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Published on Web 01/19/2007

# Catalytic Asymmetric Inverse-Electron-Demand Diels−Alder Reaction of *N*-Sulfonyl-1-Aza-1,3-Dienes

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The aza Diels−Alder reaction (ADAR) is among the most powerful and convergent strategies for the stereoselective construction of piperidine derivatives.[1] Although in recent years very important progress has been achieved in the catalytic asymmetric ADAR of dienes with imines,[2] the complementary alternative involving the asymmetric cylcloaddition between azadienes and alkenes has been hardly studied. Ghosez et al.[3] described the $Cu(OTf)_2$/BOX-catalyzed ADAR of electron-rich 2-azadienes with *N*-acyl oxazolidinones, and Bode et al.[4] have very recently reported highly asymmetric ADAR of aldimine-derived *N*-sulfonyl-1-azadienes with $\beta$-activated enals catalyzed by chiral *N*-heterocyclic carbenes. Surprisingly, the development of chiral Lewis acid catalysts for the ADAR of 1-azadienes[5] with electron-rich olefins remains undocumented, likely owing to the low reactivity of 1-azadienes (even lower than that of 2-azadienes) and the high propensity of both azadienes and electron-rich dienophiles to decompose in the presence of Lewis acids.[5d,6]

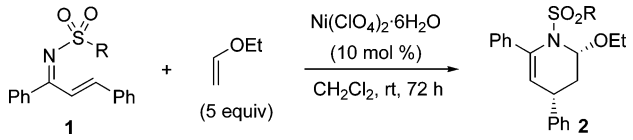
*N*-sulfonyl-1-aza-1,3-dienes were found by Boger et al. to participate as a $4\pi$ component in thermal ADAR with electron-rich dienophiles under high pressure or high temperature, exhibiting very high endo-selectivity.[6] This low reactivity has been greatly enhanced with azadienes bearing an electron-withdrawing ester group, paving the way for the development of the first asymmetric variant of this reaction using vinyl ethers bearing chiral auxiliaries.[5d] We[7] and others[8] have recently demonstrated that the use of *N*-(heteroaryl)sulfonyl groups can dramatically affect the reactivity of *N*-sulfonyl imines, allowing reactions that are not feasible with the traditional *N*-tosyl imines. In this context we describe herein a Ni-catalyzed highly enantioselective ADAR of *N*-sulfonyl 1-azadienes with vinyl ethers under mild reaction conditions. The success of this reaction relies on the use of the Kanemasa's chiral ligand[9] DBFOX−Ph and the choice of the *N*-(8-quinolinesulfonyl) group at the iminic nitrogen.

The *N*-tosylimine of chalcone (**1a**) was recovered unaltered after treatment with ethyl vinyl ether (5 equiv) in the presence of a variety of Lewis acids, such as $Cu(OTf)_2$, $Ni(ClO_4)_2 \cdot 6H_2O$, $Mg(ClO_4)_2 \cdot 6H_2O$, or $Zn(ClO_4)_2 \cdot 6H_2O$ in $CH_2Cl_2$ at room temperature (Table 1, entry 1). In the hope that the reluctance of *N*-sulfonyl $\alpha,\beta$-unsaturated ketimines to undergo Lewis acid-catalyzed ADAR could be overcome by combining the high electrophilic character of the sulfonyl group with the use of an appropriate metal-coordinating functionality, substrates **1b**−**e**, of varied electronic and coordinating nature, were evaluated in the model reaction using $Ni(ClO_4)_2 \cdot 6H_2O$ as catalyst.[10] Interestingly, while azadienes **1b** and **1c** led to the recovery of the starting material after 5 days (entries 2 and 3), the *N*-(2-pyridyl)sulfonyl and *N*-(8-quinolyl)sulfonyl derivatives **1d**[7a] and **1e**, respectively, provided the corresponding cycloadduct (**2d** and **2e**, respectively) in good yield with moderate endo-selectivity (entries 4 and 5).

Encouraged by these results, we next turned our attention to asymmetric catalysis. Unfortunately, the reaction of **1d** and **1e** in the presence of Binap, BOX, and PyBOX chiral ligands led to very low enantioselectivities (typically 0−20% ee). A maximum of 66% ee was achieved in the case of **2d** using the Bn−BOX ligand, whereas **2e** was obtained racemic in all cases. To generate a more efficient face shielding around nickel, the $Ni^{II}$ aqua complex[11,12] of the trans-chelating DBFOX−Ph ligand was tested (Table 2). Fortunately, this ligand proved to be highly efficient for the *N*-(8-quinolyl)sulfonyl imine **1e**, leading to the cycloaddition product **2e** in good yield, excellent endo-selectivity (endo/exo = >30:1) and high enantiocontrol (88% ee; entry 2). In contrast, the 2-pyridylsulfonyl azadiene **1d** provided much lower asymmetric induction under identical conditions (42% ee, entry 1). Good results were also obtained in the reaction of **1e** with propyl vinyl ether (91% ee, entry 3) and cyclohexyl vinyl ether (88% ee, entry 4) as dienophiles, while the more sterically demanding *tert*-butyl vinyl ether led to poorer results (entry 5). Cyclic dienophiles such as dihydrofuran did also participate in the ADAR with **1e** to afford the endo-adduct in 83% yield, albeit moderate asymmetric induction (58% ee at 0 °C).[13]

