

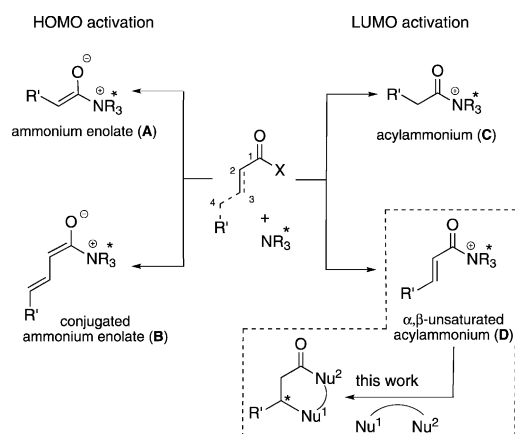
Direct Catalytic Asymmetric Synthesis of N-Heterocycles from Commodity Acid Chlorides by Employing α,β -Unsaturated Acylammonium Salts**

Sreekumar Vellalath, Khoi N. Van, and Daniel Romo*

Discovery of reactive intermediates through generic modes of substrate activation is central to the field of asymmetric organocatalysis. Methods for generating such intermediates in a catalytic asymmetric fashion have fueled the design of a variety of new and, in some cases, practical asymmetric transformations.^[1] Recently, there has been a significant expansion of the reactions that are catalyzed by chiral tertiary amines.^[2] Several activation modes employed in tertiary amine catalysis are shown in Scheme 1. Among these reactive

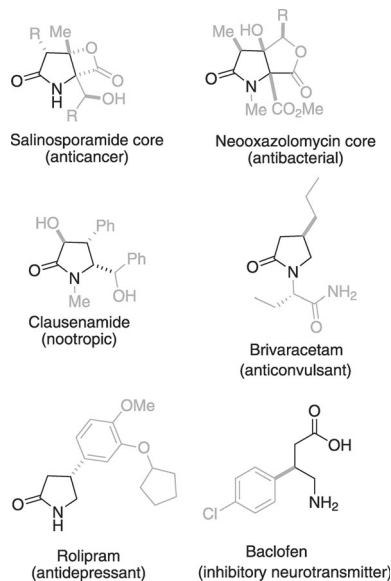
intermediates, chiral ammonium enolates (**A**)^[3,4] and acylammoniums (**C**)^[5] are the most commonly employed, whereas the conjugated ammonium enolate **B**^[6] was only recently described. However, an underexplored and versatile intermediate in this category is the chiral, α,β -unsaturated acylammonium **D**,^[7] which could deliver the ammonium enolate **A**, a versatile intermediate previously exploited by our group for aldol- β -lactonizations^[4] upon Michael addition. The potential of this chiral intermediate was first realized by Fu and co-workers, wherein a chiral pyridine promoter delivered a net [3+2] annulation of a silylated indene to afford diquinanes.^[8] Recently the Smith group utilized this intermediate in enantioselective Michael additions leading to enol lactones.^[9] Based on our interest in developing expedient routes to pyrrolidinone subunits,^[4c] we envisioned that a suitable Michael donor bearing a pendant amine, for example α - or β -aminomalonates, could serve as a bis-nucleophile to undergo an enantioselective nucleophile-catalyzed Michael/proton transfer/lactamization (NCMPL) cascade with the α,β -unsaturated acylammonium **D**. Herein, we describe the first highly enantioselective version of this cascade process with commodity acid chlorides using readily available *O*-trimethylsilylquinidine (TMSQD), thus leading to various optically active nitrogen heterocycles. We further demonstrate the utility and practicality of this organocascade process by application to a concise, scalable synthesis of a key pyroglutamic acid intermediate for an FDA-approved drug and its broader use for the syntheses of piperidinones, enol lactones, and dihydropyridones.

Pyrrolidinones or γ -lactams are frequently encountered structural subunits in numerous bioactive natural products and pharmaceuticals (Scheme 2). Examples of bioactive agents include the nanomolar inhibitor of the proteasome, salinosporamide **A**,^[10] and the antibacterial and antitumor agent neooxazolomycin.^[11] While clausenamide is used for the treatment of chronic viral hepatitis,^[12] brivaracetam^[13] and rolipram^[14] have utility for the treatment of depression and



Scheme 1. Generic modes of activation commonly used in chiral tertiary amine catalysis.

intermediates, chiral ammonium enolates (**A**)^[3,4] and acylammoniums (**C**)^[5] are the most commonly employed, whereas the conjugated ammonium enolate **B**^[6] was only recently described. However, an underexplored and versatile intermediate in this category is the chiral, α,β -unsaturated acylammonium **D**,^[7] which could deliver the ammonium enolate **A**, a versatile intermediate previously exploited by our group for aldol- β -lactonizations^[4] upon Michael addition. The potential of this chiral intermediate was first realized by Fu and co-workers, wherein a chiral pyridine promoter delivered a net [3+2] annulation of a silylated indene to



Scheme 2. Examples of pyrrolidinone-bearing and pyrrolidinone-derived natural products and drugs.

