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Acylammonium Salts as Dienophiles in Diels–Alder/Lactonization Organocascades

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Supporting Information

ABSTRACT: α,β-Unsaturated acylammonium salts, generated *in situ* from commodity acid chlorides and a chiral isothiourea organocatalyst, comprise a new and versatile family of chiral dienophiles for the venerable Diels–Alder (DA) cycloaddition. Their reactivity is unveiled through a highly diastereo- and enantioselective Diels–Alder/lactonization organocascade that generates *cis*- and *trans*-fused bicyclic γ- and δ-lactones bearing up to four contiguous stereocenters. Moreover, the first examples of DA-initiated, stereodivergent organocascades are described delivering complex scaffolds found in bioactive compounds. The origins of stereoselectivity are rationalized through computational studies. In addition, the utility of this methodology is demonstrated through a concise approach to the core structure of glaciolide and formal syntheses of fraxinellone, trisporic acids, and trisporols.

Transformations that rapidly generate complex and structurally diverse molecular architectures are essential components of modern organic chemistry.[1] In this regard, the Diels–Alder (DA) cycloaddition is arguably the most versatile and powerful transformation in chemical synthesis.[2] In particular, catalytic asymmetric DA reactions are unparalleled in their ability to rapidly and efficiently generate optically active, architecturally complex, and densely functionalized heterocycles and carbocycles from simple achiral substrates.[3] Furthermore, enantioselective organocatalytic DA variants have recently been established using iminium,[4] enamine,[5] bifunctional acid–base catalysis,[6] and hydrogen-bonding catalysis.[7] MacMillan and coworkers employed both α,β-unsaturated aldehydes[4a] and ketones[4b] in cycloadditions through iminium-activated chiral dienophiles, whereas α,β-unsaturated aldehydes[7b] and indolinones[7c] were activated through hydrogen-bonding catalysis by Rawal and Barbas, respectively. Surprisingly, however, simple acid chlorides have yet to be successfully employed in organocatalyzed DA reactions. Herein, we report the first enantioselective organocatalytic DA reactions with α,β-unsaturated acid chlorides activated *in situ* by a chiral isothiourea catalyst.

The potential of α,β-unsaturated acylammonium catalysis was first realized by Fu in asymmetric, net [3+2] annulations leading to diquinanes.[8a] Building on this early work, Smith recently employed mixed anhydrides as α,β-unsaturated acylammonium precursors for the direct synthesis of dihydropyranones and dihydropyridones.[8b] Furthermore, we demonstrated the full potential of chiral, triply reactive, α,β-unsaturated acylammonium salts for the rapid assembly of complex cyclopentanes[8c] and optically active γ-lactams and piperidones.[8d] Inspired by these studies, we sought to explore the reactivity of α,β-unsaturated acylammonium salts as dienophiles in DA reactions anticipating that these intermediates might emulate the electronic properties of activated dienophiles.

To test the reactivity of α,β-unsaturated acylammonium salts as dienophiles, we targeted the synthesis of *cis*- and *trans*-fused bicyclic γ- and δ-lactones which are ubiquitous structural motifs found in bioactive terpenoids and pharmaceuticals (Figure 1a).

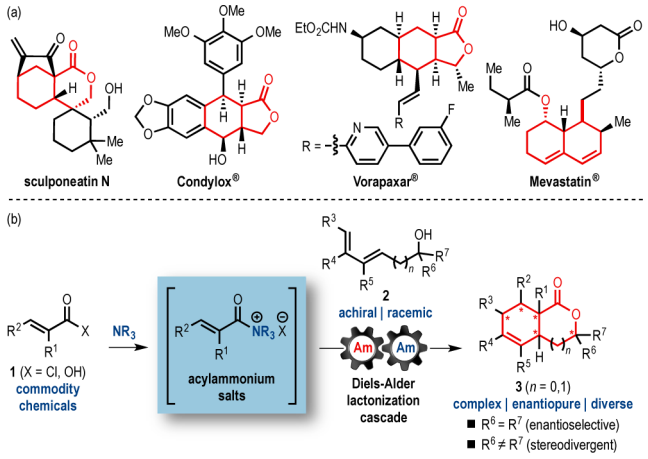

Figure 1. (a) Selected natural products and pharmaceuticals containing or derived from *cis*- or *trans*-fused bicyclic γ- or δ-lactones. (b) The described organocatalytic Diels–Alder/lactonization cascade sequence.

