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A Highly Efficient and Selective Route to Isomeric Cyclic Diazadienes

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While cyclic diazine and pyridazine derivatives represent an important class of pharmaceutically interesting scaffolds,[1,2] current synthetic methods for their preparation are limited since only one product can be prepared from a given starting material. To date, no method exists for the preparation of diverse diazine scaffolds from a common and easily prepared precursor.

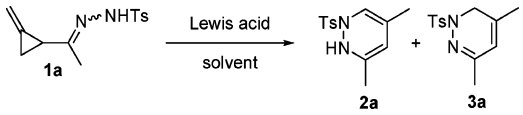
As part of our research program in strained ring chemistry, we have been interested in the synthetic utility of methylenecyclopropanes as a building block for a variety of different carbo- and heterocyclic scaffolds.[3] Recently, these highly reactive synthetic precursors have attracted considerable attention due to their ease of preparation[4] and broad range of reactivity.[5] Herein we report a flexible and highly selective ring expansion of methylenecyclopropyl hydrazones as an expedient route to a class of unusual isomeric cyclic diazadienes **2** and **3**.

Initial optimization studies using **1a** and MgI_2 showed that coordinating solvents were most effective (Table 1, entries 1−6), affording the azadiene **3a** as the major product in low to modest selectivities and in moderate combined yield. In particular, DME was ideal for this transformation, affording the ring-expanded products after relatively short reaction times in an excellent yield, albeit with modest selectivities (entries 6 and 7). We next focused on modifying the selectivity of the reaction by changing the Lewis acid,[6] and while most failed to deliver any selectivity in the reaction (entries 8−10), use of TMEDA as an additive reversed the inherent selectivity for the azadiene to now cleanly and selectively afford the dienamine product **2a** (entry 11). Reaction yields could be further improved while decreasing the reaction time by increasing the reaction temperature as well as the amount of TMEDA used (entries 12 and 13). Finally, replacing MgI_2 with either $MgCl_2$ or $MgBr_2$ in the presence of TMEDA afforded the desired diene product in good yields without any erosion in selectivity.

With suitable reaction conditions in hand, we next explored the scope of the ring expansion using a variety of substituted *N*-tosyl hydrazones (Table 2). The reaction tolerated a wide range of functionalized and nonfunctionalized aliphatic substituents (entries 1−7) to afford **2** in good to excellent yields and selectivities. In addition, our methodology also allows for the use of aromatic substituted hydrazone derivatives (entries 8 and 9), affording the ring-expanded products in good to excellent yields, though in somewhat lower, yet synthetically useful, selectivities.

Our optimization studies using non-halide containing Lewis acids[6] suggest that the mechanism does not proceed via direct halide addition in an analogous manner to our earlier work using MgI_2.[3a−e] We therefore sought to investigate the mechanism of this reaction through the use of a deuterium-labeled MCP hydrazone (**d_2-1a**) (Scheme 1). Surprisingly, this study found exclusive deuterium incorporation at the 3′-position of the dienamine product **d_2-2a**. Incorporating these findings, we propose that the reaction must proceed via initial activation of the hydrazone moiety by the Lewis acid followed by cyclization of nitrogen at the exo-methylene carbon (Scheme 2). Although this nitrogen is not highly nucleophilic, cyclization may occur through sufficient development of partial

Table 1. Lewis Acid-Catalyzed Ring Expansion of MCP Hydrazones[a]

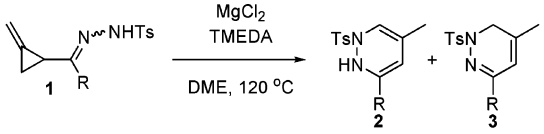


1a → 2a + 3a

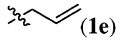
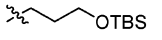
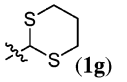
entry	Lewis acid (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)	2a:3a
1	MgI_2 (50)	THF	50	24	58	1:3.5
2	MgI_2 (50)	CH_3CN	90	1.5	76	1:1.1
3	MgI_2 (50)	toluene	90	1.5	43	1:1.8
4	MgI_2 (50)	dioxane	90	48	70	1:1
5	MgI_2 (50)	DCE	90	1.5	65	1:3.8
6	MgI_2 (50)	DME	90	1.5	90	1:2.3
7[c]	MgI_2 (10)	DME	90	1.5	92	1:1.5
8[c]	ZrI_2 (10)	DME	90	1.5	48	1:2.1
9[c]	FeI_2 (10)	DME	90	1.5	40	1:3
10[c]	SrI_2 (10)	DME	90	1.5	48	3.8:1
11[c,d]	MgI_2 (10)	DME	90	24	65	>20:1
12[c,d]	MgI_2 (10)	DME	120	2	65	>20:1
13[c,e]	MgI_2 (10)	DME	120	2	78	>20:1
14[c,e]	$MgBr_2$ (10)	DME	120	3.75	83	>20:1
15[c,e]	$MgCl_2$ (10)	DME	120	3.5	85	>20:1

[a] All reactions were performed using **1a** (0.11 mmol) and the corresponding Lewis acid and solvent (0.028 M unless otherwise noted). [b] Combined isolated yield of **2a** and **3a**. [c] Run at 0.01 M. [d] Run using 20 mol % of TMEDA. [e] Run using 100 mol % of TMEDA.