[*] Dr. S. Vellalath, K. N. Van, Prof. Dr. D. Romo
Department of Chemistry, Texas A&M University
P.O. Box 30012, College Station, TX 77842 (USA)
E-mail: romo@tamu.edu

[**] This work was supported by NSF (CHE-1112397) and the Welch Foundation (A-1280).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201306050>.

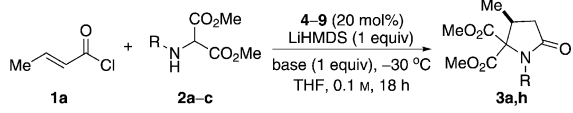
epileptic seizures, respectively. Additionally, baclofen is an inhibitory neurotransmitter and an antispastic agent.^[15] β -Substituted pyrrolidinone derivatives have been utilized for the synthesis of pyroglutamic acids^[16] and proline derivatives,^[17] with the latter used widely in organocatalysis.^[1a]

Arguably, a Michael/lactamization process involving α,β -unsaturated acid chlorides with α -aminomalonates is one of the most direct methods for the synthesis of pyrrolidinones. However, to date, only achiral promoters for this reaction have been utilized leading to racemic adducts.^[18] Until recently, most methods for the enantioselective synthesis of β -substituted pyrrolidinones were based on chiral starting materials or stoichiometric reagents.^[19] An important advancement in this area was described by Taylor and Jacobsen wherein an enantioselective Michael reaction of an unsaturated acyclic imide was catalyzed by a chiral Lewis acid.^[20] N-heterocyclic carbene (NHC) homoenolates^[21] have also been utilized for the synthesis of pyrrolidinones. Recently, Scheidt and co-workers reported the coupling of N-benzoyl hydrazones and unsaturated aldehydes, mediated by NHC/Lewis acid cooperative catalysis, thus leading to cis- γ -lactams.^[22] Rovis and co-workers reported a similar process, but using a NHC/Brønsted acid combination, for the synthesis of trans- γ -lactams.^[23] Given the importance of pyrrolidinone-containing compounds and catalytic asymmetric routes to these intermediates,^[24] we sought to develop a highly practical and scalable method for their synthesis from commodity acid chlorides employing a NCMPPL process.

We began our studies of the NCMPPL with crotonyl chloride (**1a**) as a Michael acceptor and N-benzoyl dimethyl aminomalonate (**2a**) as a bis-nucleophilic Michael donor. LiHMDS was used to form the anion from **2a** and several chiral tertiary amines were screened for in situ generation of the corresponding chiral unsaturated acylammonium (see **D** in Scheme 1). Initial exploration of reaction conditions revealed the importance of DBU as an acid scavenger and under these reaction conditions, use of *O*-trimethylsilylquinine (TMSQN; **4**) delivered the pyrrolidinone **3h** in 74% yield and 85% *ee* (Table 1, entry 1). The absence of DBU or substitution of DBU with Hünig's base returned only trace amounts of the desired product (entries 2 and 3). We next studied the *O*-benzoylquinine **5** and commercially available (DHQ)₂PHAL (**6**), however neither showed improvement in enantioselectivity (entries 4 and 5). Readily available TMSQD (**7**) marginally improved the enantioselectivity to 87% *ee* and delivered **3h** in 74% yield (entry 6). Use of chiral isothiourea catalysts, including BTM (**8**) and HBTM (**9**), gave lower enantioselectivities (entries 7 and 8). We next briefly studied the effect of nitrogen substituents on the reactivity of **2**. The N-Boc aminomalonate **2b** furnished the desired product in only trace amounts (entry 9). However, the use of the N-tosyl aminomalonate **2c** and **7** afforded the desired pyrrolidinone **3a** in 73% yield and 93% *ee* (entry 10). The use of 5 mol% **7** also provided **3a** with the same level of enantioselectivity (93% *ee*) and only slightly diminished yield (65%, entry 11).

With the optimized reaction conditions in hand for this process, we studied several β -substituted acid chlorides and found that β -aryl, β -alkyl, β -alkenyl, and β -carbonyl unsatu-

Table 1: Screening of catalysts and reaction conditions for the NCMPPL.



