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Lewis Acid Catalysis of the Intramolecular Diels-Alder Reaction of 1-Azadienes.

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Abstract. Copper (II) trifluoromethanesulfonate, its chiral bisoxazoline complex, and bismuth (III) chloride efficiently catalyze the intramolecular cycloaddition reactions of *N*-vinyloxypropyl-2-cyano-1-azadienes **2**. Both the scope of this process and the reaction conditions were studied.

The hetero Diels-Alder reaction of azadienes represents both a direct and convergent strategy for the construction of functionalized piperidines, integral components of a large number of alkaloids.[1] Devising different means to activate the azadiene system with respect to the Diels-Alder reaction has been a crucial aspect in the development of this approach as a general synthetic method. In this context, the introduction of electron-donating (NMe_2)[2a] or withdrawing (*N*-Ac[2a,b], *N*-SO_2R[2d,e]) groups onto the azadiene nitrogen has proven to be effective, as has the substitution of the C-2 position of 1-azadienes by a cyano group. Indeed, 2-cyano-1-azadienes bearing either an N-acyl or N-phenyl substituent react under thermal conditions with both electron-rich ($LUMO_{azadiene}$-controlled) and electron-poor ($HOMO_{azadiene}$-controlled) dienophiles.[3]

The development of Lewis acid catalyzed versions of the carbo-Diels-Alder reactions has clearly demonstrated the advantages inherent to these processes in terms of reaction conditions (time and temperature), as well as the control of regio and stereochemistry.[4,5] Catalytic versions of certain hetero [4 + 2] cycloadditions have also been documented which display these features. These include the cycloadditions of oxadienes with vinyl ethers (Cat = $TiCl_4$[6a], $SnCl_4$[6a,b], $EtAlCl_2$[6a], $ZnCl_2$[6c], $ZnBr_2$[6d], $Eu(fod)_3$[6e], Ti(IV) chiral complexes[6f,g], $MgClO_4$[6h], $Cu(oxaz)_2(OTf)_2$[6i,j] and Y/Yb complexes[6k]), imine ($Zn(OTf)_2$[7a], $CuClO_4$ and $Cu(OTf)_2$ complexes[7b]) and glyoxylate ($Cu(oxaz)_2(OTf)_2$[7c], $Yb(OTf)_2$[7d], BINOL-Ti[7e]) cycloadditions and Diels-Alder reactions of thiadienes (Cat = $TiCl_4$[8a], $Cu(OTf)_2$[8b], $Mg(OTf)_2$[8b], $Yb(OTf)_3$[8c], $AlCl_3/EtAlCl_2$[8d]). Earlier attempts to use Lewis acids in 2-azadiene cycloadditions ($SnCl_4$ and $EtAlCl_2$[9a], $TMSNTf_2$[9b]) have met with intermittent success,[9c] and there are, as yet, no reports on the catalysis of 1-azadiene Diels-Alder reactions.

In a continuation of our work on the intramolecular Diels-Alder reaction of 1-azadienes[10] we have shown that 2-cyano-1-azadienes such as **2a-d**, containing an electron rich enol ether dienophile component, undergo cycloaddition to give the oxazinopiperideines **3a-d** in 59-80% yield (Scheme 1). However, under the thermal conditions (toluene, 110-130°C for 24 h) employed to effect reaction of these fragile systems, partial degradation of the cycloaddition products occured. This was particularily true for the transformation of **2d** to **3d** where up to 40% loss of material was observed. In light of these findings, it was appealing to use Lewis acid catalysis to render these cycloaddition reactions possible at lower temperatures, and thereby to improve

