OL Organic Letters

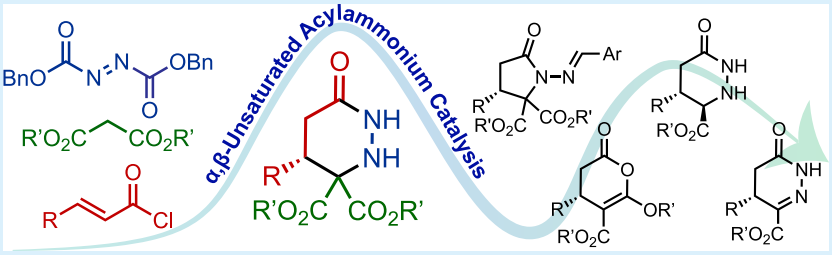
pubs.acs.org/OrgLett Letter

Multicomponent Enantioselective Synthesis of Tetrahydropyridazinones Employing Chiral α,β-Unsaturated Acylammonium Salts

Sigrid A. Kiledal, Roxane Jourdain, Sreekumar Vellalath, and Daniel Romo*

Cite This: *Org. Lett.* 2021, 23, 6622–6627 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: An enantioselective three-component reaction was developed for the synthesis of tetrahydropyridazinones employing chiral α,β-unsaturated acylammonium salts, malonates, and azodicarboxylates. An initial α-amination of a malonate with an azodicarboxylate and a subsequent chiral Lewis-base-catalyzed Michael/proton transfer/lactamization process delivered optically active tetrahydropyridazinones (up to 99:1 er). Subsequent transformations of these adducts were explored, revealing some unexpected rearrangements, and the use of an allyl methyl malonate enabled a subsequent deallylative decarboxylation and the introduction of a second stereocenter.

Multicomponent reactions (MCRs) are defined as reactions involving three or more substrates combined into a one-pot transformation. In an ideal case, the majority, if not all, of the atoms of the starting materials should be incorporated into the product.[1] There are many advantages to MCRs over traditional multistep, sequential approaches, namely, the ability to build complex structures in a single pot, which significantly increases the reaction efficiency with regard to purification, labor, and cost of materials.[1] MCR strategies provide access to high chemical diversity, enabling the rapid development of compound libraries for the pharmaceutical and agrochemical industries.[1−3] Indeed, MCRs have been used since the advent of modern organic synthesis, with an initial revolutionary MCR being the Ugi four-component condensation.[4] First reported in 1959, this MCR subsequently led to the convergent synthesis of penicillin.[5] The first enantioselective three-component MCR process involving azodicarboxylates was reported in 2003 by Barbas and coworkers entailed a sequential α-amination/aldol process.[6] The use of ketones and aldehydes is ubiquitous in such strategies through the use of enamine catalysis.[7] However, MCRs using tertiary amine, Lewis base catalysts remain rare.[1]

Chiral α,β-unsaturated acylammonium salts have recently been recognized as useful intermediates for complexity-generating reactions.[8,9] First documented by Yamamura and coworkers in the 1960s,[10] these salts did not begin to be widely used in organocatalysis until 2006, when Fu and coworkers published the use of acylammonium salts for asymmetric [3 + 2] annulations.[11] Since that time, several groups, including those of Smith,[12] Matsubara,[13] Birman,[14] Lupton[15] and ours,[16−20] have greatly expanded the utility of these versatile intermediates for enantioselective organocascade processes primarily employing chiral isothiourea catalysts developed by Birman and Smith.[12,21,22,23] We previously described a three-component MCR process for the synthesis of complex β-lactones through a Michael/Michael/aldol/β-lactonization (MMAL) sequence.[18] Furthermore, we developed an enantioselective nucleophile (Lewis base)-catalyzed Michael addition/proton transfer/lactamization organocascade reaction for the synthesis of five- to eight-membered lactams.[16,17] Building on these precedents, we set out to study the synthesis of optically active tetrahydropyridazinones through acylammonium salt intermediates. Previously, these heterocycles have been synthesized via *N*-alkylation or reductive amination with hydrazine derivatives followed by intramolecular acylation (Figure 1a).[24,25] Among these methods, only a few employ MCRs,[25] and generally, these strategies do not lend themselves

