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Mechanistic Investigation of Castagnoli–Cushman Multicomponent Reactions Leading to a Three-Component Synthesis of Dihydroisoquinolones

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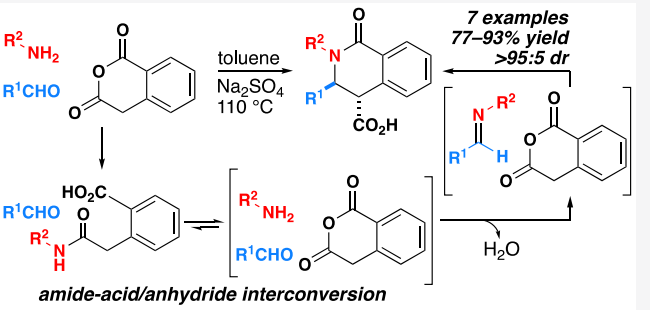
ABSTRACT: The mechanisms for the three- and four-component variants of the Castagnoli–Cushman reaction (CCR) have been investigated. A series of crossover experiments were conducted to probe the structure and reactivity of known amide-acid intermediates for the three- and four-component variants of the CCR (3CR and 4CR, respectively). Control experiments paired with *in situ* reaction monitoring with infrared spectroscopy for the 4CR align with a mechanism in which amide-acids derived from maleic anhydride can reversibly form free amine and cyclic anhydride. Although this equilibrium is unfavorable, the aldehyde present can trap the primary amine through imine formation and react with the enol form of the anhydride through a Mannich-like mechanism. This detailed mechanistic investigation coupled with additional crossover experiments supports an analogous mechanism for the 3CR and has led to the elucidation of new 3CR conditions with homophthalic anhydride, amines, and aldehydes for the formation of dihydroisoquinolones in good yields and excellent diastereoselectivity. This work represents the culmination of more than a decade of mechanistic speculation for the 3- and 4CR, enabling the design of new multicomponent reactions that exploit this novel mechanism.



INTRODUCTION

The Castagnoli–Cushman reaction (CCR) and its related three- and four-component reactions are powerful methods for the facile synthesis of densely substituted lactam products.[1,2] Lactams are commonly found in the core of natural products and other biologically relevant compounds, several of which have been synthesized using the CCR.[3−6] The CCR was first discovered in 1969, when *N*-benzylidene methylamine and succinic anhydride were combined under refluxing conditions to form γ-lactam **3**.[7] This reaction typically proceeds with high diastereoselectivity for the thermodynamically favored *trans* diastereomer; however, the mechanism for its formation has been disputed for some time.[8,9]

Lactam formation in the CCR can follow one of two mechanistic pathways. First, it was hypothesized that the reaction proceeds through an iminolysis pathway, forming *N*-acyl iminium ion **4** through acylation of the imine nitrogen (Figure 1). Subsequent intramolecular Mannich addition through carboxylic acid enolate **4b** leads to **3**. Alternatively, in analogy to the Perkin reaction, the CCR could proceed through Mannich addition of anhydride enolate **5**, followed by *N*-acylation to form lactam **3**. Earlier studies by Cushman focused on the electronic and steric influences of the CCR with homophthalic anhydride and led to the acceptance of the

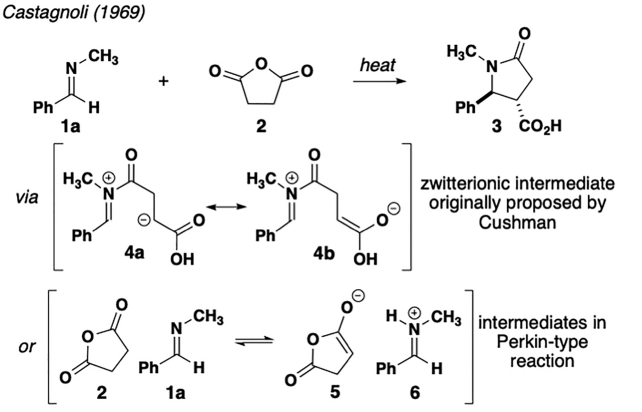


Figure 1. Initial discovery of the Castagnoli–Cushman reaction and proposed reaction pathways.

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former mechanistic pathway.[8] Reactions with less reactive *N*-aryl and *N*-sulfonyl imines can be accelerated with hydrogen bonding[10] and basic catalysts,[11,12] respectively.

The CCR also forms the basis of a three-component reaction (3CR) of homophthalic anhydride, amines, and aldehydes with Lewis acid catalysts and additives.[13−23] In one case, a diacid is used as an anhydride precursor.[24] Similar zwitterionic intermediates were proposed for the 3CR of homophthalic anhydride with amines and aldehydes, wherein the amine attacks homophthalic anhydride to form amide-acid **11**, followed by condensation with aldehyde **9** and successive Mannich addition (Figure 2A).[15] Although these ions (**12**) are

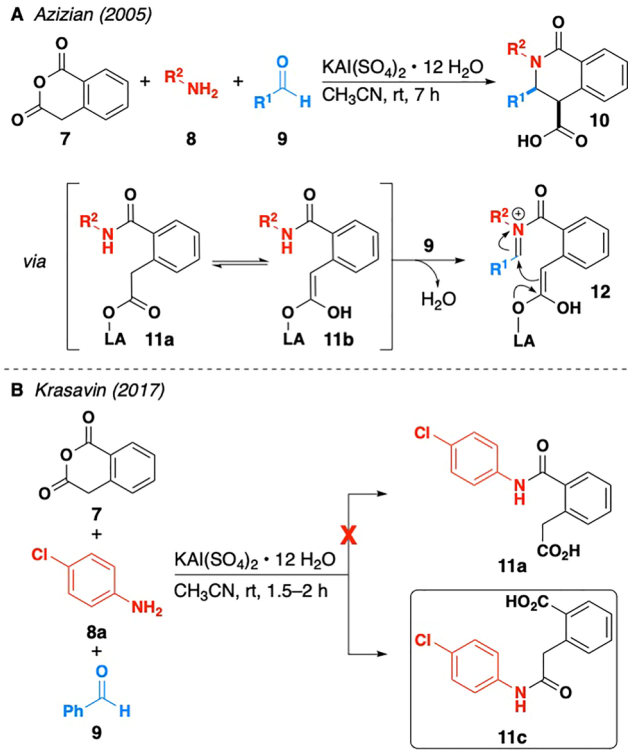

Figure 2. (A) Three-component variant and proposed mechanism. (B) Observed amide-acid intermediate in the three-component variant of the Castagnoli−Cushman reaction.