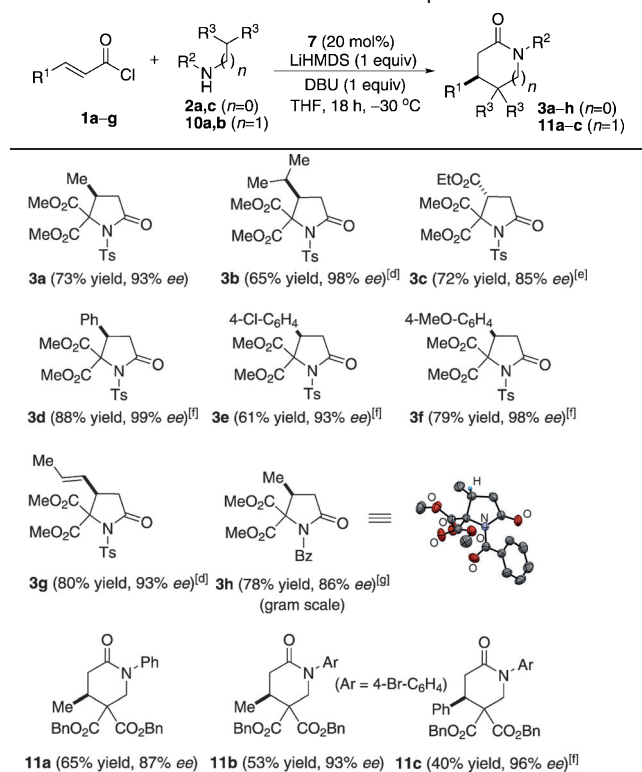
Entry ^[a]	Base	Cat.	R	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	DBU	4	Bz (2a)	74	85
2	—	4	Bz (2a)	< 5	n.d.
3	DIPEA	4	Bz (2a)	< 5	n.d.
4	DBU	5	Bz (2a)	71	84
5	DBU	6	Bz (2a)	70	85
6	DBU	7	Bz (2a)	74	87
7	DBU	8	Bz (2a)	62	23
8	DBU	9	Bz (2a)	67	40
9	DBU	7	Boc (2b)	< 5	n.d.
10	DBU	7	Ts (2c)	73	93
11 ^[d]	DBU	7	Ts (2c)	65	93

[a] The reactions were performed with 1 equiv of **2** and 1.5 equiv of **1a** and the latter was added over 5 h.^[26] [b] Yields of isolated, purified product. [c] Determined by HPLC analysis using a chiral stationary phase; entries 1, 4, 5, and 8 gave enantiomeric pyrrolidinone **3h**. [d] 5 mol% of **7** was employed as catalyst. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N,N*-Diisopropylethylamine (Hünig's base), LiHMDS = lithium bis(trimethylsilyl)amide, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

rated acid chlorides are well tolerated in the reaction and lead to pyrrolidinone derivatives in 61–88% yield and 85–99% *ee* (Table 2). In the case of ethyl fumaroyl chloride (**2c**) delivering the pyrrolidinone **3c**, the combination of **6** and Hünig's base provided superior results to those obtained with **7** and DBU, which presumably leads to product racemization. In the case of the β -aryl acid chlorides **1d–f**, the electronic properties of the arene substituents had little influence on the enantioselectivity, thus leading to the pyrrolidinones **3d–f** with 93–99% *ee*. β -Propenyl acid chloride (**1g**) led to **3g** in 80% yield and 93% *ee*. To demonstrate the practicality of the process, a gram-scale reaction was performed with **1a** and **2a** to afford crystalline **3h** in 78% yield and 86% *ee*.

We also explored β -aminomalonates (**10**) as bis-nucleophiles in the NCMPPL to access chiral piperidin-2-ones (**11**; Table 2). Following a brief screening of reaction conditions, *N*-phenyl- β -aminomalonate (**10a**) participated in a NCMPPL with **1a** to deliver the piperidinone **11a** in 65% yield and 87% *ee*. An electron-deficient *N*-aryl substituent (Ar = 4-Br-C₆H₄) led to improved enantioselectivity (93% *ee*) but a reduced yield (53%) for the piperidinone **11b** from **1a**, whereas cinnamoyl chloride (**1d**) gave 40% yield of the

Table 2: NCMP of acid chlorides with α - and β -aminomalonates.^[a–c]

