"Orthogonal" Lewis Acids: Catalyzed Ring Opening and Rearrangement of Acylaziridines

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Received March 26, 1998

In a recent paper, we demonstrated that select late transition metals can catalyze the cis−trans conformational isomerization of amides through coordination of the metal to N_a.[1] More oxophilic metals, on the other hand, prefer to coordinate to the carbonyl O. We were intrigued by the use of acylaziridines, which can rearrange to oxazolines[2] or serve as ambident electrophiles,[3] as probes for Lewis acid-catalyzed reaction pathway selectivity. It was our hypothesis that coordination of a Lewis acid to the amide nitrogen of acylaziridines (N_a) might be expected to catalyze a rearrangement to the oxazoline, whereas coordination to the carbonyl O may be better at activating the substrate toward external nucleophilic attack. We demonstrate herein that catalytic quantities of relatively oxophilic metals under certain conditions activate acylaziridines **1** predominantly toward external nucleophilic attack, whereas more azaphilic Lewis acids, which we term "orthogonal," catalyze the oxazoline rearrangement (Scheme 1).[4]

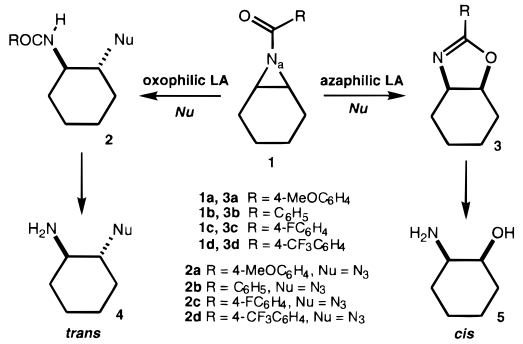
Several procedures for the Lewis acid-catalyzed asymmetric synthesis of aziridines by use of transition metal-based catalysts have emerged in the past few years.[5] However, ring-opening and expansion reactions of acylaziridines, employing catalytic quantities of metal-based Lewis acids, have not been widely reported.[6] These reactions are expected to afford useful synthetic intermediates such as **4** and **5** (Scheme 1). We focused on the reaction of acylated cyclohexenimine derivatives **1**, which are readily available from either cyclohexene[7] or cyclohexene oxide,[8] followed by acylation. Compounds **1a**−**d** were smoothly converted to ring-opened products **2a**−**d** by $TMSN_3$ in the presence of 10 mol % Yb(2,2′-biphenol)OTf (Table 1, entries a, d, g, h). The complexes $Zr(Cp)_2(SbF_6)_2$ and Ti(O-*i*-Pr)$_4$ were also found to catalyze nucleophilic attack of $TMSN_3$ (Table 1, entries b, c, e, f). Of these metals, Yb(III) complexes gave the fastest rates and most reproducible results. Conversion to the azide **2** is possible only in the presence of a Lewis acid, as no nucleophilic attack occurs on the substrates after 1 week without catalyst. To examine the effect of remote electron-withdrawing and electron-donating groups, we conducted a series of competition experiments and found that electron-*withdrawing* substituents accelerate the reaction, as indicated by a linear correlation of log[k/k_0] to Hammett σ values.[9] Electron-withdrawing substituents are expected to stabilize the leaving group during nucleophilic attack.

Table 1. Ring Opening of Acylaziridines 1a−d with $TMSN_3$

entry[a]	substrate	metal complex[b]	product	yield[c] (%)
a	**1a**	Yb(biphenol)OTf	**2a**	84
b	**1a**	Ti(O-*i*-Pr)$_4$	**2b**	64
c	**1a**	$Zr(Cp)_2(SbF_6)_2$	**2b**	57
d	**1b**	Yb(biphenol)OTf	**2b**	72
e	**1b**	Ti(O-*i*-Pr)$_4$	**2b**	67
f	**1b**	$Zr(Cp)_2(SbF_6)_2$	**2b**	58
g	**1c**	Yb(biphenol)OTf	**2c**	75
h	**1d**	Yb(biphenol)OTf	**2d**	80

[a] All reactions with Yb were performed in CH_2Cl_2; others were performed in THF. [b] 10 mol % metal. [c] Reactions took 48−72 h to full coversion as measured by ^{1}H NMR.