Received: June 17, 2021
Published: August 26, 2021

https://doi.org/10.1021/acs.orglett.1c02044
Org. Lett. 2021, 23, 6622–6627

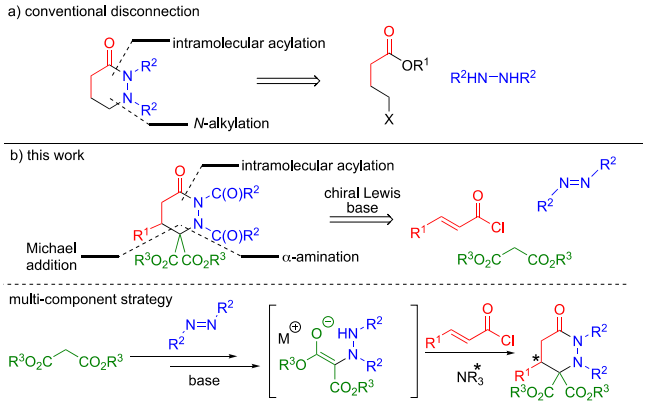


Figure 1. Synthesis of tetrahydropyridazinones. (a) Conventional disconnection toward tetrahydropyridazinones. (b) Current multicomponent strategy to tetrahydropyridizaninones employing chiral, α,β-unsaturated acylammonium salts.

to asymmetric synthesis or the preparation of more complex tetrahydropyridazinones.

The pyridazinone nucleus is represented in a variety of pharmaceutical agents at various oxidation states, with many utilized to address cardiovascular disease (Figure 2). *N*-Phenyl

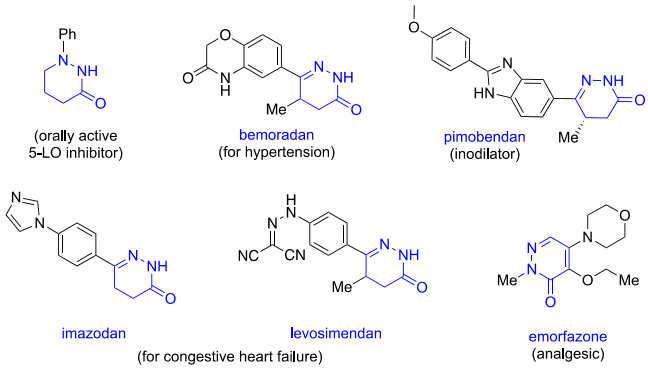
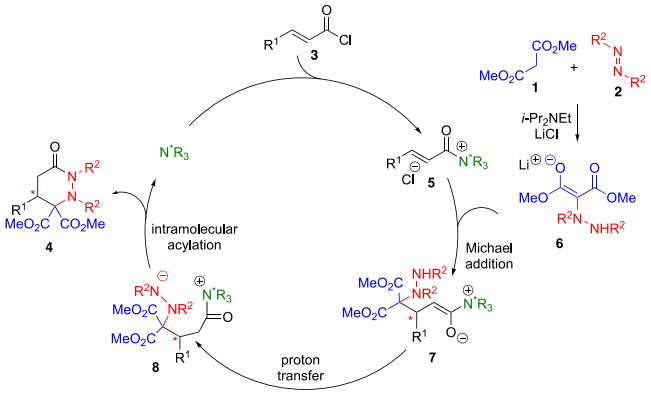


Figure 2. Examples of pharmaceutical agents possessing the pyridazinone nucleus at various oxidation states.

tetrahydropyridazinone is an orally active 5-lipooxygenase inhibitor.[26] Several 4-aryl-substituted dihydropyridazinones, including bemoradan as a racemate, are used for hypertension.[27] Pimobendan is used for heart disease in dogs, acting as an inodilator, a drug that serves as both a vasodilator and a muscle strengthening agent.[26] Other dihydropyridazinones include imazodan and levosimendan, which have utility as treatments for congestive heart failure. Finally, emorfazone, containing a fully oxidized aromatic pyridazinone as its core, is an analgesic.[28]

The potential of developing efficient routes to optically active, substituted pyridazinones, which have seen only limited interest,[29−34] provided a further impetus to study the described catalytic, asymmetric MCR involving unsaturated acylammonium catalysis. We envisioned a type of three-component MCR process, which may be more aptly named a sequential component process,[35] involving the initial *in situ* α-amination of a malonate with an azodicarboxylate, leading to the formation of an α-hydrazino malonate (Scheme 1). Subsequent proton transfers would lead to an asymmetric Michael addition of the derived hydrazino malonyl enolate **6** with various chiral, unsaturated acylammonium salt **5** to deliver

Scheme 1. Proposed Catalytic Cycle for a Three-Component MCR to Optically Active Tetrahydropyridazinones 4