We envisioned that this bicyclic architecture could be constructed in a single operation by a Diels–Alder/lactonization (DAL) cascade between acylammonium salts, generated *in situ* from acid chlorides or carboxylic acids (activated *in situ*) **1**, a chiral tertiary amine organocatalyst, and rationally designed dienes **2** (Figure 1b). We recognized the potential for further stereochemical diversity if racemic dienes bearing a pendant carbinol, e.g., (±)-**2** ($R^6 \neq R^7$), could participate in an unprecedented DA-initiated, stereodivergent[9] organocascade. This process could proceed through catalyst

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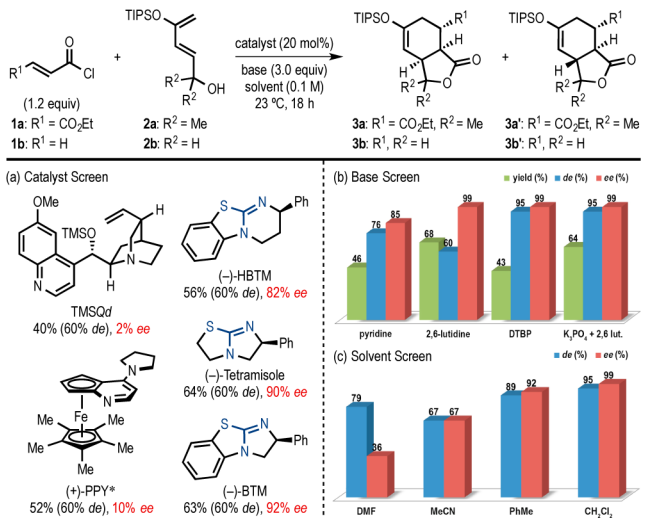
control during the DA step, independent of the resident stereocenter, and the subsequent lactonization step would generate diastereomeric lactones **3** with distinct topologies that could facilitate chromatographic separation, a common challenge for stereodivergent processes.

We initiated our studies of the DAL organocascade with a Danishefsky diene **2a** bearing a tethered tertiary alcohol to minimize competitive acylation while providing greater reactivity and synthetic versatility.[10] In the absence of a nucleophilic promoter, a significant background DAL proceeds with ethyl fumaroyl chloride (**1a**) to afford an inseparable mixture of *endo*/*exo* diastereomers of bicyclic γ-lactones **3a** and **3a′** in 21% yield (Supporting Information (SI), Table S1).

A catalyst screen revealed that chiral isothioureas[11] were superior (Table 1a) with best results obtained using

Table 1. Selected Optimization Studies of the DAL[a]

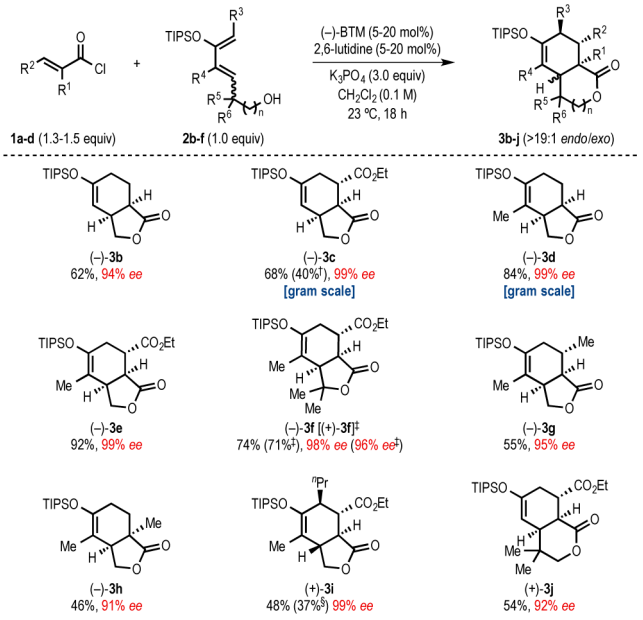


[a]Yields of isolated, purified products; *endo*/*exo* ratios determined by ^{1}H NMR analysis; ee determined by chiral-phase HPLC and only shown for *endo* diastereomer (see SI for details). Reaction conditions: (a) **1a**, **2a**, 2,6-lutidine, CH_2Cl_2; (b) **1b**, **2b**, (−)-BTM, CH_2Cl_2; (c) **1b**, **2b**, DTBP, (−)-BTM. DTBP = 2,6-*di*-*tert*-butylpyridine.