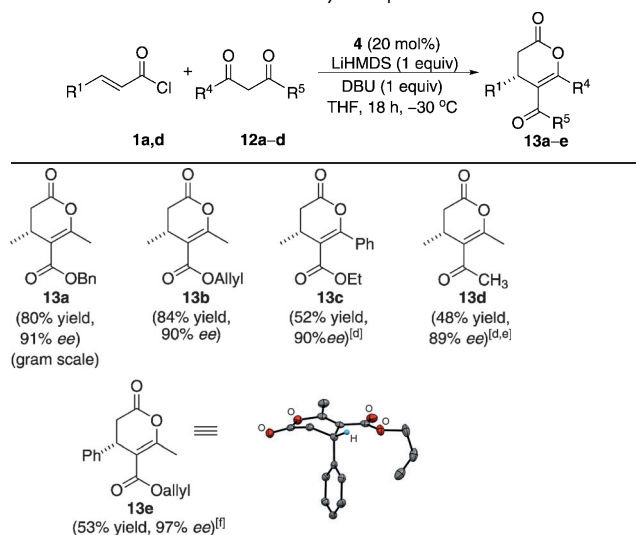


[a] Reactions were performed with 1 equiv of **2** or **10** and 1.5 equiv of **1** with the latter added over 5 h (syringe pump). [b] Yields refer to purified, isolated product. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d] This reaction was performed with 2.0 equiv of **1** and conducted at $-10\text{ }^{\circ}\text{C}$. [e] **6** and Hünig's base were used for this substrate. [f] This reaction was performed with 2.0 equiv of **1** and conducted at $-15\text{ }^{\circ}\text{C}$. [g] Inset is the ORTEP representation of the single-crystal X-ray structure of **3h**; thermal ellipsoids shown at 50% probability.^[26]

piperidinone **11c** in 96% ee. A common problem leading to reduced yields when employing β -aminomalonates as bis-nucleophiles was their degradation through a retro-aza Michael reaction. However, the simplicity of the procedure and utility of piperidin-2-ones with β -stereogenic centers, given their stimulant or depressant action on the central nervous system,^[25] make this an attractive and practical strategy to chiral β -substituted piperidin-2-ones.

Toward expanding the breadth of this strategy for heterocycle synthesis, we explored the use of 1,3-dicarbonyl compounds as bis-nucleophiles to give enol lactones (**13**; Table 3), an important structural unit of the neoflavonoid, coumarin, and iridoide^[27] family of natural products. While our studies were in progress, Smith and co-workers reported a related strategy to access aryl-substituted enol lactones by employing aryl-substituted 1,3-dicarbonyl compounds and dimeric β -aryl acid anhydrides, which are prepared from the corresponding acids.^[9] Furthermore, catalytic enol lactone synthesis has recently been investigated in some detail and been spurred on by the development of conjugated acylazolium intermediates, described independently by the groups of Lupton, Bode, and Studer.^[28] We thus sought to extend the NCMP to enol

Table 3: Nucleophile-catalyzed, Michael/proton transfer/enol lactonization of acid chlorides with dicarbonyl compounds.^[a–c]

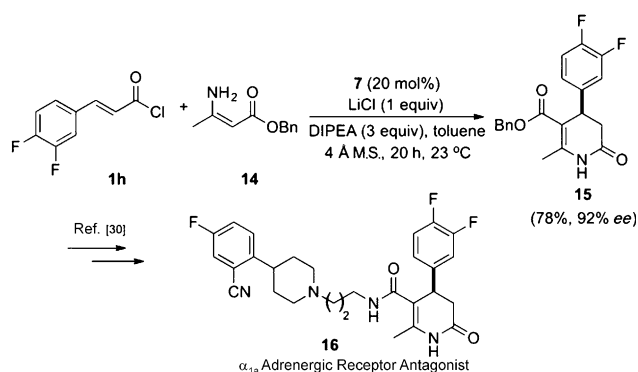


[a] The reactions were performed with 1 equiv of **12** and 1.5 equiv of **1** with the latter added over 2 h (syringe pump). [b] Yields refer to purified, isolated product. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d] **6** was used as catalyst. [e] The reaction was conducted at $0\text{ }^{\circ}\text{C}$. [f] Inset is the ORTEP representation of the single crystal X-ray structure of **13e**; thermal ellipsoids shown at 50% probability.^[26]