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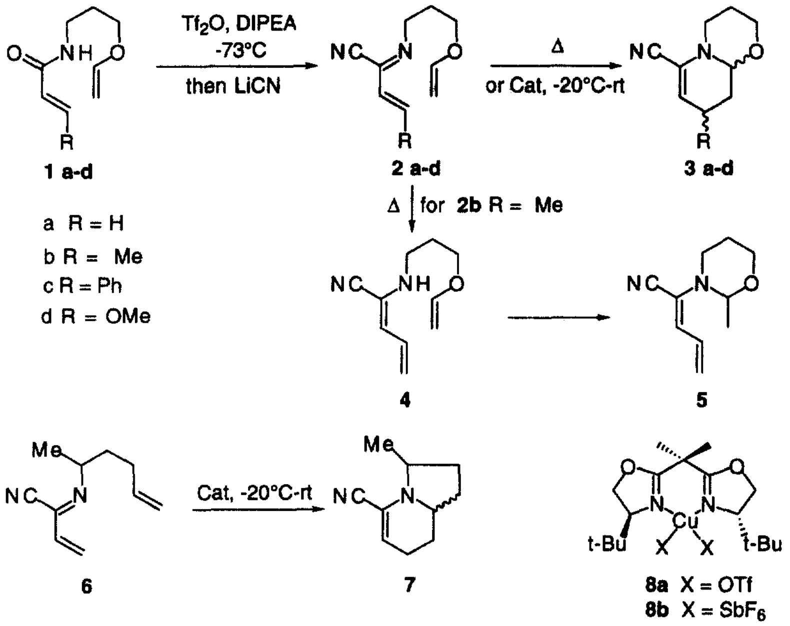
upon their selectivity. The results of a study of the Diels-Alder reactivity of azadienes **2a-d** in the presence of different Lewis acid catalysts are reported in this communication.



Scheme 1

Table 1. Intramolecular catalyzed hetero Diels Alder reactions of 2-cyano-1-azadienes.

entry	azadiene	catalyst[a]	temp.[b], °C	time, h	product	yield,[c] %	cis/trans[f]
1	**2a**	$Cu(OTf)_2$	rt	18	**3a**	19	-
2	**2a**	$Cu(OTf)_2$ + MS 3Å	rt	20	**3a**	22	-
3	**2b**	$Cu(OTf)_2$	-20	38	**3b**	60	1 : 3.7
4	**2b**	$Cu(OTf)_2$	rt	5	**3b**	53	1 : 3.6
5	**2c**	$Cu(OTf)_2$	-20	12	**3c**	71	1 : 6.4
6	**2d**	$Cu(OTf)_2$	-20	1	**3d**	31[e]	1 : 16
7	**2b**	$BiCl_3$ + MS 3Å	0	72	**3b**	69	1 : 4.8
8	**2c**	$BiCl_3$	rt	30	**3c**	82	1 : 8.3
9	**2b**	$AgSbF_6$ or AgOTf	-20 -> 20	48		0	-
10	**2b**	$TiCl_4$	-20	10	**3b**	32 (+**1b**)	1 : 4.7
11	**2b**	$Cu(oxaz)_2(OTf)_2$	rt	18	**3b**	61 (+10 **1b**)	1 : 3.6
12	**6**	$Cu(OTf)_2$	0	0.3	**7**	14[d,e]	-

a - All reactions were carried out in dry toluene, with 10 mol % of catalyst; b - Optimal temperature. At lower temperatures the reaction doesn't work or is extremely slow and doesn't advance till completion; c- Isolated yield; d - Significant degradation; e - Cyano group partially hydrolyzed to amide; f - Calculated from NMR data.

As the data in Table 1 indicates, in contrast to the purely thermal conversion of compounds **2** to tetrahydropyridine derivatives **3**, the Diels-Alder reaction of **2a-d** in the presence of 10 mol % of Lewis acid proceeded smoothly at -20°C or room temperature. For example, the intramolecular cycloaddition of azadiene

2b catalyzed by copper (II) trifluoromethanesulfonate (toluene, -20°C, 38 h - entry 3) afforded cycloadduct **3b** in 60% yield.