benzotetramisole, (−)-BTM.[11b] Extending addition times of **1a** through syringe pump addition ensured high enantioselectivity (Table S1, entries 9, 11) presumably by enabling the asymmetric DAL to compete effectively with the racemic background pathway. Further optimization studies revealed that *endo*/*exo* selectivity was highly dependent on the Brønsted base and also that pendant primary alcohols were tolerated. Thus, we next screened various Brønsted bases with diene **2b**, acid chloride **1b**, and (−)-BTM as catalyst (Table 1b). Generally, pyridine bases afforded superior levels of enantioselectivity (Table S2, entries 6−15), while substantial steric bulk adjacent to the pyridine nitrogen suppressed formation of the *exo* diastereomer with concomitant reduction in yield (Table S2, entry 8). Use of a shuttle base[12] was successful and delivered **3b** in 64% yield (95% de, 99% ee). Finally, a solvent screen revealed that chlorinated solvents provided the highest levels of diastereo- and enantioselectivity (Table 1c; Table S3, entries 8−10).

The scope of the DAL was studied under optimized conditions with dienes **2b−f** and commercially available acid chlorides **1a−d** possessing varying electronic and steric properties. Diastereoselectivities were consistent (>19:1 *endo*/*exo*), while enantioselectivities ranged from 91 to 99% ee (Scheme 1).

Scheme 1. Enantioselective DAL Organocascade[a]



[a]Yields refer to isolated, purified products; *endo*/*exo* ratios determined by ^{1}H NMR analysis; ee determined by chiral-phase HPLC. †(−)-BTM (10 mol%) was used. ‡(+)-BTM (20 mol%) was used. §(−)-BTM (5 mol%) was used.

Cis-fused bicyclic γ-lactones **3b−h** were readily obtained from (*E*)-dienes with both α- and β-substituted acid chlorides. Use of crotonoyl chloride (**1c**) and methacryloyl chloride (**1d**) led to less reactive acylammonium dienophiles, as reflected in reduced yields of cycloadducts (−)-**3g** and (−)-**3h**; however, enantioselectivity was maintained. Use of a (*Z*,*Z*)-configured diene **2e** produced the *trans*-fused bicyclic γ-lactone (+)-**3i** in 48% yield (99% ee) despite the unfavorable conformation that typically impedes effective cycloaddition.[13] Variation in tether length of the pendant alcohol as in diene **2f** (n = 1) afforded the bicyclic δ-lactone (+)-**3j** in 54% yield (92% ee). Use of the enantiomeric isothiourea catalyst, (+)-BTM, provided the enantiomeric lactone (+)-**3f** in 71% yield (96% ee). Lowered catalyst loadings of 10 and 5 mol% gave *cis*- and *trans*-fused bicyclic γ-lactones (−)-**3c** and (+)-**3i** with similar levels of enantioselectivity but diminished yields. In these cases, lower yields were due to decomposition of dienes and irreversible acylation of the tethered alcohol moiety leading to dienyl esters (e.g., see SI, p S21). The preparative utility of the DAL was demonstrated by two gram-scale reactions affording 1.4 g of (−)-**3c** (68% yield) and 4.0 g of (−)-**3d** (84% yield).

Given the terminal lactonization step, we reasoned that a stereodivergent resolution of a racemic diene possessing a pendant stereogenic carbinol using the DAL strategy would be feasible. Indeed, reaction of racemic diene (±)-**2g** bearing a pendant, secondary alcohol delivered readily separable fused, tricyclic γ-lactones (−)-**3k** (50% yield, 99% ee) and (−)-**3k′** in (35% yield, 99% ee) which are useful intermediates toward compactin[14] and forskolin.[15] The stereochemistry of (−)-**3k** and (−)-**3k′** was assigned by X-ray analysis; in the latter case following cleavage with 4-bromobenzylamine (Scheme 2a, insets; Figures S1 and S2).