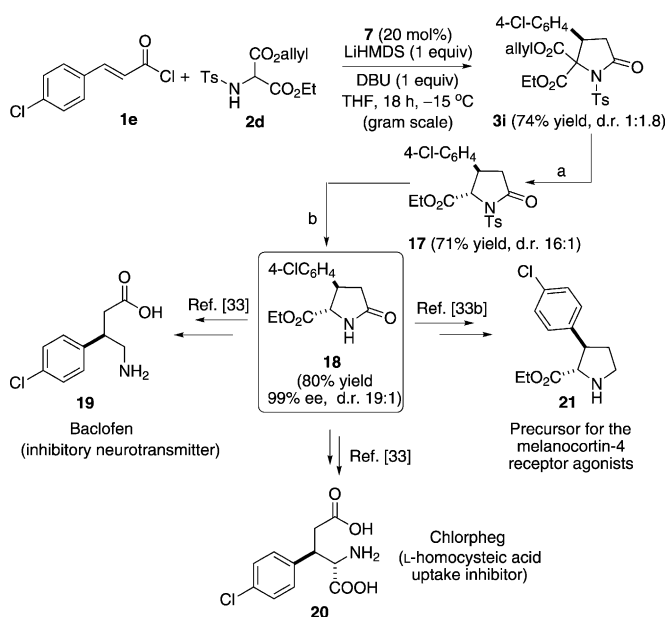
lactone synthesis, with an important feature being the use of commercially available acid chlorides. A minor alteration to our original NCMP procedure^[26] resulted in a highly enantioselective process with **1a** and benzyl acetoacetate (**12a**) using **4** as the optimal nucleophilic promoter. Under these reaction conditions, the enol lactone **13a** was obtained in 80% yield and 91% ee on a gram scale. The cascade process was also applied to allyl acetoacetate (**12b**) with **1a** and **1d**, thus delivering the enol lactones **13b** (90% ee) and **13e** (97% ee), respectively. Both an aryl- β -ketoester (**12c**) and a diketone (**12d**), participated in this process, thus providing the enol lactones **13c** (90% ee) and **13d** (89% ee), respectively, with **6** as the optimal catalyst for these substrates. This approach provides a complimentary strategy to that recently reported by Smith^[9] for enol lactone synthesis.

Another class of nitrogen heterocycles that could be accessed by this cascade process are dihydropyridinones,^[29] and their presence in several drug candidates encouraged us to apply the NCMP to these targets. After brief optimization,^[26] **7** was found to catalyze an enantioselective NCMP process between 3,4-difluorocinnamoyl chloride (**1h**) and the enamine **14** (Scheme 3). The key to success of this reaction was the use of a nonpolar solvent and LiCl as an additive, which had a profound effect on enantioselectivity (see below). This mild process delivered the dihydropyridinone **15** in 78% yield and 92% ee. This particular dihydropyridinone was targeted since it has recently been used in the synthesis of the α_{1a} adrenergic receptor antagonist **16**.^[30]

To further demonstrate the synthetic utility and practicality of this cascade process to access useful drug intermediates, we targeted a gram-scale synthesis of the pyrrolidinone

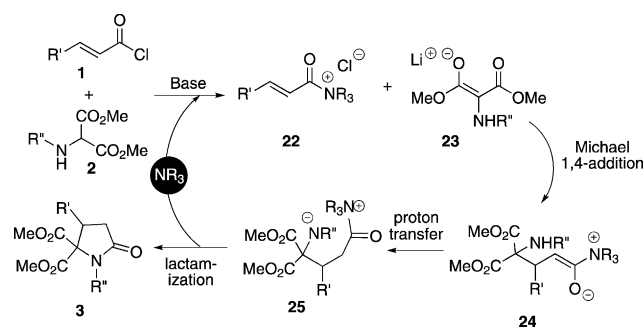


Scheme 3. Formal synthesis of the α_{1a} adrenergic receptor antagonist **16**. M.S. = molecular sieves.



Scheme 4. Reagents and conditions: a) $[\text{Pd}_2(\text{dba})_3]\cdot\text{CHCl}_3$ (10 mol%), PPh_3 (5 mol%), HCOONH_4 (2.0 equiv), 90°C , CH_3CN , 2 h; b) SmI_2 , Et_3N , $\text{H}_2\text{O}/\text{THF}$ (3:1), 23°C , 5 min. dba = dibenzylideneacetone.

