Asymmetric Diels−Alder Reactions of 2-Azadienes Catalyzed by a Chiral Copper(II) Complex. A General Route to Enantiomerically Pure Piperidones

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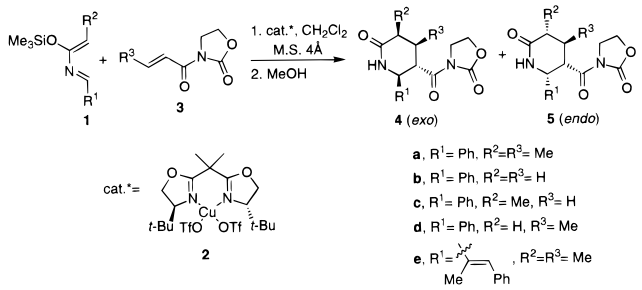
The aza Diels−Alder reaction provides a convergent and practical route to nitrogen-containing six-membered rings.[1] Successful examples of such reactions have been reported using substrates which carry a chiral auxiliary.[2] Diels−Alder cycloadditions involving iminodienophiles in the presence of a chiral Lewis acid have also been reported.[3] More recently Kobayashi et al. found that *N*-benzylidene-2-hydroxyaniline reacted as an electrophilic heterodiene in the presence of a nonracemic ytterbium catalyst. With cyclopentadiene acting as the dienophile, an adduct was obtained in good yield and with high enantiomeric purity.[4]

Diels−Alder reactions between electron-rich 2-azadienes and olefinic dienophiles activated by a chiral Lewis acid have not yet been reported despite their potential for the preparation of enantiomerically pure piperidones.[5] The success of such cycloadditions relies upon the finding of a Lewis acid which (a) activates the dienophile by complexation with an appropriate functional group and (b) does not irreversibly complex the nucleophilic nitrogen atom of the azadiene. In earlier reports, we had demonstrated the utility of 2-azadienes **1** in the regio- and diastereoselective synthesis of piperidones.[6] We had also noticed that these highly nucleophilic azadienes were often unstable in the presence of common Lewis acids which had been successfully used in Diels−Alder reactions of carbadienes.[7] Recently, we envisioned that Evans' mild Lewis acid **2** derived from copper(II) triflate and a C_2-symmetric bis(oxazoline) ligand[8] would be tolerated by the highly reactive azadiene **1** by binding selectively the bidentate imide group of dienophile **3**.

Scheme 1



Typically, azadiene **1** and imide dienophile **3** were added at −78 °C to a dichloromethane solution of complex **2** (5−8 mol %) prepared by mixing copper(II) triflate and the (*S*,*S*)-*tert*-butylbis(oxazoline) ligand[9] in the presence of 4-Å molecular sieves (Scheme 1). The solution was warmed to the appropriate temperature, and the reaction was monitored by ^{1}H NMR spectroscopy. Methanolysis of the primary adducts provided the corresponding substituted 2-piperidones. The diastereoisomeric purities were determined by ^{1}H NMR on the crude mixtures. Enantiomeric purities of the piperidones were determined by HPLC (Daicel Chiralpack AD column) after filtration of the crude mixture through silica gel.

Representative results are shown in Table 1. Under the reaction conditions, azadiene **1** was stable and did not deactivate the catalyst. Excellent results were obtained by using 2 or 3 equiv of azadiene. No reaction was observed at −78 °C (entry 1), but the copper(II) catalyst was effective between −45 °C and room temperature in terms of rate increase, diastereo-, and enantioselectivity. Over this temperature range, the *exo*-selectivity was very high (>99:1) except for the addition of the 4-unsubstituted azadiene **1b** (entry 5). The enhanced *exo*-selectivity as compared to the thermal reactions of the corresponding esters or amides probably results from the large size of the copper complex bound to the imide dienophile. The configuration of the new stereogenic centers can be predicted by the transition-state model proposed by Evans for other Diels−Alder reactions catalyzed by **2**.[8a] The observed adducts result from an *exo*-approach of the diene to the less hindered face of the square-planar complex of **2** with the dienophile (Figure 1).