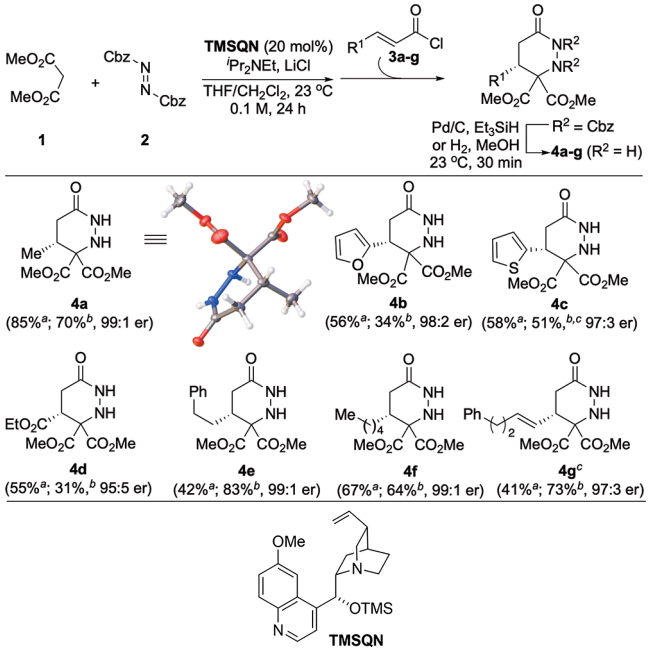
adduct **7**. Finally, proton transfer and intramolecular acylation would deliver the targeted optically active tetrahydropyridazinone **4**.

We started our investigations of this organocascade employing chiral α,β-unsaturated acylammonium salts generated from acid chlorides (*e.g.* crotonyl chloride **3a**) and TMSQN, which were previously employed in our strategy toward both γ-lactams[17] and medium-sized lactams.[16] We studied the generation of the desired bis-nucleophile **6** under thermodynamic enolization conditions (LiCl, iPr_2NEt) at ambient temperature (23 °C) to initiate addition to dibenzyl azodicarboxylate (**2**). Under these conditions, full conversion to the desired bis-nucleophile **6** was complete within ∼10 min (as determined by thin layer chromatography). To our delight, under similar conditions previously reported for the nucleophile-catalyzed Michael/proton transfer/lactamization (NCMPL), the MCR between crotonyl chloride, dibenzyl azodicarboxylate, and dimethylmalonate delivered the tetrahydropyridazinone **4a** in 70% yield with 99:1 er after hydrogenolysis of the benzylcarbamate protecting groups. The presence of carbamate rotamers made nuclear magnetic resonance (NMR) analysis difficult due to peak broadening. Thus initial adducts were directly submitted to hydrogenolysis to cleave the *N*-Cbz groups, thereby facilitating the characterization, including determination of the enantiomeric ratios, of the unprotected tetrahydropyridazinone. We briefly studied other solvents for this MCR, including CH_2Cl_2 and toluene along with other catalysts, including benzotetramisole (BTM) and homobenzotetramisole (HBTM); however, these combinations led to inferior results. Therefore, further optimization was not pursued given that our original NCMPL conditions provided useful yields of the tetrahydropyridazinone **4a**.

With this procedure in hand, we applied this method to a selection of unsaturated acid chlorides (Table 1). As noted above, directly subjecting adducts to hydrogenolysis to cleave the Cbz groups with Pd/C and either H_2 or Et_3SiH simplified characterization of the tetrahydropyridazinones by removing-rotamers for NMR and chiral high-performance liquid chromatography (HPLC) analysis. Notably, we were able to employ β-heteroaromatic acyl chlorides such as β-furyl acryloyl chloride (**3b**) and β-thienyl acryloyl chloride (**3c**) in this MCR (MCR yields of 56 and 58%, respectively; 98:2 and 97:3 er, respectively). Furthermore, ethyl fumaroyl chloride (**3d**) provided the ester-substituted tetrahydropyradazinone **4d** in 31% yield (95:5 er). Although cinnamoyl chloride did not

https://doi.org/10.1021/acs.orglett.1c02044
Org. Lett. 2021, 23, 6622−6627

Table 1. MCR Employing Unsaturated Acylammoniums for the Synthesis of Tetrahydropyridazinones