commonly invoked as intermediates, there is little precedent for their formation by the condensation of *N*-substituted amides with aldehydes. This proposed mechanism was supported by the isolation of what was thought to be regioisomer **11a**.[15] However, a later study found that the isolated amide-acid intermediate was actually **11c** (Figure 2B).[24] It was suggested that a 3CR in which amine, aldehyde, and homophthalic anhydride are simultaneously combined without additives was not possible, as amide-acid **11c** would be unproductive for lactam formation. These opposing results made it unclear how the 3CR proceeds to the lactam product if amide-acid **11a** is not formed.

The lactam-forming four-component reaction (4CR), developed in our group in 2007, emerged from initial reaction explorations of succinic anhydrides and imines.[25] Cushman used phenylsuccinic anhydride in refluxing chloroform as part of his mechanistic study of the CCR.[8] Initially, we sought to replace the phenyl ring with a group that would both facilitate the reaction and serve as a functional handle for subsequent transformations; it was found that thioaryl succinic anhydride was suitable on both counts. After this discovery, a series of control experiments led to the observation that preformation of the imine or anhydride was unnecessary: simply mixing all four of the components and heating gave the lactam product in similar yield and diastereoselectivity. At the time of discovery, we assumed that the mechanism proceeded via the same zwitterionic intermediate originally proposed by Cushman (Figure 3). Specifically, we discovered that the imine,

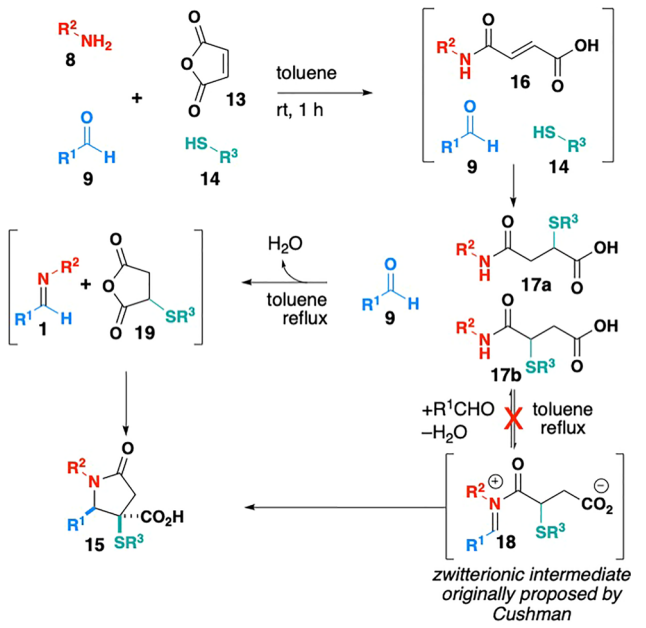

Figure 3. 17a and **17b** have been isolated as intermediates in the 4CR and lead to a single regioisomer and diastereomer of lactam **15**.

anhydride, and thiol led to the room-temperature formation of a mixture of amide-acid regioisomers. Heating this mixture with aldehyde led to a single regioisomer and diastereomer of the product. This led us to propose that the amide nitrogen was condensing with the aldehyde to form *N*-acyl iminium ion **17**, analogous to the proposed 3CR mechanism (Figure 3). The previous work on the 4CR has described the scope and utility of the 4CR, including the expansion to a variety of amines, aldehydes, and chiral thiols,[26] as well as applications to the synthesis of a complex natural product.[4,27−30] Although there are other possible nucleophiles capable of conjugate addition, most are insufficiently nucleophilic or undergo competitive reaction with the aldehyde. As a result, the 4CR has remained limited to thiol reaction partners.

Later studies of cyano-succinic anhydride with imines revealed a *Mannich*-like mechanism was operative (Scheme 1). In the case of cyano-succinic anhydrides, computational studies suggest that a rapid enol−keto tautomerization of the anhydride enabled a reaction with the imine through a Zimmerman−Traxler-like six-membered ring transition state (Scheme 1). Additionally, carboxylic acid enolate **4** was computed to be unrealistically high in energy for the CCR.[9] The Mannich-like mechanism for the reactions of cyano-succinic anhydride and imines served as a basis for explaining the previous reactions of Castagnoli and Cushman, as well as the original thiophenylsuccinic anhydride reaction and the ensuing reactions of cyano-glutaric anhydrides.[18,31] Furthermore, this mechanistic picture is consistent with an earlier proposal made by Connon for the reactions of carbonyl

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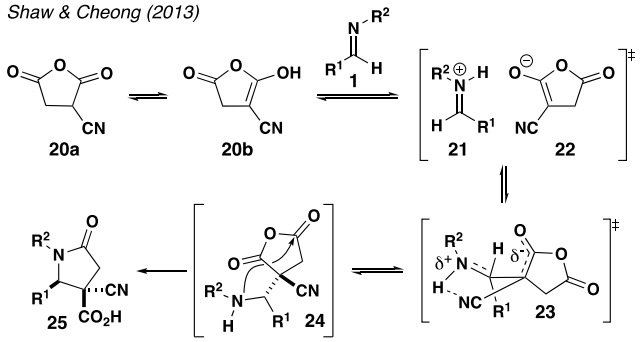
Scheme 1. Mannich-like Mechanism Computed for Cyanosuccinic Anhydride



compounds to form lactones.[32] However, while this mechanism explains the reactions of thiosuccinic anhydrides with preformed imines, it does not explain how amide-acids **17a** and **17b** proceed to the lactam product. Herein, we report detailed synthetic experiments and kinetic investigations that culminate in a novel mechanism for the 3CR and 4CR. This work upends our previous decade-old proposal and opens the door for the design of new multicomponent reactions based on the reactivity that is described.