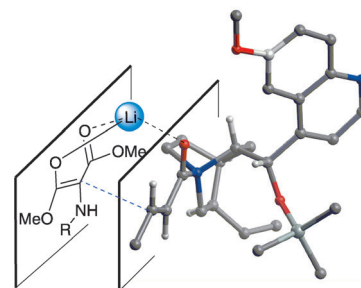
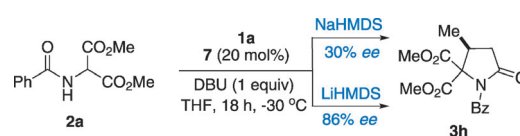
3i (Scheme 4). We also sought to demonstrate a method for removal of one of the carbonyl groups, which is required for the Michael addition process, to afford a soft nucleophile. By employing **2d** and **1e** with **7** under standard NCMLP conditions, a 74% yield of pyrrolidinone **3i**, as an inconsequential mixture of diastereomers (d.r. 1:1.8), was achieved. Submitting this adduct to the decarboxylation/protonation conditions described by Tsuji and co-workers^[31] afforded the N-tosyl-protected pyroglutamic acid **17** in 71% yield (d.r. 16:1). Subsequent removal of the tosyl group with $\text{SmI}_2/\text{H}_2\text{O}/\text{Et}_3\text{N}$ ^[32] afforded the pyroglutamic acid derivative **18** in 80% yield. The enantioselectivity of the initial Michael addition could now be determined at this stage to be 99% ee (d.r. 19:1). The ester **18** is a known and versatile advanced intermediate^[33] in the synthesis of the inhibitory neurotransmitter baclofen (**19**), L-homocysteic acid uptake inhibitor chlorphleg (**20**), and the melanocortin-4 receptor (MC4R) agonist **21**.^[34]



Scheme 5. Postulated catalytic cycle for the NCMLP process.

A tentative catalytic cycle for the NCMLP process is shown in Scheme 5. The lithiated enolate **23** first participates in a conjugate addition to the acylammonium species **22**, derived from reaction of the chiral tertiary amine (NR_3) with the acid chloride **1**. Following an intra- or intermolecular proton transfer,^[35] the acylammonium **25** undergoes intramolecular lactamization to release the tertiary amine catalyst NR_3 . We postulate that this reaction is under kinetic control given the high degree of enantioselectivity and related examples of reactions delivering high facial selectivity through 1,4-asymmetric induction.^[36]

To gain some insight into the role of the in situ formed lithium chloride and the beneficial effect of added LiCl on enantioselectivity, we conducted the NCMLP with NaHMDS as the base (Scheme 6). As anticipated, the reaction of **1a** and



Scheme 6. NCMLP reactions employing different in situ generated Lewis acids and proposed transition state arrangements showing possible role of Lewis acid (Li^+) in the NCMLP.

2a afforded **3h** with substantially reduced enantioselectivity, thus providing evidence for the important role played by the lithium cation in the transition-state arrangement. Based on our results and previously described computational studies of ammonium enolates by Lectka and co-workers,^[37] we propose the transition-state arrangement depicted in Scheme 6 for the NCMLP process leading to pyrrolidinones. Coordination of both the enolate oxygen atom and the acylammonium carbonyl oxygen atom to the lithium cation occurs on the

face of the unsaturated acylammonium opposite to the bulky OTMS and quinoline groups. This effectively blocks the *Re* face of the acylammonium and rationalizes the observed absolute stereochemistry of the pyrrolidinone products.

In summary, we have developed the first direct catalytic asymmetric synthesis of pyrrolidinones from commodity acid chlorides utilizing α,β -unsaturated acylammoniums. Importantly, formation of these intermediates clearly imparts high facial selectivity and modulates the reactivity of acid chlorides, thus biasing them toward Michael (1,4) addition versus acyl (1,2) substitution. The described methodology is operationally simple, scalable, and can be carried out using inexpensive and readily available catalysts under mild reaction conditions. We demonstrated the utility of this strategy by applications to biologically relevant N-heterocycles including pyrrolidinones, piperidin-2-ones, and dihydropyridones. Furthermore, the synthetic utility of this methodology was demonstrated by a three-step synthesis of a pyroglutamic acid ester which was previously utilized in the preparation of bioactive pyroglutamic acid derivatives. Given the ready availability of unsaturated acid chlorides (Sigma–Aldrich lists 13 and MatrixScientific lists 37 unsaturated acid chlorides) and the cinchona alkaloid catalysts^[4b] used in the NCMP, we anticipate further applications of this methodology.