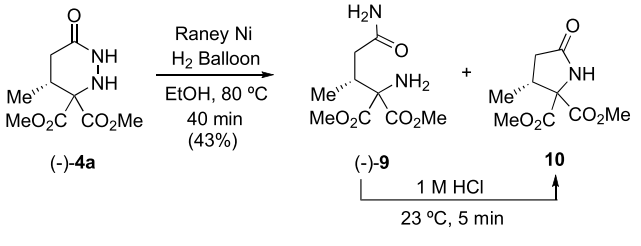


[a]Purified, isolated yield of the intermediate Cbz-protected tetrahydropyridazinones. [b]Purified, isolated yield of the Cbz-deprotected tetrahydropyridazinones **4a–g** (enantiomeric ratio (er) was determined by chiral-phase HPLC following Cbz deprotection). [c]Cbz deprotection was carried out using trimethylsilyl iodide (TMSI).

participate in this MCR, *β*-phenethyl acid chloride led to tetrahydropyridazinone **4e** in 83% yield with 99:1 er. A fatty-acid-derived acyl chloride **3f** from caprylic acid[36] also participated to afford the tetrahydropyridazinone **4f** (64% yield, 99:1 er). The dienyl acid chloride **3g** also successfully delivered the alkene-bearing tetrahydropyridazinone **4g** in 73% yield with 97:3 er. The crystalline tetrahydropyridazinone **4a** enabled structural confirmation by X-ray analysis (Table 1, inset). Other substituted cinnamoyl (*p*-OMe, *p*-F) and acryloyl chlorides (*β*-isopropyl, *β*-trifluoromethyl, and *β*-chloro) did not participate in this MCR. In addition, other diazene derivatives, namely, di-*t*-butyl azodicarboxylate (DBAD) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), did not lead to the corresponding tetrahydropyridazinones (see SI Figure S1, p S16).

We also studied further transformations of the derived tetrahydropyridazinones. Reductive cleavage of the N−N bond in tetrahydropyridazinone **4a** with Raney nickel gave the *γ*-amino amide **9** in 43% yield (Scheme 2).[32] However, this

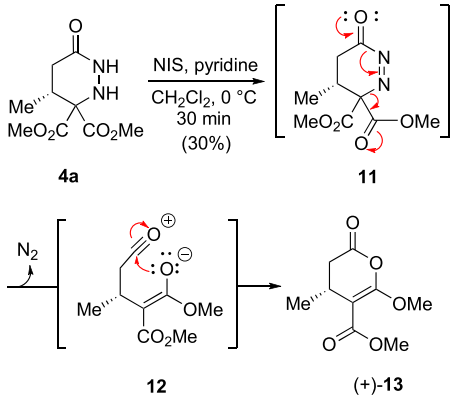
Scheme 2. Cleavage of the N−N Bond of Tetrahydropyridazinone 4a and Facile Lactamization



product was always accompanied by trace amounts of the corresponding *γ*-lactam **10** derived from facile lactamization with a loss of NH_3 under acidic conditions. Indeed, gas evolution and the distinct smell of NH_3 were first detected when $CDCl_3$ was added to the amino amide **9** for NMR analysis. Subsequently, we determined that full conversion to the *γ*-lactam **10** was possible upon stirring amino amide **9** with 1 M HCl for 5 min.

In an attempt to reoxidize the N−N bond to the diazene, treatment of tetrahydropyridazinone **4a** with *N*-iodosuccinimide (NIS)[37] instead led to enol lactone **13** (30%, unoptimized, Scheme 3). This unexpected rearrangement

Scheme 3. Oxidation of Tetrahydropyridazinone 4a and Rearrangement to Enol Lactone 13