Table 2. Dienamine Formation via Ring Expansion of Substituted MCP Hydrazones[a]



1 → 2 + 3

entry	R (1a-i)	time (h)	yield[b] (%)	2:3
1	Me (**1a**)	3.5	86	>20:1
2	Et (**1b**)	4.0	77	>20:1
3	Bn (**1c**)	4.0	70 (74[c])	10:1
4	Bu (**1d**)	4.0	91	>20:1
5	 (**1e**)	4.0	87 (84[c])	>20:1
6	 (**1f**)	4.0	81	>20:1
7	 (**1g**)	4.0	68	5:1
8	Ph (**1h**)	4.0	93 (91[c])	5:1
9	2-Furyl (**1i**)	4.0	81	15:1

[a] All reactions were performed using **1**, $MgCl_2$ (10 mol %), and TMEDA (1 equiv) in DME (0.01 M) at 120 °C. [b] Combined isolated yield of **2** and **3**. [c] 0.028 M in DME.

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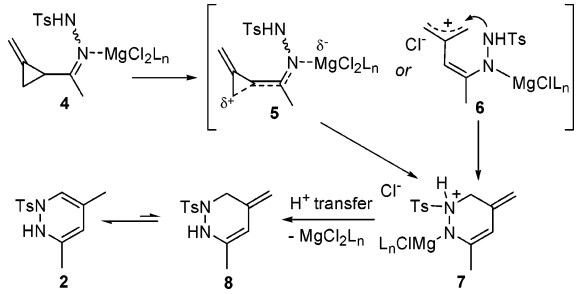
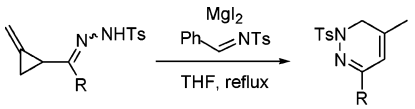
Scheme 1. Deuterium Labeling Studies

Scheme 2. Proposed Reaction Mechanism



Scheme 3. Selective Azadiene Formation



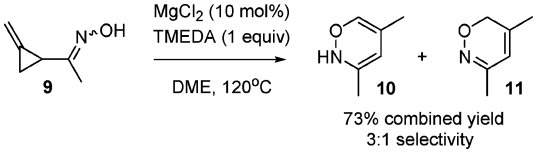
		Yield	Ratio **3**:**2**
1a	**3a**	86%	>20:1
1h	**3h**	72%	>20:1

positive charge at the 3-position of the cyclopropane ring (**5**). In fact, previous studies by Dieter found that the regioselectivity for halide-mediated ring opening of substituted cyclopropanes using weak nucleophiles could best be explained by proposing a similar intermediate.[7] The development of a positive charge in this case is crucial for cyclization to occur since a concerted process would be unlikely given the inability of the π-orbitals to align with the σ^*-orbitals of the cyclopropane ring. Alternatively, the reaction may proceed via a two-electron disrotatory ring opening to afford the zwitterionic intermediate **6**. While zwitterionic ring openings of activated MCPs of this type are rare, an analogous intermediate has been proposed by Monti and co-workers for the $TiCl_4$-mediated addition of allylic silanes to activated MCP ketones.[8] We note that although the formation of a ring-opened intermediate would be expected to result in significant deuterium scrambling at carbons 1 and 3′, a significant memory effect (i.e., cyclization of **6** occurs prior to bond rotation) could account for the observed deuterium labeling in **d$_2$-2a**.

Since the addition of ligand played an important role in the outcome of the reaction, we were interested in whether the catalyst system could be modified to selectively afford the azadiene product. In fact, use of MgI_2 in the presence of *N*-benzylidene toluenesulfonamide was found to reverse the selectivity of the reaction to favor the azadiene product in good yields and in excellent selectivities (Scheme 3). While studies to determine the reason for this drastic reversal in selectivity are ongoing, product interconversion studies using the less stable dienamine **2a**[9] under these reaction conditions failed to afford the observed azadiene **3a**, suggesting that the product is produced directly from the reaction and not via dienamine isomerization.

Finally, we report our preliminary studies on the extension of the dienamine-selective conditions ($MgCl_2$/TMEDA) to MCP oximes. Reaction of oxime **9** selectively afforded the desired oxazene **10** in modest selectivity and good yield (Scheme 4).

Scheme 4. $MgCl_2$-Mediated Rearrangement of Oximes



In summary, we have reported a novel and selective Lewis acid-mediated ring expansion of methylenecyclopropyl hydrazones to cyclic dienamines and azadienes in good to excellent yields and in excellent selectivities. Additional studies have found that the choice of Lewis acid and ligand was key in selectively obtaining either the azadiene or dienamine products. Further exploration of the reaction scope and mechanistic studies to determine the origin of this highly unusual and reversal in selectivity are ongoing.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Single-point calculations using Spartan at the RB3LYP level show an energy difference of 19.8 kcal/mol between the more stable azadiene and dienamine.

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