RESULTS AND DISCUSSION

Initial studies began by probing the mechanism of the 3CR. A series of experiments were conducted to understand the structure and reactivity of the amide-acid intermediate formed in this reaction. First, when homophthalic anhydride was heated in the presence of benzylamine for 1 h, a single amide-acid intermediate **26** was observed, the structure of which was determined by X-ray crystallography (Figure 4A). The same product was observed when the reaction was performed at room temperature for 24 h. This product was consistent with the regioisomer (**11b**) isolated and observed by Krasavin in the development of the 3CR of homophthalic diacid, aldehydes, and amines, as well as other similar reports.[24,33,34] A crossover experiment was performed to probe the reaction mechanism of the 3CR. When amide-acid **26a** was isolated and treated with *p*-Cl-benzylamine in refluxing toluene for 6 h, a mixture of amide-acids **26a** and **26b** was observed by LCMS (Figure 4B). Next, amide-acid **26a** was isolated, combined with benzaldehyde, and heated in toluene, resulting in product **27a** in >95:5 dr and 82% yield (Figure 4C). Additionally, mixing homophthalic anhydride, benzylamine, and benzaldehyde in refluxing toluene yielded lactam **27a** in 84% yield and >95:5 dr for the *trans* diastereomer. To the best of our knowledge, this is the first instance of a three-component CCR with homophthalic anhydride, amines, and aldehydes without the necessity of a Lewis acid leading to dihydroisoquinolone products **27**.

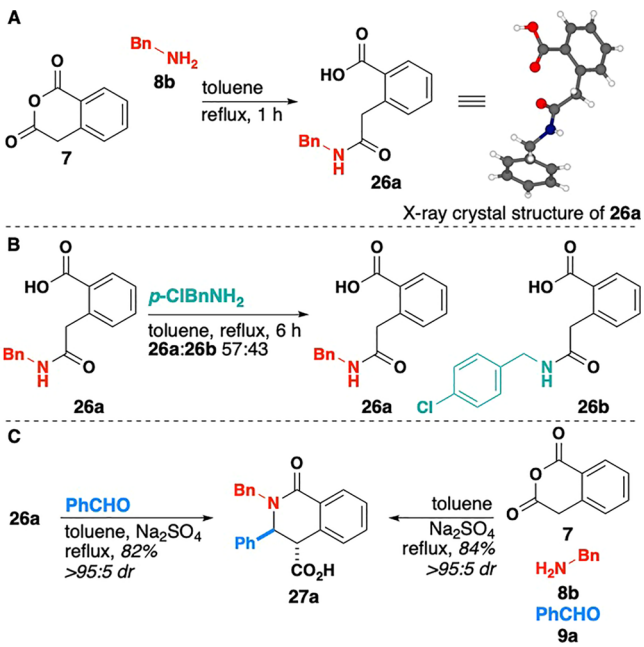


Figure 4. (A) Reaction of homophthalic anhydride and benzylamine leads to a single regioisomer of amide-acid **26**. (B) Crossover experiment with **26a** and *p*-chlorobenzylamine leads to a mixture of amide-acids. (C) Heating **26a** with benzaldehyde and Na_2SO_4 leads to a single diastereomer of the CCR product.

Interested in expanding the scope of this three-component reaction of homophthalic anhydride, amines, and aldehydes, we screened a variety of dehydrating agents. Interestingly, the reaction proceeds comparably regardless of the dehydrating agent used and can proceed in the absence of a dehydrating agent, as well.[35] When the reaction was run for 6 h, a mixture of *cis* and *trans* diastereomers was observed. Presumably, the kinetic *cis* diastereomer is formed first, and under reaction conditions, it can epimerize to the *trans* diastereomer over time. Following screening, a series of substrates were synthesized using this three-component method. The reaction tolerates a variety of amine components, including primary and secondary aliphatic amines as well as benzyl and aryl amines. Both aromatic and aliphatic aldehyde-derived imines also provided tetrahydroisoquinolone products in good yields and excellent diastereoselectivity for the *trans* diastereomer (Figure 5).

Similar crossover experiments were performed for the 4CR (Figure 6). Several experimental observations were important in deciphering the mechanism. (1) At room temperature, the mixture of maleic anhydride, benzylamine, *p*-tolSH, and benzaldehyde led to the quantitative production of a 1:1 mixture of amide-acid regioisomers **17a** and **17b**. (2) Heating this mixture under anhydrous refluxing toluene conditions led to the formation of a single regioisomer of product, γ-lactam **15a**. (3) Additionally, **17a** and **17b** were also observed when **17b** was prepared, separated from **17a**, and refluxed independently; also, when benzaldehyde was added to **17b** and proceeded to partial conversion, a mixture of **17a** and **17b** was produced along with lactam **15a**. Two final experiments were informative. When isolated, **17b** was heated in the presence of a second thiophenol (*p*-methoxythiophenol), **17a** and **17b** were observed as expected, while the products of thiol exchange (**35a** and **35b**) were negligible as determined by NMR and LCMS.[35] When this same experiment was performed in the presence of a second amine (*p*-Cl-benzylamine), **17a** and **17b** were observed in addition to exchange products **34a** and **34b**.

Further investigation of the relative rates of the potential first steps leading to **17a** and **17b** using infrared spectroscopy *in situ* (React-IR) to monitor reaction progress was informative (Scheme 2). First, acylation of benzylamine with maleic anhydride proceeds instantaneously at ambient temperature in THF with a half-life ($t_{1/2}$) of <1 min. Second, the conjugate addition of *p*-tolSH to maleic anhydride showed no back-