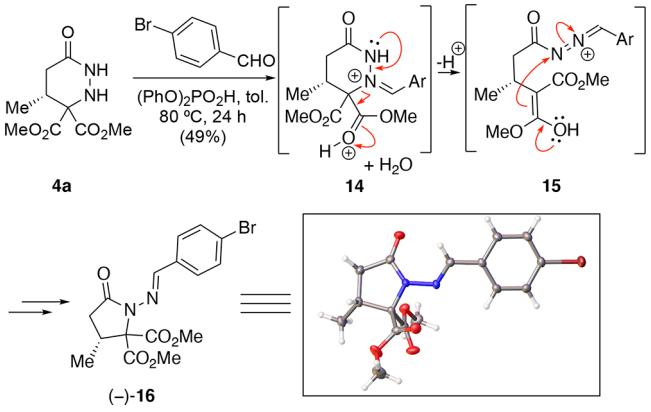


may be a result of the facile loss of N_2 gas from the targeted and presumed intermediate diazene **11**. An additional driving force for the loss of N_2 is the stability of the derived malonate enolate, leading to the formation of the intermediate zwitterionic acylium ion/enolate **12**. The acylium ion **12** could then undergo lactonization to give enol lactone **13**. Interestingly, to the best of our knowledge, 6-alkoxy enol lactones similar to **13** have not been previously described in the literature. Whereas it would seem that this type of adduct could be obtained by the addition of malonates to acid chlorides, to date, we have found that this type of reaction leads only to C-acylation rather than Michael additions in attempted reactions with unsaturated acylammonium salts. On the contrary, *β*-ketoesters do provide 6-alkyl and 6-aryl enol lactones upon reaction with unsaturated acylammonium salts, as we previously described.[17]

We anticipated that subjecting **4a** to a condensation with *p*-bromobenzaldehyde would deliver an azomethine ylide that might undergo a subsequent [3 + 2] cycloaddition;[38] however, condensation with *p*-bromobenzaldehyde resulted in the formation of a rearranged *N*-imino pyrrolidinone **16** (Scheme 4). This process may proceed through the initial formation of the targeted iminium **14**; however, the facile cleavage of the C−N bond, driven by the stability of the derived malonate enol and the subsequent reclosure onto the electrophilic nitrogen, could deliver the observed *N*-imino *γ*-lactam **16**. The structure of this unexpected rearranged product was verified by X-ray analysis (Scheme 4, inset). The presence of the heavy atom also confirmed the absolute stereochemistry and correlates with Michael additions we have previously reported employing TMSQN-derived unsaturated acylammonium salts.[16,17] The absolute stereochemistry of the other tetrahy-

https://doi.org/10.1021/acs.orglett.1c02044
Org. Lett. 2021, 23, 6622−6627

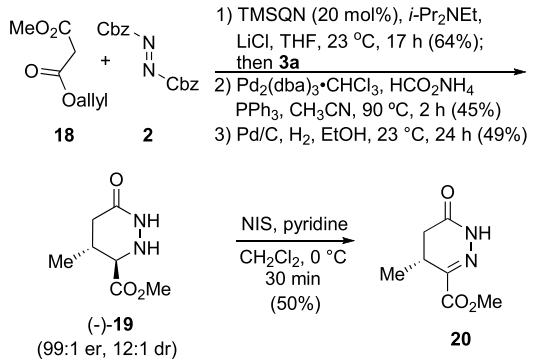
Scheme 4. Attempted Formation of an Azo-methine Ylide Leading to the *N*-Imino γ-Lactam 16



dropyridazinones **4b–g** previously described was assigned by analogy.

We also sought to introduce a second stereocenter through the use of an allylmalonate-containing Michael donor that would enable a subsequent deallylative decarboxylation following the formation of the tetrahydropyridazinone. Indeed, directly subjecting the derived allyl methyl malonate tetrahydropyridazinone, obtained as an ∼1:1 mixture of diastereomers, to conditions described by Tsuji[39] afforded the anti-disubstituted tetrahydropyridazinone **19** (12:1 dr) following Cbz deprotection (Scheme 5). The enantioselectivity observed in this sequence was in line with that of other MCRs described herein (99:1 er).

Scheme 5. Deallylative Decarboxylation of an Allylmethyl-Malonate-Derived Tetrahydropyridazinone and Subsequent Oxidation



Because the two unexpected rearrangements previously described could in part be due to the presence of the electron-withdrawing geminal diester moiety, we reinvestigated these reactions with monoester **19** derived from deallylative decarboxylation. The attempted condensation of monoester (−)-**19** with *p*-bromobenzaldehyde led to the same rearrangement previously observed (cf. Scheme 4; see the SI for further details, Scheme S1, p S16). However, the oxidation of monoester **19** with NIS led to the expected imine **20** in 50% yield, presumably derived from N−N oxidation and tautomerization. The derived dihydropyridazinone **20** is reminiscent of the heterocyclic cores found in the previously described pharmaceutical agents (cf. Figure 2).

