent screening indicated chloroform to be the solvent of choice. Thus, with a 10 mol % of **4b,** (*R*)-**3** was obtained in high yield (89%), but the *ee* was very low (9% ee) (entry 2). We explored the effect of substutuents at the 3,3'-positions and 6,6'-positions of BINOL moieties on the reaction. The use of catalyst **4c**[11a] bearing 2-naphthyl substituents at the 3,3'-positions afforded (*R*)-**3** in quantitative yield (99%) with 17% ee (entry 3). Catalyst **4d**[11a] having sterically demanding 1-naphthyl substituents at the 3,3'-positions improved the *ee* (39% ee), whereas the yield dropped considerably (75%). (entry 4). Since the addition of molecular sieve to reaction mixture often provides a better stereoselectivity of the organocatalyzed asymmetric reaction, the **4d**-catalyzed reaction was carried out with MS 4Å (50 mg), but the *ee* considerably decreased (entry 5). Introduction of electron-withdrawing substituents to the 3,3'-position of BINOL moiety resulted in a increase in reaction rate. For example, 3,3'-[3,5-$(CF_3)_2C_6H_3]_2$BINOL-derived *N*-triflylphosphoramide **4e**[11a] exhibited higher catalytic activity to accomplish the reaction within 10 h, giving (*R*)-**3** in 75% yield, while the enantioselectivity was low (19% ee) (entry 6). The reaction catalyzed by **4f**,[11b] which bears bulky 2,4,6-tri(isopropyl)phenyl substituents at the 3,3'-position of the BINOL moiety, gave (*R*)-**3** with the highest *ee* (87% ee) in moderate yield (67%) (entry 7). Next, we have synthesized catalyst **4g** by introducing strongly electron-withdrawing $CF_3$ groups to the 6,6'-positions of catalyst **4f**. A significant improvement of catalytic performance was observed by the employment of **4g** in the reaction. Even at 5 mol % loading of **4g**, the ADA reaction between **1a** and **2** smoothly took place to complete the reaction within 24 h, affording adduct (*R*)-**3** in 75% yield with good enantioselectivity (85% ee) (entry 10). BINOL-derived *N*-triflylthiophosphoramide **4h**,[11c] which have stronger acidity than *N*-triflylphosphoramides,[9] failed to catalyze the reaction between **1a** and **2**, because of the $H^+$-promoted polymerization of diene **1a** (entry 11).

Further investigation revealed that the *N*-protecting groups of imines profoundly influence the enantioselectivity and the yields of the **4g**-catalyzed ADA reaction. By replacing *N*-tosyl group of phenylimine **2** with *N*-$SO_2$-2-naphthyl group, the enantioselectivity and the yield of the aza-Diels-Alder adduct considerably increased. We were pleased to find that 5 mol % loading of catalyst **4g** effectively promoted the reaction of *N*-$SO_2$-2-naphthyl phenylimine **2a** and 1,3-dimethylbutadiene **1a**, furnishing the corresponding adduct **3aa** in high yield (87%) with high enantioselectivity (93% ee) at room temperature (Table 2, entry 1). As a *N*-protecting group, *N*-$SO_2$-1-naphthyl was ineffective, making the reaction very sluggish. Moreover, phenylimines having 4-MeOPh, $PhCH_2$, Cbz, and BOC as *N*-protecting groups failed to undergo the **4g**-catalyzed reaction with **1a**.

We then turned our attention to the substrate scope of the **4g**-catalyzed ADA reaction in chloroform at room temperature. Table 2 shows that 5-10 mol % loadings of catalyst **4g** allowed the complete conversion of aryl- and alkenyl-substituted imines in the reaction with unactivated acyclic dienes (3 eq.), giving the corresponding adducts in good yields with very high *ee* (entries 2-13). A series of aromatic imines having aromatic rings substituted with Me, MeO, and Cl smoothly reacted with 1,3-dimethylbutadiene **1a** with 5 mol % of **4g**, affording the corresponding adducts **3** in good yields (70-81%) with high enantiomeric excess (85-96% ee) (entries 2-6). Furthermore, sterically demanding 1-naphthylimine **2g** effectively underwent the **4g**-catalyzed reaction with **1a**, furnishing **3ag** in 71% yield with 98% ee (entry 7). It should be noted that the reaction of 1,3-dimethylbutadiene **1a** or isoprene **1b** with (*E*)-*β*-phenylethenyl-