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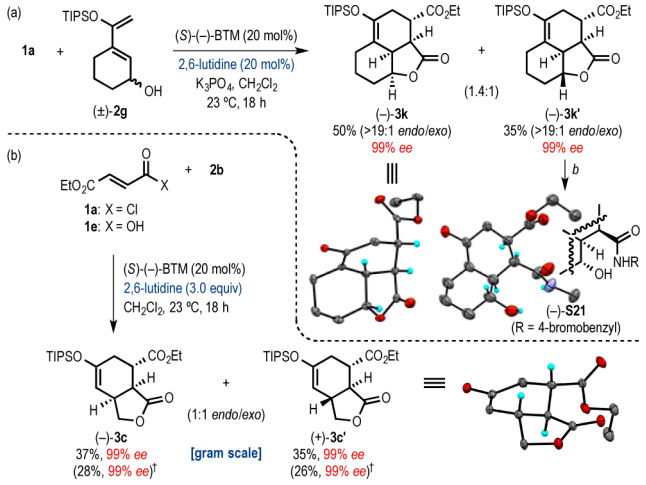
Scheme 2. Stereodivergent DAL Organocascades[a]

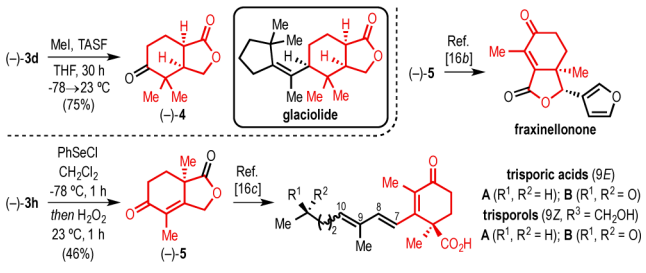


[a]Yields and ratios of isolated, purified products; ee determined by chiral-phase HPLC. Insets are single crystal X-ray structures in ORTEP format (50% probability; TIPS and 4-bromobenzyl groups are removed for clarity). Reaction conditions: 4-$BrC_6H_4CH_2NH_2$, THF, 23 °C, 36 h (73%). †Reaction performed with carboxylic acid **1e** activated *in situ* by TsCl (SI, p S35).

During optimization studies, we noted the profound impact of the Brønsted base on *endo*/*exo* selectivities, and sought access to *trans*-fused bicyclic lactones through judicious combination of a Lewis and Brønsted base to enhance *exo* selectivity. Indeed, use of 2,6-lutidine (3.0 equiv) with (−)-BTM and diene **2b** altered the *endo*/*exo* selectivity to furnish readily separable *cis*- and *trans*-fused bicyclic γ-lactones (−)-**3c** (37%, 99% ee) and (+)-**3c**′ (35%, 99% ee) (Scheme 1b). We cannot speculate regarding the origins of this Brønsted base dependence at this time, however we are investigating this phenomena further through both experimentation and computation. We also studied *in situ* activated carboxylic acids in this context, to expand the substrate repertoire of the DAL, and found that activation of *mono*-ethyl fumarate (**1e**) with TsCl afforded (−)-**3c** and (+)-**3c**′ with identical enantiopurity but slightly reduced yields. The absolute configuration of bicyclic γ-lactone (+)-**3c**′ was determined by X-ray anomalous dispersion (Figure S3). These data, in conjunction with detailed 2D NMR analysis and both predicted and calculated (*vide infra*) lowest energy transition states, enabled assignment of relative and absolute configurations of cycloadducts **3b**–**j**.

We next sought to demonstrate the utility of the enantioenriched lactones obtained through the DAL (Scheme 3). Bicyclic γ-lactone (−)-**3d** was converted to α,α-dimethyl-

Scheme 3. Synthetic Utility of Bicyclic γ-Lactones



lactone (−)-**4** corresponding to the core of glaciolide,[16a] a degraded and rearranged diterpenoid, via regioselective α-methylation. Direct α-selenylation of silyl enol ether (−)-**3h** followed by oxidative elimination delivered enone (−)-**5**, an intermediate previously employed as a racemate toward fraxinellonone,[16b] and the fungal pheromones, trisporic acids and trisporols.[16c]

To understand the origins of the enantio- and diastereoselectivity induced by (−)-BTM, all four possible transition state structures (TSSs) for the catalyzed DAL were compared to each other and to background DA cycloadditions proceeding directly with acid chloride. Analysis of the lowest energy conformations of each TSS indicates a kinetic preference (1–2 kcal/mol) for *endo* approach (Figure 2) and an even larger