In summary, we developed an enantioselective, sequential, three-component organocascade process enabling a one-pot synthesis of β-substituted, optically active tetrahydropyridazinones from azo dicarboxylates, malonates, and acid chlorides through the intermediacy of chiral, α,β-unsaturated acylammonium salts. We studied several transformations of the derived tetrahydropyridazinones, which led to some unanticipated reactions. The attempted oxidation of tetrahydropyridazinone **4a** led to the rapid loss of N_2 gas and the formation of a novel 6-alkoxy enol lactone **13**. The attempted formation of an azomethine ylide from tetrahydropyridazinone **4a** led to an unexpected rearrangement to an *N*-imino γ-lactam. Finally, the use of allyl methyl malonate as a Michael donor enabled a subsequent deallylative decarboxylation and the introduction of a second stereocenter with 12:1 dr.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02044.

Experimental procedures including further optimization studies of the MCR toward tetrahydropyridazinones (Table S1) and X-ray diffraction and compound characterization (PDF)

Accession Codes

CCDC 2084772−2084773 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Daniel Romo − *Department of Chemistry & Biochemistry, Baylor University, Waco, Texas 76706, United States;* orcid.org/0000-0003-3805-092X; Email: Daniel_Romo@baylor.edu

Authors

Sigrid A. Kiledal − *Department of Chemistry & Biochemistry, Baylor University, Waco, Texas 76706, United States*

Roxane Jourdain − *Department of Chemistry & Biochemistry, Baylor University, Waco, Texas 76706, United States*

Sreekumar Vellalath − *Department of Chemistry & Biochemistry, Baylor University, Waco, Texas 76706, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02044

Author Contributions

The initial MCR process was performed by S.V. All authors contributed to the examples presented. S.A.K. performed many of the subsequent transformations of the tetrahydropyridazinones. R.J. identified the rearrangement to the enol lactone upon the attempted oxidation to the diazene. The manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acs.orglett.1c02044
Org. Lett. 2021, 23, 6622−6627

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CHE-1800411) and partially supported by the Welch Foundation (AA-1280) and Baylor University. We thank Jamie M. Suzuki (Baylor University) and Adam J. Youman (Baylor University) for their contributions at various stages of this project. We thank Prof. Kevin Klausmeyer (Baylor University) for securing the X-ray structures of compound **4a** and **16**.

