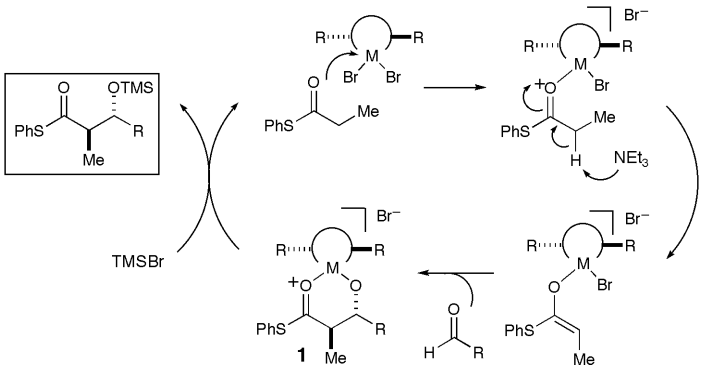
Chapter 4

Summary of Doctoral Research

I. Design of a Conceptually Novel Lewis Acid-Catalyzed Enantioselective *Anti* Aldol Reaction

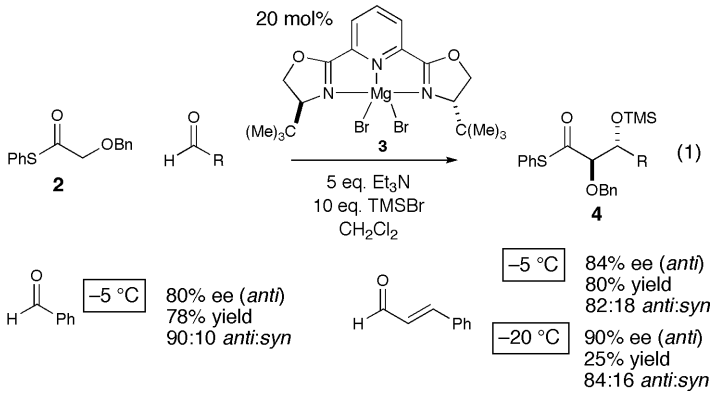
Our group has sought to develop a platform for enantioselective catalysis involving Lewis acid activation of unmodified carbonyls. In the context of a direct aldol reaction, we envisioned that catalyst turnover might be achieved *via* silylation of covalently bound catalyst-aldolate adduct **1** using an appropriate silyl halide source (Scheme 1).

Scheme 1. Proposed catalytic cycle for novel aldol reaction



After extensive optimization, we found that tridentate magnesium PyBOX complex **3** was a suitable catalyst for the formation of enantioenriched aldol adducts **4** from thioester **2** (Figure 1). Most notably, *anti* reaction diastereoselection was observed (82:18 to 90:10 *anti*:*syn*), a reaction manifold that has traditionally been difficult to access.

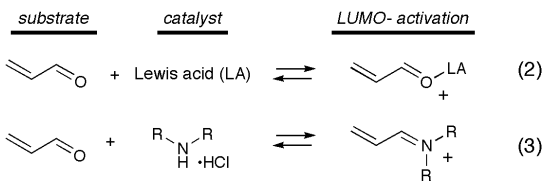
Figure 1. Direct *Anti* Aldol Reaction



Mechanistic studies indicate that the reaction proceeds *via* an open transition state involving silyl activation of the aldehyde electrophile and subsequent addition of a catalytically generated chiral enolate; this mechanism operates in contrast to the traditional Mukaiyama aldol pathway. Significantly, this new reaction technology represents the first direct method for *anti*-aldol catalysis using metal salts.

II. Enantioselective Organocatalytic [1,3]-Dipolar Cycloaddition and *Exo* Selective Cycloaddition Reactions

A major focus of our research has been the development of a general strategy for enantioselective organocatalysis. We have found that chiral secondary amines act as LUMO-lowering catalysts *via* the reversible formation of iminium ions from □,□-unsaturated aldehydes (Equation 3).