To evaluate the scope of this cycloaddition protocol with regard to the 1-azadiene counterpart, ketimines **6e**−**16e** were surveyed under the optimal experimental conditions (Table 3). Good yields (61−75%) and high levels of endo-selectivity and enantioselectivity

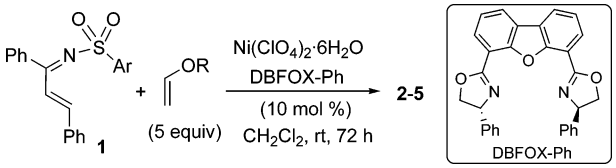
***Table 1.*** Effect of the Sulfonyl Group in the Ni-Catalyzed ADAR




| entry | R | azadiene | endo/exo[a] | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | *p*-Tol | **1a** | | | *c* |
| 2 | $NMe_2$ | **1b** | | | *c* |
| 3 | 2-thienyl | **1c** | | | *c* |
| 4 | 2-pyridyl | **1d** | 84:16 | **2d** | 73 |
| 5 | 8-quinolyl | **1e** | 70:30 | **2e** | 62 |

[a] By HPLC. [b] Of isolated endo adduct. [c] Starting material recovered.

***Table 2.*** Ni-Catalyzed Asymmetric ADAR with DBFOX−Ph Ligand



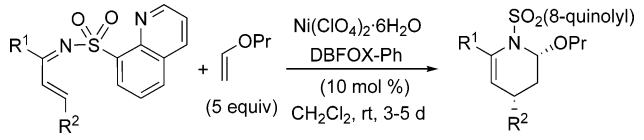

| entry | azadiene | R | endo/exo[a] | product | yield (%)[b] | ee (%)[a,b] |
|---|---|---|---|---|---|---|
| 1 | **1d** | Et | 98:2 | **2d** | 80 | 42 |
| 2 | **1e** | Et | 97:3 | **2e** | 73 | 88 |
| 3 | **1e** | *n*-Pr | 98:2 | **3e** | 66 | 91 |
| 4 | **1e** | Cy | 98:2 | **4e** | 70 | 88 |
| 5 | **1e** | *t*-Bu | 80:20 | **5e** | 35 | 68 |

[a] Determined by HPLC. [b] Of the endo adduct after chromatograpy.



10.1021/ja0658766 CCC: $37.00 

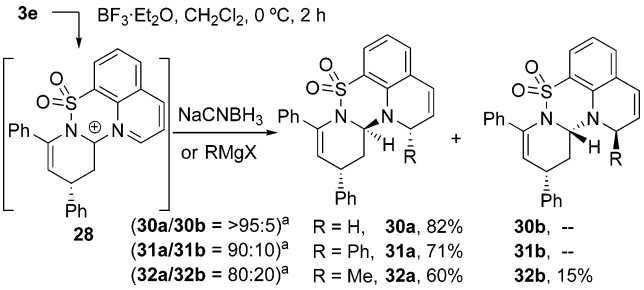
***Table 3.*** Structural Variations at the 1-Azadiene




| entry | $R^1$ | $R^2$ | imine | endo/exo[a] | product | yield (%)[b] | ee (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | Ph | **1e** | 98:2 | **3e** | 66 | 91 |
| 2 | Ph | *p*-$FC_6H_4$ | **6e** | 98:2 | **17e** | 75 | 92 |
| 3 | Ph | 2-Naph | **7e** | 97:3 | **18e** | 69 | 90 |
| 4 | Ph | *p*-$MeOC_6H_4$ | **8e** | 98:2 | **19e** | 65 | 80 |
| 5 | Ph | 2-Furyl | **9e** | 97:3 | **20e** | 52 | 77 |
| 6 | Ph | *t*-Bu | **10e** | 98:2 | **21e** | 61 | 84 |
| 7 | *p*-$ClC_6H_4$ | Ph | **11e** | 97:3 | **22e** | 73 | 90 |
| 8 | *p*-$CF_3C_6H_4$ | Ph | **12e** | 97:3 | **23e** | 69 | 91 |
| 9 | 2-Naph | Ph | **13e** | 98:2 | **24e** | 67 | 6 |
| 10 | *p*-$ClC_6H_4$ | CH═CH−Ph | **14e** | 98:2 | **25e** | 63 | 92 |
| 11 | *p*-$CNC_6H_4$ | CH═CH−Ph | **15e** | 98:2 | **26e** | 70 | 92 |
| 12 | CH═CHPh | Ph | **16e** | 90:10 | **27e** | 68 | 20 |

[a] Determined by HPLC. [b] Of the endo adduct after chromatography.