■ REFERENCES

(1) de Graaff, C.; Ruijter, E.; Orru, R. V. A. Recent developments in asymmetric multicomponent reactions. *Chem. Soc. Rev.* **2012**, *41*, 3969−4009.
(2) Hulme, C.; Gore, V. Multi-component Reactions: Emerging Chemistry in Drug Discovery From Xylocain to Crixivan. *Curr. Med. Chem.* **2003**, *10*, 51−80.
(3) Koes, D.; Khoury, K.; Huang, Y.; Wang, W.; Bista, M.; Popowicz, G. M.; Wolf, S.; Holak, T. A.; Dömling, A.; Camacho, C. J. Enabling large-scale design, synthesis and validation of small molecule protein-protein antagonists. *PLoS One* **2012**, *7*, e32839.
(4) Ugi, I. The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8−21.
(5) Ugi, I. From Isocyanides via Four-Component Condensations to Antibiotic Syntheses. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810−819.
(6) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. Organo-catalytic Asymmetric Assembly Reactions: One-Pot Synthesis of Functionalized β-Amino Alcohols from Aldehydes, Ketones, and Azodicarboxylates. *Org. Lett.* **2003**, *5*, 1685−1688.
(7) Guillena, G.; Ramón, D. J.; Yus, M. Organocatalytic enantioselective multicomponent reactions (OEMCRs). *Tetrahedron: Asymmetry* **2007**, *18*, 693−700.
(8) Vellalath, S.; Romo, D. Asymmetric Organocatalysis: The Emerging Utility of α,β-Unsaturated Acylammonium Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 13934−13943.
(9) Bitai, J.; Westwood, M. T.; Smith, A. D. α,β-Unsaturated acyl ammonium species as reactive intermediates in organocatalysis: an update. *Org. Biomol. Chem.* **2021**, *19*, 2366−2384.
(10) Kato, K.; Shizuri, Y.; Hirata, Y.; Yamamura, S. Reactions of 4-hydroxy-6-methyl-2-pyrone with α,β-unsaturated acyl chlorides. *Chem. Commun.* **1968**, *0*, 324−325.
(11) Bappert, E.; Muller, P.; Fu, G. C. Asymmetric [3 + 2] annulations catalyzed by a planar-chiral derivative of DMAP. *Chem. Commun.* **2006**, 2604−2606.
(12) Robinson, E. R. T.; Fallan, C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. Anhydrides as α,β-unsaturated acyl ammonium precursors: isothiourea-promoted catalytic asymmetric annulation processes. *Chem. Sci.* **2013**, *4*, 2193−2200.
(13) Fukata, Y.; Okamura, T.; Asano, K.; Matsubara, S. Asymmetric Isomerization of ω-Hydroxy-α,β-Unsaturated Thioesters into β-Mercaptolactones by a Bifunctional Aminothiourea Catalyst. *Org. Lett.* **2014**, *16*, 2184−2187.
(14) Ahlemeyer, N. A.; Birman, V. B. Asymmetric Catalytic Synthesis of Thiochromenes via an Acyl Transfer-Initiated Cascade. *Org. Lett.* **2016**, *18*, 3454−3457.
(15) Pandiancherri, S.; Ryan, S. J.; Lupton, D. W. 1,3-Dipolar cycloaddition of unstabilised azomethine ylides by Lewis base catalysis. *Org. Biomol. Chem.* **2012**, *10*, 7903.
(16) Kang, G.; Yamagami, M.; Vellalath, S.; Romo, D. Enantioselective Synthesis of Medium-Sized Lactams via Chiral α,β-Unsaturated Acylammonium Salts. *Angew. Chem., Int. Ed.* **2018**, *57*, 6527−6531.
(17) Vellalath, S.; Van, K. N.; Romo, D. Direct Catalytic Asymmetric Synthesis of N-Heterocycles from Commodity Acid Chlorides by Employing α,β-Unsaturated Acylammonium Salts. *Angew. Chem., Int. Ed.* **2013**, *52*, 13688−13693.
(18) Van, K. N.; Romo, D. Multicomponent, Enantioselective Michael−Michael-Aldol-β-Lactonizations Delivering Complex β-Lactones. *J. Org. Chem.* **2018**, *83*, 632−643.
(19) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. Acylammonium Salts as Dienophiles in Diels−Alder/Lactonization Organocascades. *J. Am. Chem. Soc.* **2014**, *136*, 4492−4495.
(20) Liu, G.; Shirley, M. E.; Van, K. N.; McFarlin, R. L.; Romo, D. Rapid assembly of complex cyclopentanes employing chiral, α,β-unsaturated acylammonium intermediates. *Nat. Chem.* **2013**, *5*, 1049−1057.
(21) (a) Birman, V. B.; Li, X. Benzotetramisole: A Remarkably Enantioselective Acyl Transfer Catalyst. *Org. Lett.* **2006**, *8*, 1351−1354. (b) Birman, V. B.; Li, X. Homobenzotetramisole: An Effective Catalyst for Kinetic Resolution of Aryl-Cycloalkanols. *Org. Lett.* **2008**, *10*, 1115−1118. (c) Zhang, Y.; Birman, V. B. Homobenzotetramisole-Catalyzed Kinetic Resolution of α-Aryl, α-Aryloxy and α-Arylthioalkanoic Acids. *Adv. Synth. Catal.* **2009**, *351*, 2525−2529. (d) Ahlemeyer, N. A.; Streff, E. V.; Muthupandi, P.; Birman, V. B. Dramatic Acceleration of an Acyl Transfer-Initiated Cascade by Using Electron-Rich Amidine-Based Catalysts. *Org. Lett.* **2017**, *19*, 6486−6489.
(22) Matviitsuk, A.; Greenhalgh, M. D.; Taylor, J. E.; Nguyen, X. B.; Cordes, D. B.; Slawin, A. M. Z.; Lupton, D. W.; Smith, A. D. Unanticipated Silyl Transfer in Enantioselective α,β-Unsaturated Acyl Ammonium Catalysis Using Silyl Nitronates. *Org. Lett.* **2020**, *22*, 335−339.
(23) Matviitsuk, A.; Greenhalgh, M. D.; Antunez, D. B.; Slawin, A. M. Z.; Smith, A. D. Aryloxide-Facilitated Catalyst Turnover in Enantioselective α,β-Unsaturated Acyl Ammonium Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 12282−12287.
(24) Brooks, D. W.; Basha, A.; Kerdesky, F. A. J.; Holms, J. H.; Ratajcyk, J. D.; Bhatia, P.; Moore, J. L.; Martin, J. G.; Schmidt, S. P.; Albert, D. H.; Dyer, R. D.; Young, P.; Carter, G. W. Structure-activity relationships of the pyridazinone series of 5-lipoxygenase inhibitors. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1357−1360.
(25) Mantovani, A. C.; Goulart, T. A. C.; Back, D. F.; Zeni, G. Synthesis of Pyridazinones through the Copper(I)-Catalyzed Multi-component Reaction of Aldehydes, Hydrazines, and Alkynylesters. *Chem. - Eur. J.* **2014**, *20*, 12663−12668.
(26) Asif, M. A Review on Pyridazinone Ring Containing Various Cardioactive Agents. *Chem. Rev.* **2019**, *1*, 66−77.
(27) Combs, D. W.; Rampulla, M. S.; Bell, S. C.; Klaubert, D. H.; Tobia, A. J.; Falotico, R.; Haertlein, B.; Lakas-Weiss, C.; Moore, J. B. 6-Benzoxazinylpyridazin-3-ones: potent, long-acting positive inotrope and peripheral vasodilator agents. *J. Med. Chem.* **1990**, *33*, 380−386.
(28) Takaya, M.; Sato, M.; Terashima, K.; Tanizawa, H.; Maki, Y. A new nonsteroidal analgesic-antiinflammatory agent. Synthesis and activity of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone and related compounds. *J. Med. Chem.* **1979**, *22*, 53−58.
(29) Geng, Y.-H.; Hua, Y.-Z.; Jia, S.-K.; Wang, M.-C. Direct Asymmetric α-Selective Mannich Reaction of β,γ-Unsaturated Ketones with Cyclic α-Imino Ester: Divergent Synthesis of Cyclo-canaline and Tetrahydro Pyridazinone Derivatives. *Chem. - Eur. J.* **2021**, *27*, 5130−5135.
(30) Provencher, B. A.; Bartelson, K. J.; Liu, Y.; Foxman, B. M.; Deng, L. Structural Study-Guided Development of Versatile Phase-Transfer Catalysts for Asymmetric Conjugate Additions of Cyanide. *Angew. Chem., Int. Ed.* **2011**, *50*, 10565−10569.
(31) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. Switchable selectivity in an NHC-catalysed dearomatizing annulation reaction. *Nat. Chem.* **2015**, *7*, 842−847.
(32) Shen, L.-T.; Sun, L.-H.; Ye, S. Highly Enantioselective γ-Amination of α,β-Unsaturated Acyl Chlorides with Azodicarboxylates: Efficient Synthesis of Chiral γ-Amino Acid Derivatives. *J. Am. Chem. Soc.* **2011**, *133*, 15894−15897.
(33) Chen, X.-Y.; Xia, F.; Cheng, J.-T.; Ye, S. Highly Enantioselective γ-Amination by N-Heterocyclic Carbene Catalyzed [4 + 2] Annulation of Oxidized Enals and Azodicarboxylates. *Angew. Chem., Int. Ed.* **2013**, *52*, 10644−10647.