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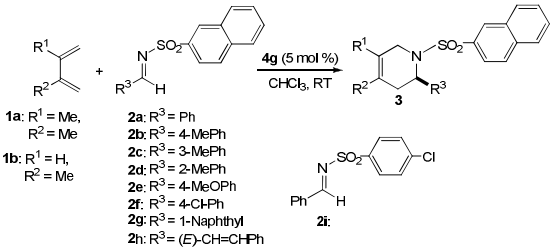
substituted imine **2h** took place selectively at the C=N bond of **2h** to afford the corresponding aza-Diels-Alder adducts **3ah** and **3bh** in good yields (92% and 98%, respectively) with very high enantioselectivities (96% ee and 97% ee, respectively) with no trace of the Diels-Alder adducts (entries 8 and 12). The ADA reactions of less reactive isoprene **1b** with arylimines **2** needed 10 mol % loading of **4g** in addition to longer reaction time for the reaction completion (140-300 h) (entries 9-12). However, the reactions exhibited the very high level of enantioselectivities (83-97% ee), affording the corresponding adducts **3ba**, **3bb**, and **3bh** in moderate-to-high yields (58-98%). Next, we examined the catalytic enantioselective ADA reaction of unactivated diene **1a** with in situ formed aliphatic imines.

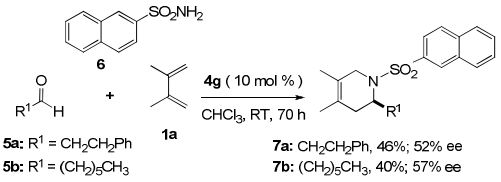
Aliphatic imines have been often problematic dienophiles even in the asymmetric ADA reaction with reactive Danishefsky's diene, since aliphatic imines are enolizable and prone to decomposition.[2e]

**Table 2.** Aza-Diels-Alder reaction catalyzed by **4g**.[a,b]




| Entry[b] | Diene | Imine | *t* (h) | Product | Yield [%][c] | *Ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 48 | **3aa** | 87 | 93 |
| 2 | **1a** | **2b** | 62 | **3ab** | 70 | 89 |
| 3 | **1a** | **2c** | 62 | **3ac** | 81 | 85 |
| 4 | **1a** | **2d** | 96 | **3ad** | 76 | 96 |
| 5 | **1a** | **2e** | 62 | **3ae** | 74 | 87 |
| 6 | **1a** | **2f** | 72 | **3af** | 71 | 94 |
| 7 | **1a** | **2g** | 91 | **3ag** | 71 | 98 |
| 8 | **1a** | **2h** | 43 | **3ah** | 92 | 96 |
| 9[e] | **1b** | **2a** | 300 | **3ba** | 58 | 94 |
| 10[e][f] | **1b** | **2a** | 140 | **3ba** | 68 | 83 |
| 11[e] | **1b** | **2b** | 300 | **3bb** | 50 | 95 |
| 12[e] | **1b** | **2h** | 120 | **3bh** | 98 | 97 |
| 13 | **1a** | **2i** | 38 | **3ai**[g] | 64 | 89 |

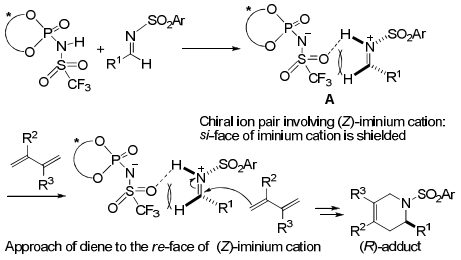
[a]Absolute configuration of product **3** was assigned by analogy with compound **3ai** (entry 13). [b]Reaction of 0.75 mmol of butadienes **1** and 0.25 mmol of imines **2** was conducted with 5 mol % loading of **4g** at room temperature unless otherwise noted. [c]Isolated yield. [d]Obtained by chiral HPLC analysis. [e]Reaction was conducted with 10 mol % of **4g**. [f]Reaction was conducted at 50 °C. [g]Absolute configuration of compound **3ai** was unequivocally determined by X-ray crystallographic analysis.