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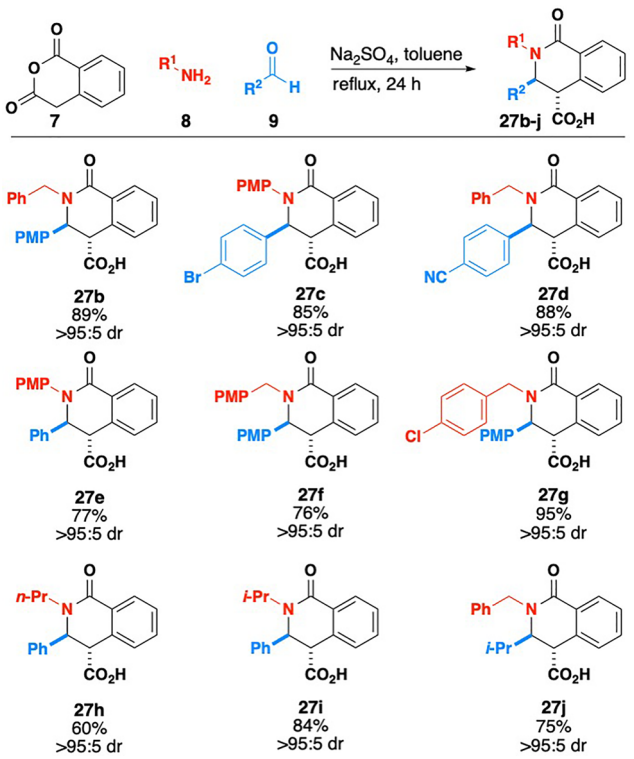
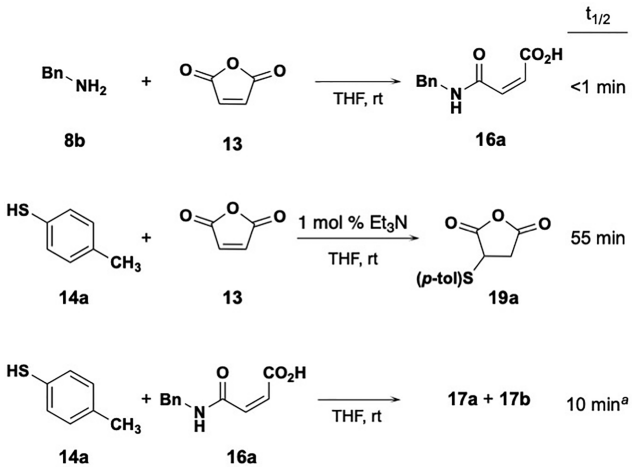


Figure 5. Substrate scope of the 3CR leading to dihydroisoquinolone products **27**.

ground rate. Consistent with the conditions for the reaction on a preparative scale, this reaction proceeded ($t_{1/2}$ = 55 min) at room temperature once a catalytic quantity of triethylamine was added. The kinetic profile of the reaction of **16a** with *p*-tolSH was found to be more complex than those of the previous reactions, and the $t_{1/2}$ was not determined. However, it was found that stirring the reaction mixture at room temperature results in 50% conversion to a mixture of amide-acids **17a** and **17b** in 10 min. Taken together, these experiments support the idea that **17a** and **17b** are intermediates to a reaction with benzaldehyde that leads to

Scheme 2. Relative Rates of the Addition of Benzylamine and *p*-tolSH to Maleic Anhydride



[a]Time to reach 50% conversion.

the final formation of the lactam 4CR product. Further control experiments, including the investigation of natural abundance kinetic isotope effects, failed to produce any insight into the final critical steps of this 4CR.[16]

On the basis of these results, we hypothesize that the mechanisms of the 3CR and 4CR both proceed through the initial formation of amide-acids **26** and **17**, respectively, which are in equilibrium with the anhydride (**7** and **19**) and amine **8** (Figure 7A,B). In this scenario, a carboxylic acid would serve as a nucleophile capable of breaking an amide bond, which was consistent with the exchange reactions described above. Similar reactions have also been described in the literature.[36−38] The mechanistic picture that emerged for the 3CR involves the attack of the amine on the phenylacetyl carbonyl of homophthalic anhydride to provide amide-acid **26**, which is in equilibrium with homophthalic anhydride **7** and amine **8** (Figure 7A). In the presence of aldehyde, the amine can condense to form imine, which can then proceed through Mannich addition to provide *cis* product **10**. Under refluxing

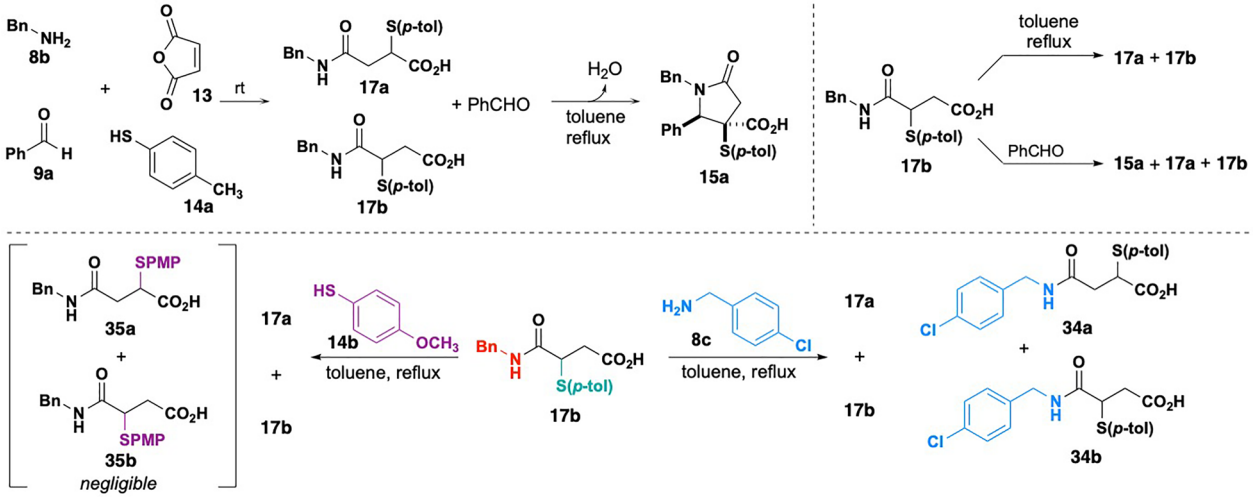


Figure 6. Lactam-forming 4CR proceeds via isomeric amide-acids **17a** and **17b** (top left). Isolated **17b** equilibrates with regioisomer **17a** under refluxing conditions and in the presence of benzaldehyde proceeds to the product (top right). Isolated **17b** undergoes regioisomerization and amide scrambling when heated in the presence of **8b** (bottom).