https://doi.org/10.1021/acs.orglett.1c02044
Org. Lett. 2021, 23, 6622−6627

(34) Mao, J.-H.; Wang, Z.-T.; Wang, Z.-Y.; Cheng, Y. N-Heterocyclic Carbene-Catalyzed Oxidative Annulations of α,β-Unsaturated Aldehydes with Hydrazones: Selective Synthesis of Optically Active 4,5-Dihydropyridazin-3-ones and Pyridazin-3-ones. *J. Org. Chem.* **2015**, *80*, 6350−6359.
(35) Ramón, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634.
(36) Zhao, Y.; Chen, Y.; Newhouse, T. R. Allyl-Palladium-Catalyzed α,β-Dehydrogenation of Carboxylic Acids via Enediolates. *Angew. Chem., Int. Ed.* **2017**, *56*, 13122−13125.
(37) Russell Bowman, W.; Anthony Forshaw, J.; Hall, K. P.; Kitchin, J. P.; Mott, A. W. Reduction of Ag(I) by 1-acyl-2-arylhydrazines: Mechanism of photographic infectious development. *Tetrahedron* **1996**, *52*, 3961−3972.
(38) Dorn, H.; Otto, A. Syntheses by Means of 1-Alkylidene- and 1-(Arylalkylidene)-3-pyrazolidone N,N-Betaines, a New Type of Stable Azomethine Imine. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 214−215.
(39) Tsuji, J.; Yamakawa, T. A convenient method for the preparation of 1-olefins by the palladium catalyzed hydrogenolysis of allylic acetates and allylic phenyl ethers with ammonium formate. *Tetrahedron Lett.* **1979**, *20*, 613−616.

https://doi.org/10.1021/acs.orglett.1c02044
Org. Lett. 2021, 23, 6622−6627