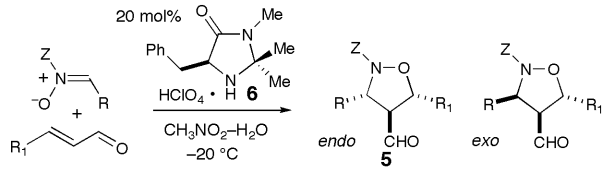


As part of these studies, we have extended our LUMO-lowering organocatalysis strategy to [3+2] cycloadditions between nitrones and α,β-unsaturated aldehydes to provide isoxazolidines **5**, useful synthons for the construction of amino acids, β-lactams, amino carbohydrates, and alkaloids.

It has been established that α,β-unsaturated aldehydes are generally poor substrates for metal-catalyzed nitrone cycloadditions, presumably due to the preferential coordination of Lewis acids to nitrone oxides in the presence of monodentate carbonyls. In contrast, we expected amine catalysts to be inert to nitrone association, thereby enabling α,β-unsaturated aldehydes to participate in iminium activation and subsequent [3+2] cycloaddition. Importantly, this methodology would allow, for the first time, simple aldehydes to function as dipolarophiles in a nitrone cycloaddition.

After investigating the effects of solvent and co-catalyst, it became apparent that LUMO-lowering organocatalysis could be successfully applied to the [3+2] cycloaddition.[1] A range of nitrones are compatible with a variety of aldehyde dipolarophiles in the presence of a catalytic quantity of chiral imidazolidinone **6** (70–98% yield, 81:19 to 99:1 *endo*:*exo*, 90–99% ee) (Table 1).

Table 1. Organocatalyzed dipolar cycloadditions between representative nitrones and dipolarophiles

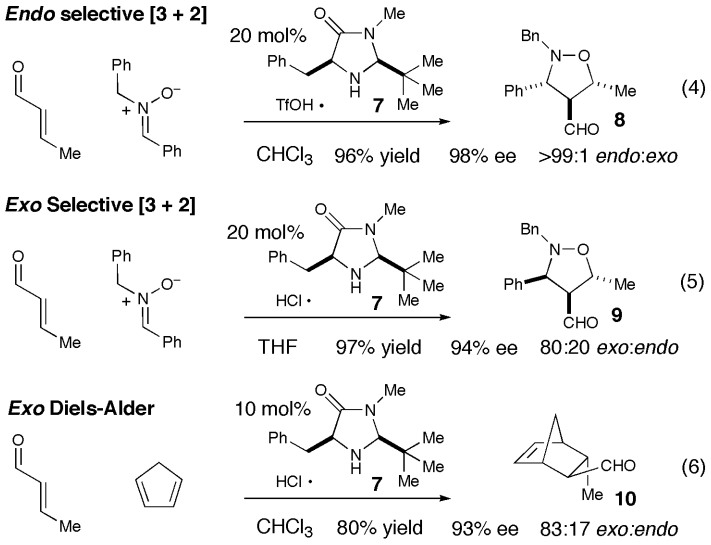


entry	Z	R	R_1	*endo*:*exo*	yield	% ee (*endo*)
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Me	C_6H_4Cl-4	Me	93:7	76	94
6	Bn	C_6H_4OMe-4	Me	98:2	93	91
7	Me	C_6H_4Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	*c*-hex	Me	99:1	70	99
10	Bn	Ph	H	81:19	72	90
11	Bn	Ph	H	86:14	80	92
12	Bn	C_6H_4Me-4	H	85:15	80	90
13	Bn	C_6H_4Cl-4	H	80:20	80	91
14	Bn	2-naph	H	81:19	82	90
15	Bn	C_6H_4OMe-4	H	91:9	83	90

As an extension of this methodology, we investigated the catalytic activity of *tert*-butyl substituted imidazolidinone **7** (Equation 4). Catalyst **7** afforded isoxazolidinone **8** in 96% yield with 98% ee and >99:1 *endo*:*exo* selectivity after ten hours. These findings represent a marked improvement in reaction rate as well as enantio- and diastereoselectivity for the [3+2] cycloaddition.