The absolute configuration of piperidone **4a** was established by conversion to the corresponding crystalline thioester **6** which was submitted to X-ray diffraction analysis.[10] By analogy, the

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Table 1. Catalytic Asymmetric Cycloadditions of 2-Azadienes **1**

entry	R^1	R^2	R^3	cat. (mol %)	react. temp (°C)	product (*exo*:*endo*) [a]	yield (%) [b]	e.e. (%) [c]
1	Ph	Me	Me	8	-78	-	0	-
2	Ph	Me	Me	8	-45	**4a** (>99:1)	80	95.1
3	Ph	Me	Me	8	r.t.	**4a** (>99:1)	96	94
4	Ph	Me	Me	5	r.t.	**4a** (>99:1)	85	93.4
5	Ph	H	H	8	-45	**4b**+**5b** (6.1:1)	83 [d]	98.3 [e]
6	Ph	Me	H	8	-45	**4c** (>99:1)	96	98.3
7	Ph	H	Me	8	r.t.	**4d** (>99:1)	80	93
8	Me, Ph	Me	Me	8	r.t.	**4e** (>99:1)	98	90
9	Me, Ph	Me	Me	8	-45	**4e** (>99:1)	62	95.4

[a] *exo*/*endo* selectivity was measured by ^{1}H NMR spectroscopy. [b] Reactions conducted with 2 or 3 equiv of azadiene **1** relative to dienophile **3**. [c] ee were determined by HPLC (Daicel Chiralpack AD column). [d] Mixture of *endo*/*exo* diastereoisomers not separable by column chromatography. [e] ee of **4b**.

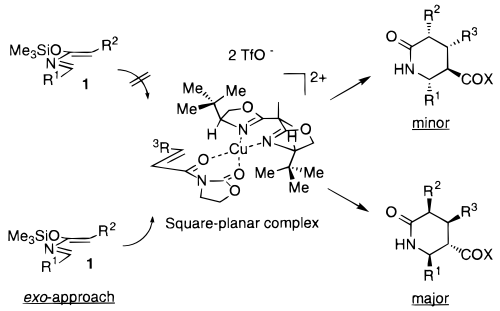
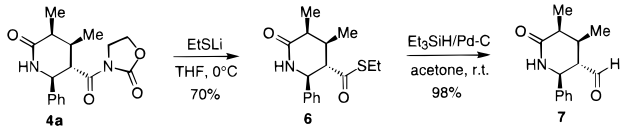


Figure 1.

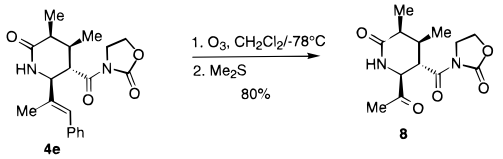
other piperidones which all showed the same (+)-sign of optical rotation, were assigned the same absolute configuration as **6**. The resulting piperidones can be submitted to functional group transformations without loss of enantiomeric purity, as shown by the conversion of **4a** into the corresponding aldehyde **7**[11] via the thioester **6**[12] (Scheme 2).

Although we had shown that 2-azadienes bearing a substituent other than a phenyl or an ether group at C-1 were difficult to prepare, we overcame this limitation by using azatriene **1e**

Scheme 2



Scheme 3



prepared following the general procedure described earlier.[6g] The β-methylstyryl group was selected as a potential acetyl group equivalent. Compound **1e** cycloadded to *trans*-crotonimide **3** in the presence of catalyst **2** to give the corresponding piperidone **4e** in high enantiomeric purity (Table 1, entries 8 and 9). Ozonolysis of the double bond followed by treatment with dimethyl sulfide generated the acetyl substituent without epimerization (Scheme 3). The structure and stereochemistry of **8** were confirmed by X-ray diffraction analysis.[13]

The present work thus allows the one-step preparation of quite complex piperidones of high enantiomeric purities and confirms the functional group tolerance of catalyst **2** which remains efficient in the presence of highly reactive substrates such as 2-azadienes **1**. The substitution pattern as well as the relative and absolute configurations of the created stereogenic centers can be designed by an appropriate selection of reaction partners. The experiment shown in Scheme 3 further extends the scope of this asymmetric synthesis of piperidine derivatives which are common substructures in natural and biologically active compounds.

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Supporting Information Available: Experimental procedures for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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