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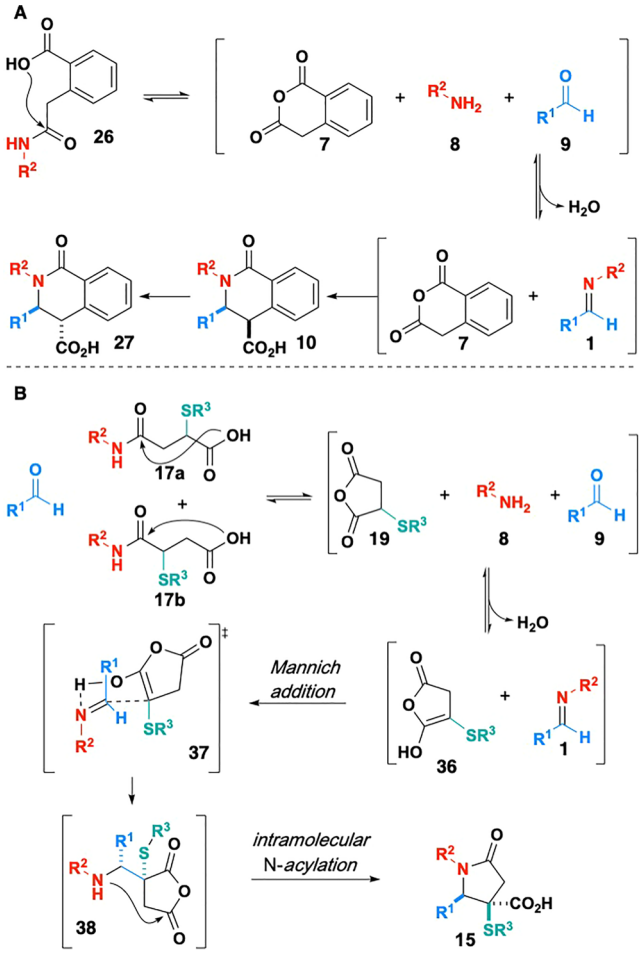

Figure 7. (A) Proposed mechanism of the three-component CCR. (B) Proposed mechanism of the four-component CCR.

conditions, the *cis* lactam epimerizes to *trans* isomer **27** over 24 h. Furthermore, the 4CR is consistent with a similar mechanism of rapid formation of amide-acid regioisomers **17** (Figure 7B), followed by equilibration of the regioisomer amide-acids with their corresponding anhydride **19**. Although this process is unfavorable, it is driven forward by the subsequent rapid formation of the imine. Once the imine is formed, it can react with the anhydride through a Mannich-like mechanism in a Zimmerman−Traxler transition state **37** to form γ-lactam **15**.

In summary, we have provided experimental evidence for the proposed mechanism of the 3CR and 4CR of the Castagnoli−Cushman reaction. These reactions proceed through analogous amide-acid intermediates that are formed through initial nucleophilic attack of the amine on the anhydride. This half-amide is in equilibrium with the anhydride and amine, which, in the presence of aldehyde, can condense to form imine and proceed through the classic CCR. This mechanistic investigation led to the development of new reaction conditions for the 3CR and allowed for the synthesis of a small series of dihydroisoquinolone products derived from alkyl and aryl amines and aldehydes. The multicomponent variants of the CCR have been shown to proceed with substrate tolerances, yields, and reactivities comparable to those of their classic CCR counterparts. The utility of multicomponent CCRs rests in the ability to achieve γ- and δ-lactams in a one-pot single-reaction format. Our new understanding of the mechanism of the 3CR will enable the development of novel multicomponent reactions using anhydrides and anhydride derivatives with reactivity similar to that of homophthalic anhydride.

EXPERIMENTAL PROCEDURES

Materials and Instrumentation. Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. ^{1}H NMR spectra and proton-decoupled ^{13}C NMR spectra were recorded on a 400 or 800 MHz Bruker or 600 MHz Varian NMR spectrometer. ^{1}H chemical shifts (δ) are reported in parts per million relative to TMS (s, δ 0). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), and m (multiplet). Complex splitting will be described by a combination of these abbreviations, i.e., dd (doublet of doublets). ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (t, δ 77.4) unless otherwise noted. High-resolution mass spectra were recorded on either positive or negative ESI mode. Melting points were recorded on an EZ-melting apparatus and were uncorrected. Infrared spectra were recorded on a Mettler Toledo ReactIR 700 (serial number B929971514) with a liquid N_2 MCT detector fitted with a DiComp probe (serial number B939349478). The system was filled with liquid N_2 and allowed to cool for 1 h before being used. Chromatographic purifications were performed by flash chromatography with silica gel (Fisher, 40−63 μm) packed in glass columns or by use of a Teledyne Isco Combi-Flash. The eluting solvent for the purification of each compound was determined by thin-layer chromatography (TLC) on glass plates coated with silica gel 60 F254 and visualized by ultraviolet light.

Note that for the three-component reaction, the reaction mixture must be heated to at least 110 °C to fully epimerize from the *cis* to *trans* diastereomer. Use of aluminum beads resulted in poor diastereoselectivity, whereas silicone oil baths led to excellent diastereoselectivity.

Synthesis of Amide-Acids for Crossover Experiments. *2-[2-(Benzylamino)-2-oxoethyl]benzoic Acid (**26a**).* To a flame-dried round-bottom flask was added homophthalic anhydride (0.81 g, 5.0 mmol), and the mixture was dissolved in CH_2Cl_2 (10.0 mL, 0.5 M). Benzylamine (0.54 mL, 5.0 mmol) was added, and the reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated in vacuo and characterized without further purification to provide **26a** (1.3 g, 96%), a single regioisomer, as an off-white crystalline solid: mp range 135.3−140.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.38 (t, J = 6.0 Hz, 1H), 7.83 (dd, J = 7.7, 1.5 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.38−7.17 (m, 7H), 4.27 (d, J = 5.9 Hz, 2H), 3.92 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 170.1, 168.6, 139.6, 137.0, 131.9, 131.5, 131.2, 130.2, 128.2, 127.1, 126.7 (two carbons), 42.2, 40.5; IR 2961.0 (broad), 2153.4, 1716.5, 1619.0, 1552.3 cm^{-1}; AMM (ESI-TOF) m/z calcd for $C_{16}H_{14}NO_3^-$ [M − H]$^-$ 268.0979, found 268.0981.