***Scheme 1.*** Stereoselective Transformations of the Cycloadducts




[a] From the crude $^1H$ NMR spectra.

(77−92% ee) were achieved in most cases. Aryl substituents of varied electronic and steric nature at the *β*-position ($R^2$) are well tolerated (entries 1−5), although electron-rich groups lead to a slight decrease in enantioselectivity (entries 4 and 5). Even the substrate **10e**, with a *tert*-butyl group as $R^2$ proved to be suitable (entry 6, 84% ee). In contrast, substitution compatibility at the iminic carbon proved to be more limited. While *p*-substituted aryl groups were compatible, a dramatic drop in the enantioselectivity was observed with the more sterically demanding 2-naphthyl group (6% ee, entry 9). Particular attention is given to the results obtained in the reaction of azatrienes **14e** and **15e** (entries 10 and 11), affording with complete chemocontrol the corresponding 4-alkenyl-substituted piperidines **25e** and **26e** in 92% ee in both cases. In contrast, the cycloaddition of the *N*-sulfonyl imine of dba (**16e**) took place with low enantiocontrol (entry 12), highlighting again the sensitivity of this protocol to substitution at the iminic carbon.

Some interesting results have been obtained in the Lewis acid-promoted nucleophilic displacement of the alkoxy group, which is known to proceed with inversion of configuration[5d] (Scheme 1). Transformation of **3e** into the 2-hydroxy derivative **29**[13] was readily performed in 88% yield with complete stereoselectivity by treatment with $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ and further hydrolysis of the resulting intermediate quinolinium salt **28**. Alternatively, trapping of intermediate **28** with hard nucleophiles such as hydride ($NaCNBH_3$) or Grignard reagents resulted, unexpectedly, in the selective attack to the α-position of the bicyclic quinoline ring system, affording the tetracyclic compounds **30**−**32** in good yields. High stereoselectivities were obtained in the cases in which two new stereogenic centers are generated (products **31** and **32**), the major isomers **31a** and **32a** being isolated pure in 71% and 60% yield, respectively. The stereochemistry of the diastereomers **32a** and **32b** was established by NMR experiments, and unequivocally confirmed by X-ray crystallographic analysis of enantiopure **32b**,[13] otherwise allowing the assignment of the absolute configuration of the ADAR endo cycloadducts. It is worthy of mention that products **30**−**32** can be considered as chiral nonracemic [1,2,4]benzothiadiazine-5,5-dioxide derivatives, which have proven to be potential drugs for memory and learning disorders and neurodegenerative disease.[14]

In summary, the combination of the (8-quinolyl)sulfonyl moiety at the iminic nitrogen and $Ni^{II}$-DBFOX as catalyst has led to the development of an efficient chiral Lewis acid-mediated inverse-electron-demand Diels−Alder reaction of 1-azadienes, providing highly functionalized piperidine derivatives in good yields with excellent endo-selectivity and enantioselectivities typically in the range of 77−92% ee. Initial experiments that highlight the synthetic potential of these cycloadducts have also been presented.

**Acknowledgment.** Financial support by the Ministerio de Educación y Ciencia (MEC, BQU2003-0508) and the UAM/Consejería de Educación de la Comunidad Autónoma de Madrid (08/PPQ/001) is gratefully acknowledged. J.E. thanks the MEC for a predoctoral fellowship. We also thank Jordi Benet-Buchholz (ICIQ) for the X-ray structure of **32b**.

**Supporting Information Available:** Experimental procedures and characterization data of new compounds (CIF), copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) $Ni(ClO_4)_2{\cdot}6H_2O$ showed the highest reactivity among all Lewis acids tested. $CH_2Cl_2$ proved to be the optimal solvent (DCE led to poorer endo-selectivity while no reaction was observed in toluene, $Et_2O$, or THF).

(11) The nickel catalyst was generated in situ by stirring equimolar amounts of $Ni(ClO_4)_2{\cdot}6H_2O$ and DBFOX−Ph in $CH_2Cl_2$ at room temperature for 4−5 h. Lower catalyst-aging time resulted in a significant loss of enantioselectivity.

(12) The reaction of **1e** with ethyl vinyl ether catalyzed by $Ni(ClO_4)_2{\cdot}6H_2O$−DBFOX (10 mol %) in the presence of molecular sieves led to racemic **2e** in 68% yield (endo/exo = 90:10).

(13) See Supporting Information for details.

(14) For an example on the preparation of a chiral [1,2,4]benzothiadiazine-5,5-dioxide with activity as AMPA receptor modulator, see: Cobley, C. J.; Foucher, E.; Lecouve, J.-P.; Lennon, I. C.; Ramsdem, J. A.; Thominot, G. *Tetrahedron: Asymmetry* **2003**, *14*, 3431.

JA0658766