Received: July 12, 2013

Published online: October 31, 2013

Keywords: enols · heterocycles · natural products · organocatalysis · synthetic methods

- [1] a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; d) C. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; e) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320–332; *Angew. Chem. Int. Ed.* **2012**, *51*, 314–325.
- [2] S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012.
- [3] a) D. Borrmann, R. Wegler, *Chem. Ber.* **1967**, *100*, 1575–1579; b) H. Wynberg, E. G. H. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166–168; c) M. A. Calter, *J. Org. Chem.* **1996**, *61*, 8006–8007; d) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832; e) G. S. Cortez, R. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945–7946; f) C. Zhu, X. Shen, S. A. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352–5353; g) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518–6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360; h) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2011**, *133*, 2714–2720; For a review, see: i) M. J. Gaunt, C. C. C. Johansson, *Chem. Rev.* **2007**, *107*, 5596–5605.
- [4] a) C. A. Leverett, V. C. Purohit, D. Romo, *Angew. Chem.* **2010**, *122*, 9669–9673; *Angew. Chem. Int. Ed.* **2010**, *49*, 9479–9483; b) H. Nguyen, S. Oh, S. H. Henry-Riyad, D. Sepulveda, D. Romo, *Org. Synth.* **2011**, *88*, 121–137; c) H. Nguyen, G. Ma, T. Fremgen, T. Gladysheva, D. Romo, *J. Org. Chem.* **2011**, *76*, 2–12; d) G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin, D. Romo, *Nat. Chem.* **2013**, DOI: 10.1038/NCHEM.1788.
- [5] a) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810; b) J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 7230–7231; c) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.* **1998**, *120*, 1629–1630; d) V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227; e) C. Joannesse, C. P. Johnston, C. Concellón, C. Simal, D. Philp, A. D. Smith, *Angew. Chem.* **2009**, *121*, 9076–9080; *Angew. Chem. Int. Ed.* **2009**, *48*, 8914–8918; For a review, see: f) C. E. Müller, P. R. Schreiner, *Angew. Chem.* **2011**, *123*, 6136–6167; *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042.
- [6] a) P. S. Tiseni, R. Peters, *Angew. Chem.* **2007**, *119*, 5419–5422; *Angew. Chem. Int. Ed.* **2007**, *46*, 5325–5328; b) P. S. Tiseni, R. Peters, *Chem. Eur. J.* **2010**, *16*, 2503–2517; c) L.-T. Shen, L.-H. Sun, S. Ye, *J. Am. Chem. Soc.* **2011**, *133*, 15894–15897.
- [7] For reports of achiral α,β -unsaturated acylammoniums, see: a) K. Kato, Y. Shizuri, Y. Hirataa, S. Yamamura, *Chem. Commun.* **1968**, 324–325; b) L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 1717–1719.
- [8] E. Bappert, P. Müller, G. C. Fu, *Chem. Commun.* **2006**, 2604–2606.
- [9] E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin, A. D. Smith, *Chem. Sci.* **2013**, *4*, 2193–2200.
- [10] T. A. Gulder, B. S. Moore, *Angew. Chem.* **2010**, *122*, 9534–9556; *Angew. Chem. Int. Ed.* **2010**, *49*, 9346–9367.
- [11] a) T. Mori, K. Takahashi, M. Kashiwabara, D. Uemura, *Tetrahedron Lett.* **1985**, *26*, 1073–1076; b) K. Takahashi, M. Kawabata, D. Uemura, *Tetrahedron Lett.* **1985**, *26*, 1077–1078.
- [12] N. Ning, J. Sun, G. Du, N. Han, J. Zhang, N. Chen, *Neurosci. Lett.* **2012**, *523*, 99–103.
- [13] M. A. Rogawski, *Br. J. Pharmacol.* **2008**, *154*, 1555–1557.
- [14] M. Anada, O. Mita, H. Watanabe, S. Kitagaki, S. Hashimoto, *Synlett* **1999**, 1775–1777.
- [15] J.-M. Becht, O. Meyer, G. Helmchen, *Synthesis* **2003**, 2805–2810.
- [16] C. Nájera, M. Yus, *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
- [17] P. Haldar, J. K. Ray, *Tetrahedron Lett.* **2003**, *44*, 8229–8231.
- [18] M. Ghosh, G. K. Kar, J. K. Ray, B. G. Chatterjee, *Synth. Commun.* **1983**, *13*, 667–675.
- [19] a) W. Hartwig, L. Born, *J. Org. Chem.* **1987**, *52*, 4352–4358; b) J. Ezquerra, C. Pedregal, I. Merino, J. Florez, J. Barluenga, S. Garcia-Granda, M. A. Llorca, *J. Org. Chem.* **1999**, *64*, 6554–6565; c) C. H. Yoon, D. L. Flanagan, B.-D. Chong, K. W. Jung, *J. Org. Chem.* **2002**, *67*, 6582–6584; d) M. Oba, N. Nishiyama, K. Nishiyama, *Chem. Commun.* **2003**, 776–777; e) V. A. Soloshonok, H. Ueki, R. Tiwari, *J. Org. Chem.* **2004**, *69*, 4984–4990; f) M. K. Ghorai, D. P. Tiwari, *J. Org. Chem.* **2010**, *75*, 6173–6181.
- [20] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205.
- [21] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331–6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205–6208; b) K. Y. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127; c) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905–908.
- [22] D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766–771.
- [23] X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466–12469.
- [24] a) For metal-catalyzed conjugate addition of boronic acids to α,β -unsaturated γ -lactams, see: C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2011**, *13*, 788–791; b) for intramolecular cyclizations, see: W. Xu, A. Kong, X. Lu, *J. Org. Chem.* **2006**, *71*, 3854–3858; c) X. Bantreil, G. Prestat, A. Moreno, D. Madec, P. Fristrup, P.-O. Norrby, P. S. Pregosin, G. Poli, *Chem. Eur. J.* **2011**, *17*, 2885–2896; d) N. Armanino, E. M. Carreira, *J. Am. Chem. Soc.* **2013**, *135*, 6814–6817.
- [25] L. M. Jackman, R. L. Webb, H. C. Yick, *J. Org. Chem.* **1982**, *47*, 1824–1831.