*2-{2-[(4-Chlorobenzyl)amino]-2-oxoethyl}benzoic Acid (**26b**).* To a flame-dried round-bottom flask was added homophthalic anhydride (0.081 g, 0.5 mmol), and the mixture was dissolved in toluene (1.0 mL, 0.5 M). *p*-Chlorobenzylamine (0.060 mL, 0.5 mmol) was added, and the reaction mixture was stirred for 30 min. The reaction mixture was concentrated in vacuo and characterized without further purification to afford **26b**, a single regioisomer, as a white crystalline solid (0.134 g, 96%): mp range 172.7−173.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (t, J = 6.1 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.42−7.23 (m, 6H), 4.25 (d, J = 6.0 Hz, 2H), 3.92 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 170.4, 168.7, 138.8, 137.0, 132.1, 131.7, 131.3, 131.2, 130.3, 129.1, 128.2, 126.9, 41.7, 40.7; AMM (ESI-TOF) m/z calcd for $C_{16}H_{13}ClNO_3^-$ [M − H]$^-$ 302.0589, found 302.0594.

*Synthesis of **S1** and **S2**.* To a flame-dried round-bottom flask were added 3-(p-tolylthio)dihydrofuran-2,5-dione (1.55 g, 7 mmol) and *p*-chlorobenzylamine (0.851 mL, 7 mmol), and the mixture was

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dissolved in acetone (70 mL, 0.1 M). After 10 min, K_2CO_3 (0.967 mg, 7 mmol), KI (1.162 g, 7 mmol), and *p*-methoxybenzyl chloride (1.03 mL, 7 mmol) were added, and the reaction mixture was stirred overnight. The crude reaction mixture was concentrated in vacuo, dissolved in EtOAc and H_2O, extracted with EtOAc (3 × 20 mL), and dried over Na_2SO_4. Purification by gradient flash column chromatography (20−100% EtOAc/hexanes) afforded regioisomer **S1** as an off-white amorphous solid (0.393 g, 12%) and **S2** (0.080 g, 3%) as an off-white amorphous solid.

*4-Methoxybenzyl 4-[(4-Chlorobenzyl)amino]-4-oxo-3-(p-tolylthio)butanoate (**S1**).* The structure of **S1** was assigned on the basis of the comparison of *J* coupling values:[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 8.4, 6.4 Hz, 4H), 7.23−7.18 (m, 2H), 7.14−7.02 (m, 4H), 6.94−6.82 (m, 2H), 6.66 (s, 1H), 5.15−4.94 (m, 2H), 4.46−4.28 (m, 2H), 3.95 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.80 (s, 3H), 3.12 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.78 (dd, *J* = 16.9, 6.3 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 169.9, 159.7, 138.8, 136.4, 133.3, 133.1, 130.2, 130.1, 129.1, 128.8, 128.5, 127.7, 114.0, 66.7, 55.3, 48.3, 43.3, 36.7, 21.1; AMM (ESI-TOF) *m*/*z* calcd for $C_{26}H_{26}ClNO_4SNa^+$ [M + Na]$^+$ 506.1163, found 506.1182.

*4-Methoxybenzyl 4-[(4-Chlorobenzyl)amino]-4-oxo-2-(p-tolylthio)butanoate (**S2**).* The structure of **S2** was assigned on the basis of the comparison of *J* coupling values:[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.09 (m, 8H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.90−6.80 (m, 2H), 6.12 (t, *J* = 5.8 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.95 (d, *J* = 11.9 Hz, 1H), 4.39−4.23 (m, 2H), 4.07 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.79 (s, 3H), 2.73 (dd, *J* = 15.1, 9.3 Hz, 1H), 2.58 (dd, *J* = 15.2, 5.8 Hz, 1H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 169.5, 159.6, 139.0, 136.6, 134.5, 133.2, 130.1, 129.8, 129.0, 128.7, 127.9, 127.5, 113.8, 66.9, 55.3, 46.3, 42.8, 38.2, 21.2; AMM (ESI-TOF) *m*/*z* calcd for $C_{26}H_{26}ClNO_4SNa^+$ [M + Na]$^+$ 506.1163, found 506.1173.

*4-[(4-Chlorobenzyl)amino]-4-oxo-2-(p-tolylthio)butanoic Acid (**34a**).* To a flame-dried round-bottom flask was added **S2** (0.050 g, 0.103 mmol), and the mixture was dissolved in dichloromethane (5.15 mL, 0.02 M). TFA (0.052 mL, 0.2M) was added, and the reaction mixture was stirred overnight. The reaction mixture was concentrated in vacuo. Hexanes (10 mL) were added, followed by diethyl ether (10 mL), and a white solid precipitated. The solid was filtered and used without further purification (0.023 g, 62%): mp range 130.1−131.9 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.41−7.36 (m, 2H), 7.32−7.23 (m, 4H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.32 (d, *J* = 3.2 Hz, 2H), 3.99 (dd, *J* = 8.8, 6.6 Hz, 1H), 2.79 (dd, *J* = 15.4, 8.8 Hz, 1H), 2.63 (dd, *J* = 15.4, 6.6 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 174.7, 172.4, 140.1, 138.8, 135.3, 133.9, 130.8, 130.1, 130.1, 129.5, 47.9, 43.3, 39.0, 21.2; AMM (ESI-TOF) *m*/*z* calcd for $C_{18}H_{17}ClNO_3S^-$ [M − H]$^-$ 362.0623, found 362.0626.