Scheme 1. Rearrangement and Ring Opening of Acylaziridines



Unlike their acyclic amide counterparts, acylaziridines are highly pyramidalized at nitrogen, which makes the acylaziridine nitrogen more basic. Experimental[10] as well as theoretical[11] evidence indicates that acylaziridines may undergo N-protonation. This behavior stands in sharp contrast to that of simple amides, which undergo preponderant O-protonation under all circumstances.[12] We obtained a crystal structure of **1d** that clearly indicates pyramidalization of the aziridine nitrogen (Figure 1);[13] aziridine **1d** exhibits an out-of-plane angle of 68°, as defined by Ohwada,[14] and a C−N bond length of 1.388 Å. These data differ significantly from those of normal amides, which are essentially planar (out-of-plane angles < 10°) and have C−N bond lengths less than 1.34 Å.[14]

We decided to investigate metals classically thought of as more azaphilic, specifically the salts $Zn(OTf)_2$, $Cu(OTf)_2$, and $Sn(OTf)_2$, to enhance the possibility of N-coordination. These metal salts did not catalyze the addition of nucleophiles to

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(13) Crystals of 1d were obtained by slow evaporation of CH_2Cl_2. Crystal data for **1d**: triclinic, P1; a = 6.6677(7) Å, b = 8.2722(9) Å, c = 12.1198(13) Å, V = 628.29(12) Å^3; Z = 2; d_{calcd} = 1.423 Mg/m^3; $F(000)$ = 280; μ(Mo Kα) = 0.120 mm^{-1}; λ(Mo Kα) = 0.710 73 Å; 3567 reflections measured, 2133 observed ($I > 2\sigma(I)$); 172 variables; R = 0.0705, R_w = 0.1811, GOF = 1.034.

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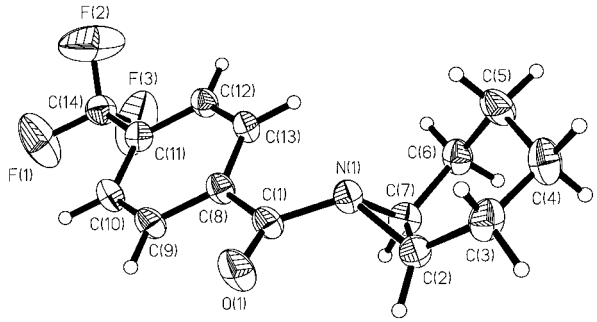


Figure 1. Crystal structure of **1d** (50% ellipsoids). Selected bond distances (Å): O(1)−C(1) 1.225(4); C(1)−N(1) 1.388(4). Selected torsion angles (deg): C(1)−N(1)−C(2)−C(7) 112.9; O(1)−C(1)−N(1)−C(2) 39.1.

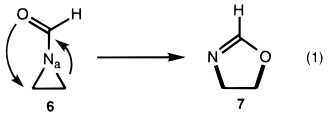
Table 2. Rearrangements of Acylaziridines 1a−d

entry[a]	substrate	metal[b]	time[c] (h)	product	yield (%)
a	**1a**	$Cu(OTf)_2$	6	**3a**	89
b	**1a**	$Sn(OTf)_2$	10	**3a**	83
c	**1a**	$Zn(OTf)_2$	7	**3a**	63
d	**1b**	$Cu(OTf)_2$	48	**3b**	80
e	**1b**	$Sn(OTf)_2$	48	**3b**	30
f	**1b**	$Cu(OTf)_2$	7	**3b**	84
g	**1b**	$Sn(OTf)_2$	12	**3b**	87
h	**1b**	$Zn(OTf)_2$	12	**3b**	74
i	**1c**	$Cu(OTf)_2$	7	**3c**	80
j	**1c**	$Sn(OTf)_2$	15	**3c**	79
k	**1c**	$Zn(OTf)_2$	12	**3c**	60
l	**1d**	$Cu(OTf)_2$	16	**3d**	76
m	**1d**	$Sn(OTf)_2$	24	**3d**	67
n	**1d**	$Zn(OTf)_2$	24	**3d**	62

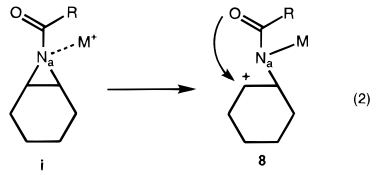
[a] All reactions were run in THF/DME (20/1) except those in entries d and e, which were in CH_2Cl_2. [b] 10 mol % metal. [c] Time to full conversion by ^1H NMR.