- [26] See the Supporting Information for full details. CCDC 927700 (**3h**) and CCDC 927701 (**13e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [27] a) F. Geu-Flores, N. H. Sherden, V. Courdavault, V. Burla, W. S. Glenn, C. Wu, E. Nims, Y. Cui, S. E. O'Connor, *Nature* **2012**, *492*, 138–142; b) M. S. Islam, K. Ishigami, H. Watanabe, *Tetrahedron* **2007**, *63*, 1074–1079; c) T. E. Prisinzano, *J. Nat. Prod.* **2009**, *72*, 581–587.
- [28] a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177; b) J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810–8812; c) S. De Sarkar, A. Studer, *Angew. Chem.* **2010**, *122*, 9452–9455; *Angew. Chem. Int. Ed.* **2010**, *49*, 9266–9269; d) Z. Q. Zhu, X.-L. Zheng, N.-F. Jiang, X. Wan, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 8670–8672; e) Z.-Q. Rong, M.-Q. Jia, S.-L. You, *Org. Lett.* **2011**, *13*, 4080–4083; f) F.-G. Sun, L.-H. Sun, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 3134–3138.
- [29] a) B. Wanner, J. Mahatthananchai, J. W. Bode, *Org. Lett.* **2011**, *13*, 5378–5381; b) S. R. Yetra, A. Bhunia, A. Patra, M. V. Mane, K. Vanka, A. T. Biju, *Adv. Synth. Catal.* **2013**, *355*, 1089–1097.
- [30] P. G. Nantermet, J. C. Barrow, H. G. Selnick, C. F. Homnick, R. M. Freidinger, R. S. L. Chang, S. S. O'Malley, D. R. Reiss, T. P. Broten, R. W. Ransom, D. J. Pettibone, T. Olah, C. Forray, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1625–1628.
- [31] J. Tsuji, T. Yamaeawa, *Tetrahedron Lett.* **1979**, *20*, 613–616.
- [32] T. Ankner, G. Hilmersson, *Org. Lett.* **2009**, *11*, 503–506.
- [33] a) M.-Y. Chang, P.-P. Sun, S.-T. Chena, N.-C. Chang, *Tetrahedron Lett.* **2003**, *44*, 5271–5273; b) M. Oba, T. Saegusa, N. Nishiyama, K. Nishiyama, *Tetrahedron Lett.* **2009**, *65*, 128–133.
- [34] J. A. Tran, F. C. Tucci, M. Arellano, W. Jiang, C. W. Chen, D. Marinkovic, B. A. Fleck, J. Wen, A. C. Foster, C. Chen, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1931–1938.
- [35] Use of a perdeuterated bis-nucleophile did not lead to significant deuterium incorporation of the intermediate ammonium enolate **24**, thus suggesting that the proton transfer is not exclusively intramolecular.
- [36] S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716.
- [37] a) S. France, H. Wack, A. E. Taggi, A. M. Hafez, T. R. Wagerle, M. H. Shah, C. L. Dusich, T. Lectka, *J. Am. Chem. Soc.* **2004**, *126*, 4245–4255; b) C. Dogo-Isonagie, T. Bekele, S. France, J. Wolfer, A. Weatherwax, A. E. Taggi, D. H. Paull, T. Dudding, T. Lectka, *Eur. J. Org. Chem.* **2007**, 1091–1100.