The choice of solvent and co-catalyst had a remarkable effect on the [3+2] cycloaddition using catalyst **7**. When THF was employed as solvent with HCl as co-catalyst, the *exo* cycloaddition adduct **9** was preferentially formed (80:20 *exo*:*endo*) (Equation 5). Imidazolidinone **7** was found to catalyze an *exo* selective organocatalytic Diels-Alder cycloaddition as well (Equation 6). To our knowledge, this is the first

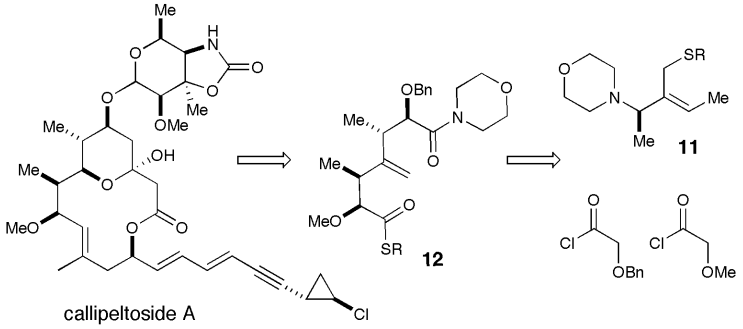
example of an *exo* selective, enantioselective catalytic Diels-Alder reaction. We are currently exploring the origins and scope of these *exo* selective processes.



III. Progress towards the Total Synthesis of Callipeltoside A

Callipeltoside A (Scheme 3), an architecturally complex natural product isolated from the lithistid sponge *Callipelta* sp., is known to protect cells infected with HIV and to inhibit *in vitro* proliferation of NSCLC-N6 and P388 cells.

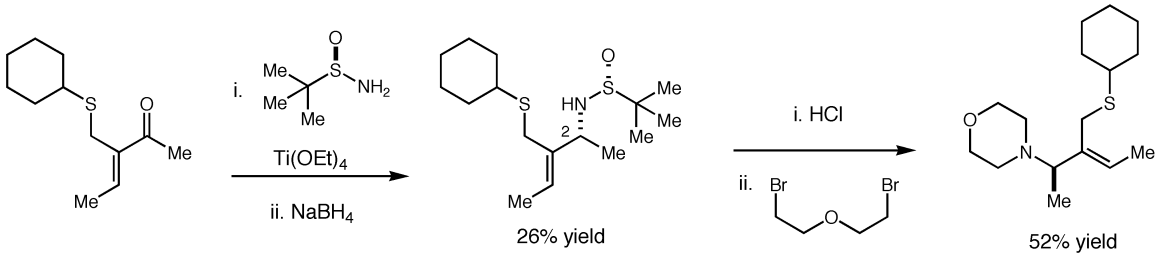
Scheme 2. Tandem Claisen provides access to callipeltoside A



We envisioned that a synthetic approach to callipeltoside A might be established around the tandem amino-sulfide acyl-Claisen rearrangement, a new cascade technology developed in our laboratories.[2] More specifically, we envisioned that treatment of **11** with two discreet acid chlorides would afford the acyclic stereochemical core **12** of callipeltoside A (Scheme 3).

