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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 β-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]

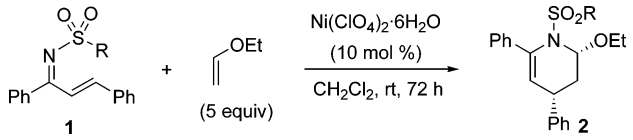
N-sulfonyl-1-aza-1,3-dienes were found by Boger et al. to participate as a 4π component in thermal ADAR with electron-rich dienophiles under high pressure or high temperature, exhibiting very high endo-selectivity.[6] This low reactivity has been greatly enhanced with azadienes bearing an electron-withdrawing 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 α,β-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

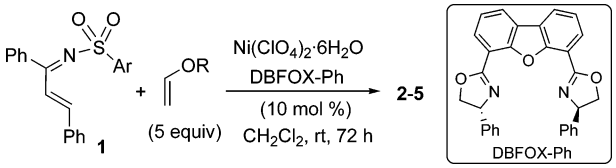
Table 1. Effect of the Sulfonyl Group in the Ni-Catalyzed ADAR



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.

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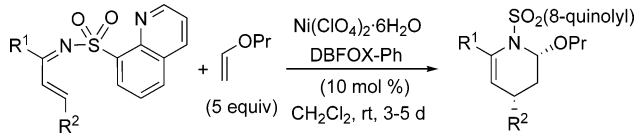
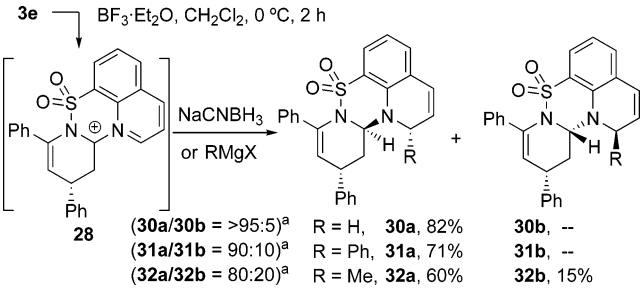
Table 3. Structural Variations at the 1-Azadiene



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.

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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.

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