**Scheme 2.** Three component aza-Diels-Alder reaction.

Thus, the three-component ADA reaction of aliphatic aldehydes **5**, 2-naphthalenesulfonamide **6**, and diene **1a** was carried out with 10 mol % loading of catalyst **4g** in chloroform, furnishing the aza-Diels-Alder adducts **7** (Scheme 2).The ADA reaction of 2-phenylethyl-substituted imine derived from **6** with 3-phenylpropionaldehyde **5a** gave **7a** in 46% yield with 52% ee. Under the same reaction conditions, the ADA reaction of hexyl-substituted imine derived from heptanal **5b** and **6** afforded **7b** in 40% yield with 57% ee. Although the yields and enantioselectivities of the reactions remain moderate, the present method is potentially promising as a highly stereoselective route to chiral alkyl-substituted tetrahydropyridines and piperidines, which are ubiquitous structural feature of alkaloid natural products and drug candidates.[1]

To shed light on the mechanism accounting for the observed enantioselectivity of the **4g**-catalyzed ADA reaction, DFT calculations of the substrates and the catalyst-substrate adduct were carried out. The mechanism of the activation of imines by Brønsted acid catalysts has not been fully clarified. However, in view of the strong acidities of *N*-triflylphosphoramids,[9] it is reasonable to assume that **4g**-catalyzed ADA reaction proceeds via complete protonation of imine dienophile, which affordes ion pair **A** consisting of chiral amide anion and (*Z*)-iminium cation (Scheme 3).[12] The $^{19}F$ NMR spectra of the mixture of **4f** and phenylimine **2a** (**4f**/**2a** = 1/10, $CDCl_3$) indicated that the $\delta(^{19}F)$ of $CF_3$ group of **4f** is shifted to -80.5 ppm from -78.3 ppm upon the addition of **2a**, suggesting a variation of the local charge around $CF_3$ group.




**Scheme 3.** Mechanism accounting for enantioselectivity.

Approach of diene to the *re*-face of iminium cation takes place to afford (*R*)-aza-Diels-Alder adduct. The *si*-face of the iminium cation is considered to be shielded by the amide anion. (*Z*)-Iminium cation is likely bound to the chiral amide anion by a hydrogen bond

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to oxygen atom of $SO_2$ moiety of the amide anion (charges of two oxygen atoms: -0.53 for O---H and -0.65; Mulliken charges calculated at B3LYP/6-31G(d) level). Although nitrogen atom of the amide anion (-0.67) and oxygen atom of O=P moiety (-0.55) bear large negative charges, hydrogen bond formation of iminium cation with amide nitrogen as well as oxygen of O=P moiety seems to be difficult due to steric repulsion (Figure 1). It is probable that the iminium cation involved in ion pair **A** has (*Z*)-geometry, because linear (*E*)-iminium cation is too bulky in sterically congested environment of the amide anion (Figure 1). With these assumptions in mind, we optimized the simplified structure of chiral ion pair **A** at B3LYP/6-31G(d) level. The results of the theoretical calculations are in fair agreement with the speculated reaction mechanism. The optimization of simplified structure of **A** discloses that a hydrogen bond between the iminium cation and oxygen atom of $SO_2$ moiety of amide anion is formed so as to avoid the steric repulsion between the *i*-Pr group on BINOL and *N*-tosyl group of the (*Z*)-iminium cation. H-Bond length (1.56 Å) as well as the N-H-O angle (172°) indicate the formation of a fairly strong H-bond,[13] suggesting that the ion pair **A** is effectively stabilized by the H-bonding. The *i*-Pr substituent on the BINOL shields the *si*-face of the iminium cation. The addition of diene to the iminium cation takes places at the exposed *re*-face of the iminium cation, predicting the sense of asymmetric induction.

In conclusion, in the presence of new Brønsted acid catalyst, unactivated acyclic dienes react with aryl- and alkeny-substituted imines to give the ADA-adducts in good yields with high enantioselectivities.[14] However, the reaction of alkyl-substituted imines remained moderate *ee* and moderate yields.

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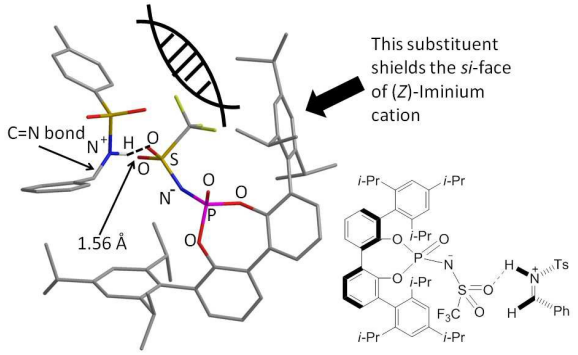


**Figure 1.** Simplified structure of chiral ion pair **A** optimized at B3LYP/6-31G(d) level. Hydrogen atoms without polar one are omitted for clarity.

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14 Under the same conditions, cyclopentadiene failed to undergo the ADA reaction with phenylimine because of the polymerization of cyclopentadiene. Cyclohexadines reacted with phenylimine, giving the corresponding adducts (86%, *endo*/*exo* = 50/50. 43% ee (*endo*), 12% ee (*exo*).