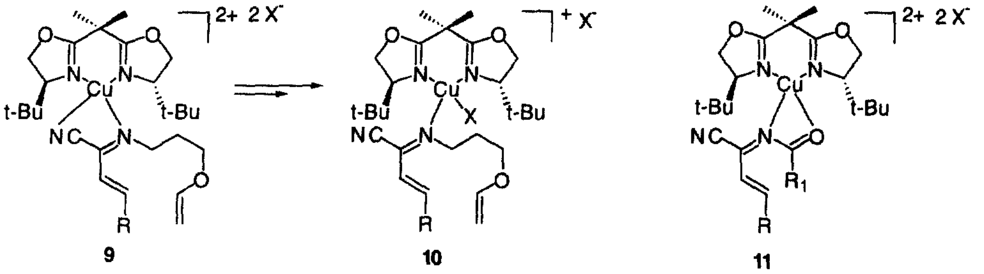
Of the Lewis acids tested as catalysts for this aza Diels-Alder reaction, the best results were obtained with $Cu(OTf)_2$ (entries 3-6) and $BiCl_3$ (entries 7,8). Silver salts (AgOTf and $AgSbPF_6$) were totally inactive,[11] while addition of $TiCl_4$ caused partial degradation, probably due to the presence of traces of HCl. In contrast to the results obtained by Evans *et al.* for cyclopentadiene-*N*-acylacryloylamide cycloadditions,[12] $Cu(OTf)_2$ itself was shown to be a more active catalyst for azadiene reactions than the chiral bisoxazoline complexes **8a** and **8b**.

Unlike the cycloadditions of oxadienes,[6a-j] the azadiene catalyzed reactions turned out to be extremely sensitive to the solvent employed. Thus, whereas the expected cycloaddition products were obtained in good yields using benzene or toluene as the reaction medium, rapid decomposition of the starting material was observed for the more polar solvents (CH_2Cl_2 and THF).

Important also was the finding that, despite the possible double bond (imine to enamine) isomerization upon coordination of the azadiene nitrogen in **2b** with the catalyst [$Cu(OTf)_2$ (entries 3,4) or $BiCl_3$ (entry 7)], no trace of the isomerized compound **4**, or the corresponding cyclic enamine **5** observed under thermal conditions,[10] was detected. (entry 7). However, extended reaction times were required for complete transformation.[13] This led in some cases to the loss of catalytic activity due to slow catalyst hydrolysis. Nevertheless, this could be avoided by addition of powdered molecular sieves 3 Å (entries 2, 7).[14]

Interestingly, the presence of a substituent on C-4 appears to be important for the catalytic reaction to be efficient. Indeed, all attempts to catalyze the cycloaddition of acryloyl derivatives **2a** and **6** resulted in low product yields, prolonged reaction times and significant degradation. An attempt was made to rationalize this result in terms of the differences in the electron density on nitrogen. However, MOPAC calculations of charge distribution (AM1 level) show that although there is some increase of partial charge on N-1 (from -0.17 for **2a** to -0.20 for **2d**), it is too small to explain the difference in reactivities of **2a/6** and **2b-d**. This leads us to suggest that the variation in the catalysis efficiency observed in these reactions may be a function of the stabilization of the azadiene-copper complex and of the products formed that results when the 4-substituent is present.

The very low asymmetric induction observed in the reaction of **2b** with **8a** (α_D = +0.4 (c=1.0 CH_2Cl_2), ee 8%)[15] suggests that the cyano-group is not coordinated to the copper cation, and that the reaction proceeds via a one-point diene-catalyst complex **10**, which is less highly organized than the two-point complex **9** (Scheme 2).[16,12] Following from this argument, improved enantioselectivity may be observed in the Diels-Alder reactions of *N*-acyl-1-azadienes, which can, in principle, form complexes of type **11**.



Scheme 2

The search of other nitrogen-coordinating catalysts compatible with the acid sensitive nature of 1-azadienes, as well as work toward the development of asymmetric aza Diels-Alder reactions are ongoing.

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