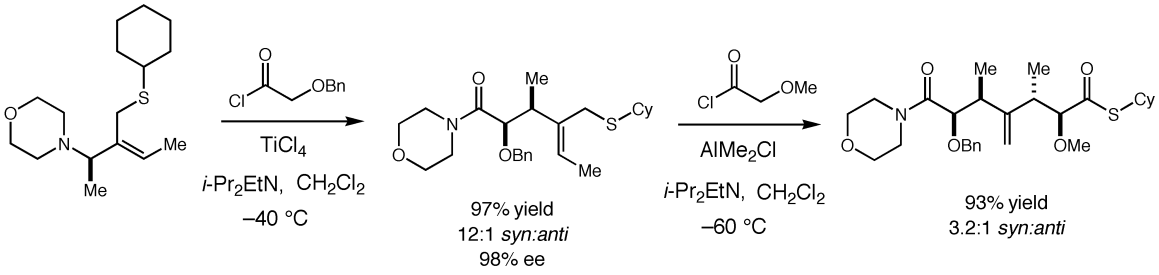
The allylic amino-sulfide precursor to the Claisen rearrangement (Scheme 4) is readily available in enantioenriched form from methyl vinyl ketone using Ellman's sulfinimine technology.

Scheme 3. Preparation of enantiopure allylic amino-sulfide



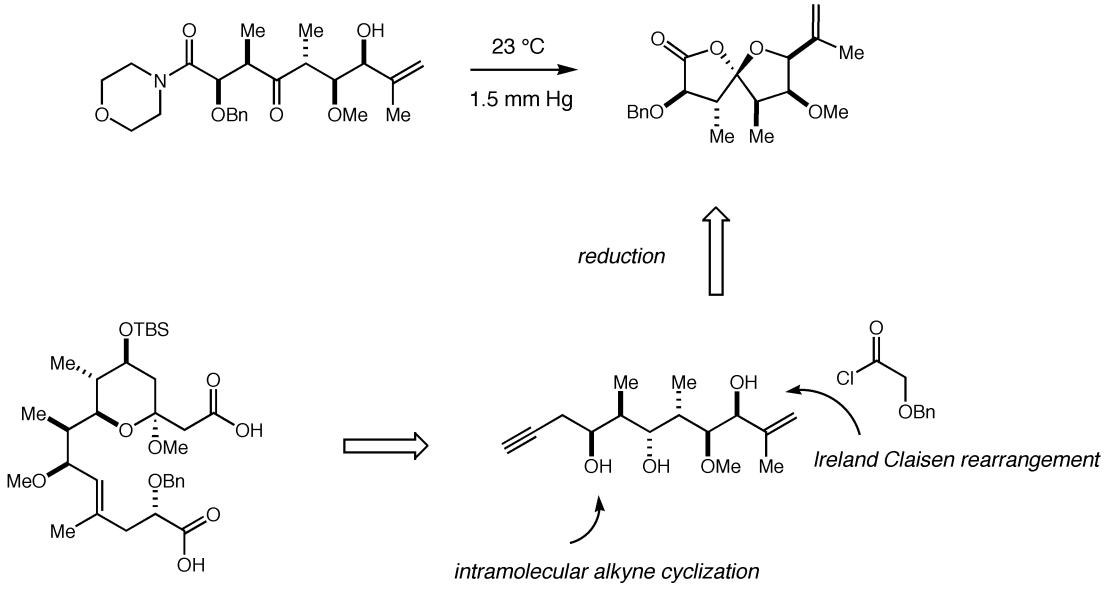
The key tandem Claisen rearrangement was accomplished as a two-step sequence, using catalytic $TiCl_4$ followed by stoichiometric $AlMe_2Cl$ to afford the acyclic stereochemical array in high yield and stereoselectivity (Scheme 5).

Scheme 4. Tandem amino-sulfide acyl-Claisen rearrangement



Key steps in the synthesis subsequent to the tandem acyl-Claisen rearrangement (Scheme 5) include reductive opening of a spirocycle, Ireland Claisen rearrangement, and formation of the tetrahydropyran moiety through an intramolecular carbonylative cyclization reaction. Synthesis of the macrolactone core was not achieved due to difficulties removing a benzyl protecting group; alteration of the protecting strategy should allow for facile completion of the total synthesis.

Scheme 5. Synthetic route subsequent to tandem acyl-Claisen rearrangement



IV. References

(1) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

(2) Seo, J.; Falsey, J. R.; Wiener, J. J. M.; MacMillan D. W. C., unpublished results.