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. In this regard, the Diels–Alder (DA) cycloaddition is arguably the most versatile and powerful transformation in chemical synthesis. 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. Furthermore, enantioselective organocatalytic DA variants have recently been established using iminium, enamine, bifunctional acid–base catalysis, and hydrogen-bonding catalysis. MacMillan and co-workers employed both α,β-unsaturated aldehydes and ketones in cycloadditions through iminium-activated chiral dienophiles, whereas α,β-unsaturated aldehydes and indolones 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. Building on this early work, Smith recently employed mixed anhydrides as α,β-unsaturated acylammonium precursors for the direct synthesis of dihydropyrano[3,4-c]pyrroles and dihydropyridones. Furthermore, we demonstrated the full potential of chiral, triply reactive, α,β-unsaturated acylammonium salts for the rapid assembly of complex cyclopentanes and optically active γ-lactams and piperidones. 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 1).
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. 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 isothioureas11 were superior (Table 1a) with best results obtained using benzetramisole, (–)-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 Bronsted base and also that pendant primary alcohols were tolerated. Thus, we next screened various Bronsted 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 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 diastereoisos 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).

Table 1. Selected Optimization Studies of the DAL

| Catalyst | Base | TIPSO | Yield | De | Ee   |
|----------|------|-------|-------|----|------|
| (a) 1a   | Me   | R1 = H | 12%   | 99%| 99%  |
| (b) 2b   | 1b   | R1 = H | 20%   | 99%| 99%  |
| (c) 3b   | CHCl2 | Me     | 60%  | 99%| 99%  |

“Yields refer to isolated, purified products; endo/exo ratios determined by 1H 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, CH2Cl2; (b) 1b, (–)-BTM, CH2Cl2; (c) 1b, 2b, DTBP, (–)-BTM, CH2Cl2.

Cis-fused bicyclic γ-lactones 3b–h were readily obtained from (E)-diienes 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 cycloaducts (–)-3g and (–)-3h; however, enantioselctivity 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 enantioselctivity 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 carbinoil 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 compactin14 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).

Scheme 1. Enantioselective DAL Organocascade"
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-lactone (−)-4 corresponding to the core of glaciolide,16a a degraded and rearranged diterpenoid. 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 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 catalysts17 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 ↔ σ*C−H/σ*C−H interactions that disfavor the alternative conformation with a...
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 intramolecular 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 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 form a final, catalyst-bound cycloadduct 7.

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In summary, we have unveiled a new and versatile family of chiral dienophiles, α,β-unsaturated acylammonium salts, that undergo enantioselective and stereo-divergent 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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