*4-[(4-Chlorobenzyl)amino]-4-oxo-3-(p-tolylthio)butanoic Acid (**34b**).* To a flame-dried round-bottom flask was added **S1** (0.384 g, 0.8 mmol), and the mixture was dissolved in dichloromethane (40.0 mL, 0.02 M). TFA (4.0 mL, 0.2M) was added, and the reaction mixture was stirred overnight. The reaction mixture was concentrated in vacuo. Hexanes (15 mL) were added, followed by diethyl ether (15 mL), and a white solid precipitated. The solid was filtered and used without further purification (0.243 g, 83%): mp 123.9−126.6 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (t, *J* = 6.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.24 (qd, *J* = 15.5, 6.0 Hz, 2H), 3.97 (dd, *J* = 9.5, 5.3 Hz, 1H), 2.76 (dd, *J* = 16.7, 9.5 Hz, 1H), 2.29 (s, 3H), 1.09 (t, *J* = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.3, 170.3, 138.7, 138.3, 133.8, 131.7, 130.1, 129.4, 129.1, 128.5, 46.5, 42.0, 37.0, 21.1; AMM (ESI-TOF) *m*/*z* calcd for $C_{18}H_{17}ClNO_3S^-$ [M − H]$^-$ 362.0623, found 362.0628.

*2-Benzylisoquinoline-1,3(2H,4H)-dione (**S3**).* To a flame-dried round-bottom flask was added homophthalic anhydride (0.81 mg, 0.5 mmol), and the mixture was dissolved in toluene (1.0 mL). Benzylamine (0.0054 mL, 5.0 mmol) was added, and the reaction mixture was stirred at reflux for 24 h. The reaction mixture was then cooled and concentrated in vacuo. Purification by gradient flash column chromatography (20−100% EtOAc/hexanes) gave **S3** (69.8 mg, 56%) as an off-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48−7.41 (m, 3H), 7.32−7.26 (m, 3H), 7.26−7.22 (m, 1H), 5.19 (s, 2H), 4.07 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 164.9, 137.1, 134.1, 133.7, 129.3, 129.0, 128.4, 127.8, 127.5, 127.1, 125.4, 43.3, 36.5; AMM (ESI-TOF) *m*/*z* calcd for $C_{16}H_{14}NO_2^+$ [M + H]$^+$ 252.1019, found 252.1024.

Liquid Chromatography-Mass Spectrometry Experiments. *Three-Component Amide-Exchange Experiment.* To a flame-dried microwave vial were added **26a** (0.135 g, 0.5 mmol) and *p*-cholorobenzylamine (0.036 mL, 0.5 mmol), and the mixture was dissolved in toluene (4.5 mL, 0.5 M) and heated to reflux. After 6 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The mixture was analyzed using liquid chromatography-mass spectrometry, which gave masses corresponding to amides **26a** and **26b**.

Imide-Exchange Experiment. To a flame-dried microwave vial was added **S3** (0.055 g, 0.22 mmol). **S3** was dissolved in toluene (1.0 mL, 0.22 M), then *p*-cholorobenzylamine (0.027 mL, 0.22 mmol) added, and the reaction mixture heated to reflux. After 24 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The mixture was analyzed using liquid chromatography-mass spectrometry, which gave masses corresponding to only **S3** and *p*-chlorobenzylamine.

Four-Component Amide-Exchange Experiment. To a flame-dried microwave vial were added **17b** (0.100 g, 0.30 mmol) and *p*-cholorobenzylamine (0.036 mL, 0.30 mmol), and the mixture was dissolved in toluene (4.5 mL, 0.066 M) and heated to reflux. After 17 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The reaction mixture was cooled to room temperature and concentrated in vacuo. The mixture was analyzed using liquid chromatography-mass spectrometry, which gave masses corresponding to amides **17a**, **17b**, **34a**, and **34b**.

Four-Component Thiol-Exchange Experiment. To a flame-dried microwave vial were added **17b** (0.100 g, 0.30 mmol) and *p*-methoxythiophenol (0.036 mL, 0.30 mmol), and the mixture was dissolved in toluene (4.5 mL, 0.066 M) and heated to reflux. After 17 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The mixture was analyzed using liquid chromatography-mass spectrometry, which gave masses corresponding to **17a**, **17b**, and negligible quantities of **35a** and **35b**.

General Procedure for the Synthesis of Dihydroisoquinolones (27). Homophthalic anhydride (81.0 mg, 0.5 mmol) and Na_2SO_4 (1 equiv) were added to a flame-dried microwave vial under argon and dissolved in toluene (1.0 mL, 0.5 M). Aldehyde (0.5 mmol, 1 equiv) and amine (0.5 mmol, 1 equiv) were added sequentially, and the vial was sealed shut. The vial was then placed in a silicone oil bath and heated to 110 °C. After 24 h, the reaction mixture was concentrated in vacuo. The crude reaction mixture was purified using gradient flash column chromatography (EtOAc/hexanes).

*trans-2-Benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27a**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified by gradient flash column chromatography (40−100% EtOAc in hexanes) to afford **27a** (0.150 g, 84%), a single diastereomer, as a white solid. **27a** was also prepared on a 1 mmol scale. In this experiment, **27a** was purified by sequential trituration from hexanes and then ether to afford (0.285 g, 80%) a single diastereomer as a white solid. Finally, **27a** was also prepared in two steps from **26a**. **26a** (0.134 g, 0.5 mmol) and Na_2SO_4 (0.071 g, 0.5 mmol) were added to a flame-dried microwave vial under argon and dissolved in toluene. Benzaldehyde (0.051 mL, 0.5 mmol) was added to the reaction mixture, and the vial was sealed shut. The vial was then placed in a silicone oil bath and heated to 110 °C. After 24 h, the reaction mixture was concentrated in vacuo. The crude reaction mixture was purified using gradient flash column chromatography (40−100% EtOAc in hexanes) to afford **27a** (0.146 g, 82%), a single diastereomer, as a white solid: mp 220.2−224.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.46 (dtd, *J* = 25.4, 7.5, 1.4 Hz, 2H), 7.26−7.21 (m, 5H), 7.18−7.12 (m, 3H), 7.11−7.06

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(m, 1H), 7.06−7.02 (m, 2H), 5.66 (d, J = 14.5 Hz, 1H), 5.11 (s, 1H), 3.87 (s, 1H), 3.70 (d, J = 14.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.1, 163.8, 138.2, 136.5, 132.3, 131.3, 129.3, 129.1, 128.9 (two carbons), 128.8, 128.4, 128.3, 128.1, 127.6, 126.3, 60.1, 50.9, 49.0; AMM (ESI-TOF) m/z calcd for $C_{23}H_{18}NO_3^-$ $[M - H]^-$ 356.1292, found 356.1293.