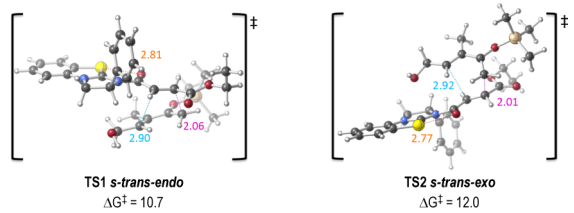
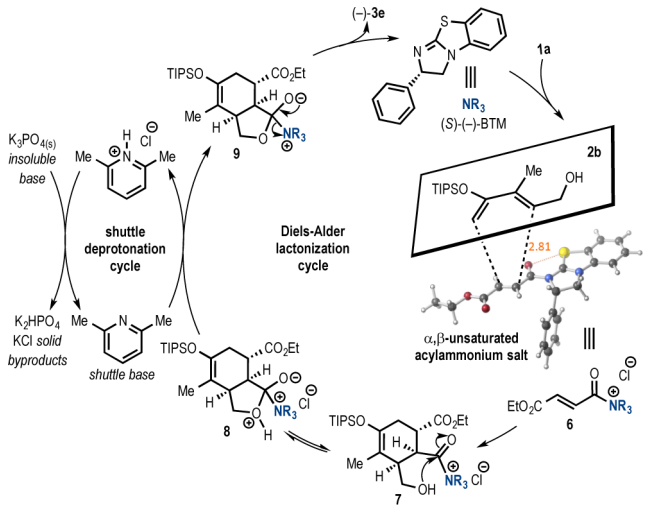


Figure 2. Calculated transition structures for the DA step of the DAL optimized at the M06-2X/6-31G(d) level with an implicit solvent model [SMD (dichloromethane)]. Gibbs free energies in kcal/mol shown are relative to the reactants. Selected bond distances are shown (Å).

preference (>5 kcal/mol) for approach of diene from the bottom face of the dienophile opposite the phenyl substituent of (−)-BTM, leading to the observed major enantiomer (SI, pp S49–S130).

This selectivity model is predicated on a preference for a close contact between the carbonyl oxygen and sulfur atom of the catalyst restricting rotation about the C–N bond of the acylammonium salt (see inset, Scheme 4). Such a preference is indeed found in isolation (2.81 Å) and in the TSSs (2.81 and 2.77 Å, *endo*/*exo*, respectively). The apparent S–O attraction for isothiourea catalysts[17] appears in this case to be driven by a combination of orbital interactions (probed with NBO; Figures S9 and S10), in particular, lone pair$_S$ ↔ $\sigma^*_{C-H}/\sigma_{C-H}$ interactions that disfavor the alternative conformation with a

Scheme 4. Postulated Reaction Pathway for the DAL



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O−C−N−C dihedral angle of 180°. Furthermore, the catalyzed DA reaction is predicted to have a lower activation barrier than the background reaction (Figures S5 and S6). A postulated reaction pathway is illustrated in Scheme 4. Reaction of acid chloride **1a** with (−)-BTM forms acylammonium salt **6** that undergoes endo-selective intermolecular DA with diene **2b** to form an initial, catalyst-bound cycloadduct **7**. The presumed tetrahedral intermediate **8** then enters a shuttle deprotonation cycle in which catalytic 2,6-lutidine relays its proton to stoichiometric K_3PO_4 and undergoes intramolecular lactonization to form **3e** and regenerate the catalyst.

In summary, we have unveiled a new and versatile family of chiral dienophiles, α,β-unsaturated acylammonium salts, that undergo enantioselective and stereodivergent DAL organocascades rapidly generating complex and stereochemically diverse scaffolds. This scalable process proceeds under mild conditions, provides excellent relative and absolute stereocontrol, and utilizes readily prepared dienes, commodity acid chlorides, and commercially available organocatalysts. A prominent feature of the described methodology is the use of a DA reaction to initiate an organocascade; a strategy with limited precedent.[18] The utility of the DAL was demonstrated by conversion of the derived bicyclic lactones to several core structures of natural products constituting formal syntheses in some cases. Computational results suggest kinetic preference for an *endo* TS with enantiocontrol ascribed to stereoelectronic and conformational preferences of the acylammonium salt dienophiles. Further applications and mechanistic investigations are underway to delineate the scope of this methodology.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and characterization details for all new compounds, computational data, crystallographic data, HPLC traces, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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