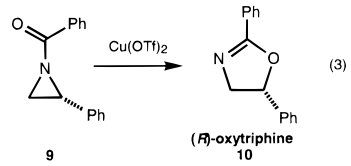
acylaziridines, but instead promoted the rearrangement of **1a**−**d** to 2-aryloxazolines **3a**−**d** (Table 2).[15] In fact, the rearrangement proceeded smoothly in the presence of a variety of nucleophiles (enol silanes, TMSCN, $TMSN_3$, and water) and also in their absence. Although the oxazoline rearrangement proceeds at room temperature in CH_2Cl_2, it does so only very slowly (months). However, **1b** was converted to **3b** by 10 mol % $Cu(OTf)_2$ in 80% yield after 2 days, with the mass balance accounted for by unconverted starting material. Under the same conditions, $Sn(OTf)_2$ showed only 30% conversion (Table 2, entries d, e). The reaction rate can be greatly accelerated by the use of THF/DME, which promoted full conversion of **1b** to **3b** in 7 h by Cu(II) in 84% yield (Table 2, entry f). Whereas $Sn(OTf)_2$ is an inefficient catalyst in CH_2Cl_2, in THF/DME it isomerizes **1b** to **3b** in under 12 h in 87% yield (Table 2, entry g). Likewise, this isomerization proceeds in the presence of 10 mol % $Zn(OTf)_2$ with minimal loss of yield (entries c, h, k, n).

Competition experiments on the rearrangement led us to conclude that electron-*donating* substituents increase the rate of reaction.[16] This trend is *opposite* to that of the Lewis acid-catalyzed additions (**1** to **2**) analyzed above. A literature report proposed the uncatalyzed oxazoline rearrangement to be a concerted process.[17] We have calculated transition states at 6-31G* for the Lewis acid-catalyzed and the uncatalyzed versions, both of which can be viewed as orbital symmetry disallowed "frontside" nucleophilic attacks. The calculated energy of activation ($\Delta G^{\ddagger}$) for the transformation of **6** to **7** (eq 1) is 57 kcal/mol. When a Li^+ ion is coordinated to N_a this energy is marginally lowered to a still prohibitively high 53 kcal/mol,[18] which suggests that the isomerization is not concerted in organic media.[19]



Alternatively, the reaction can proceed by a heterolytic pathway in a stepwise fashion. This alternative is in accord with the rate accelerations we observed in better cation-solvating organic solvents. Substituent effects for the oxazoline rearrangement are also understandable in terms of enhanced nucleophilicity of the carbonyl oxygen in intermediate **8**, where metal−N_a-coordination is expected to leave the carbonyl group free to attack the cis face of the incipient cationic center (eq 2). The fact that oxophilic metals do not catalyze the rearrangement implies that metal coordination to N_a is an essential feature of the rearrangement.





To determine the regio- and stereochemistry of rearrangement, optically active substrate (*R*)-**9** was synthesized by literature methods.[20] The reaction of (*R*)-**9** with 10 mol % $Cu(OTf)_2$ produced the enantiomerically pure natural product (*R*)-oxytriphine **10** (eq 3), whose stereo- and regiochemistry was determined by comparison to authentic material.[21] The exclusive formation of enantiomerically pure **10** indicates that a carbocation, solvated from the backside or in the form of a tight ion pair to preserve stereochemistry, could be an intermediate in this pathway.

Acknowledgment. The authors thank Dr. Victor G. Young, Jr., director of the X-ray Crystallographic Laboratory at the University of Minnesota, for obtaining the crystal structure of **1d**. T.L. thanks the NIH (R29 GM54348) for support of this work. D.F. thanks JHU for a Marks Fellowship, and C.C. thanks the Organic Division of the American Chemical Society for a Graduate Fellowship (sponsored by Organic Reactions, Inc.).

Supporting Information Available: Experimental procedures, spectroscopic data for all new compounds, protocols for mechanistic experiments, and tables of crystal data (15 pages).

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