*trans-2-Benzyl-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27b**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified by gradient flash column chromatography (20−100% EtOAc inhexanes) to afford **27b** (0.142 g, 89%), a single diastereomer, as a yellow solid: mp 102.4−105.3 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.28 (dd, J = 7.5, 1.6 Hz, 1H), 7.46 (dtd, J = 20.9, 7.5, 1.4 Hz, 2H), 7.23 (dd, J = 6.9, 2.7 Hz, 2H), 7.13 (dd, J = 5.3, 1.9 Hz, 3H), 7.09 (d, J = 7.3 Hz, 1H), 6.95 (d, J = 8.6 Hz, 2H), 6.76−6.74 (m, 2H), 5.64 (d, J = 14.7 Hz, 1H), 5.04 (s, 1H), 3.83 (s, 1H), 3.74 (s, 3H), 3.68 (d, J = 14.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.3, 163.8, 159.5, 136.7, 132.4, 131.6, 130.3, 129.5, 129.3, 129.0, 128.9, 128.5, 128.5, 127.7, 127.7, 114.4, 59.8, 55.4, 51.2, 49.0; AMM (ESI-TOF) m/z calcd for $C_{24}H_{20}NO_4^-$ $[M - H]^-$ 386.1398, found 386.1400.

*trans-3-(4-Bromophenyl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27c**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified first by trituration with hexanes, followed by gradient flash column chromatography (20−100% EtOAc in hexanes) to afford **27c** (0.192, 85%), a single diastereomer, as an off-white solid. ^1H NMR data match the reported literature spectrum:[24] ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 7.8 Hz, 4H), 7.25 (d, J = 8.7 Hz, 3H), 7.16 (d, J = 8.3 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 5.62 (s, 1H), 4.19 (s, 1H), 3.74 (s, 3H).

*trans-2-Benzyl-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27d**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified by gradient flash column chromatography (20−100% EtOAc in hexanes) to afford **27d** (0.167 g, 88%), a single diastereomer, as an off-white amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 7.4, 1.8 Hz, 1H), 7.54−7.37 (m, 4H), 7.23−7.16 (m, 2H), 7.16−7.02 (m, 6H), 5.43 (d, J = 14.5 Hz, 1H), 5.18 (s, 1H), 3.96 (d, J = 14.5 Hz, 1H), 3.81 (d, J = 1.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.3, 163.6, 143.7, 135.9, 132.7, 132.7, 130.7, 129.2, 129.2, 129.1, 128.9, 128.6, 128.4, 127.9, 127.1, 118.1, 112.2, 60.1, 50.7, 49.6; AMM (ESI-TOF) m/z calcd for $C_{24}H_{17}N_2O_3^-$ $[M - H]^-$ 381.1245, found 381.1246.

*trans-2-(4-Methoxyphenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27e**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified by gradient flash column chromatography (20−100% EtOAc in hexanes) to afford **27e** (0.144 g, 77%), a single diastereomer, as a brown amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.20 (dd, J = 5.8, 3.4 Hz, 1H), 7.41 (dd, J = 5.7, 3.3 Hz, 2H), 7.21−7.14 (m, 6H), 7.13−7.08 (m, 2H), 6.78−6.71 (m, 2H), 5.52 (d, J = 1.4 Hz, 1H), 3.96 (d, J = 1.5 Hz, 1H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.3, 164.3, 158.5, 139.0, 134.9, 132.7, 132.6, 129.6, 129.3, 128.9, 128.7, 128.5, 128.2, 128.1, 126.6, 114.4, 65.3, 55.4, 51.7; AMM (ESI-TOF) m/z calcd for $C_{23}H_{18}NO_4^-$ $[M - H]^-$ 372.1241, found 372.1241.

*trans-2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27f**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified by gradient flash column chromatography (EtOAc in hexanes) to afford **27f** (0.158 g, 76%), a single diastereomer, as a yellow amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.27−8.21 (m, 1H), 7.43 (qt, J = 7.4, 3.6 Hz, 2H), 7.22−7.13 (m, 2H), 7.08 (dd, J = 6.9, 1.8 Hz, 1H), 6.99−6.91 (m, 2H), 6.79−6.66 (m, 4H), 5.57 (d, J = 14.4 Hz, 1H), 5.10−5.01 (m, 1H), 3.82 (d, J = 1.5 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.63 (d, J = 14.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.5, 163.7, 159.3, 159.0, 132.2, 131.6, 130.3, 130.2, 129.3, 129.1, 128.8, 128.7, 128.3, 127.5, 114.2, 113.7, 59.5, 55.3, 55.2, 51.2, 48.3; AMM (ESI-TOF) m/z calcd for $C_{25}H_{22}NO_5^-$ $[M - H]^-$ 416.1503, found 416.1506.

*trans-2-(4-Chlorobenzyl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27g**).* The title compound was prepared according to the general three-component reaction procedure. The crude reaction mixture was purified by gradient flash column chromatography (EtOAc in hexanes) to afford **27g** (0.200 g, 95%), a single diastereomer, as a white solid: mp range 247.3−249.3 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (dd, J = 7.2, 2.0 Hz, 1H), 7.49−7.37 (m, 2H), 7.30 (d, J = 2.3 Hz, 4H), 7.23−7.17 (m, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.22 (d, J = 15.1 Hz, 1H), 5.18 (s, 1H), 4.03 (s, 1H), 3.84 (d, J = 15.0 Hz, 1H), 3.66 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 172.1, 163.5, 158.7, 136.5, 133.9, 132.1, 131.8, 130.8, 130.0, 129.7, 128.9, 128.2, 128.0, 127.3, 127.0, 114.1, 60.8, 55.1, 51.0, 48.6; IR 2949.0, 2831.6, 1697.8, 1641.5 cm^{-1}; AMM (ESI-TOF) m/z calcd for $C_{24}H_{19}ClNO_4^-$ $[M - H]^-$ 420.1008, found 420.1011.

*trans-1-Oxo-3-phenyl-2-propyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27h**).* Homophthalic anhydride (162.0 mg, 1.0 mmol) and Na_2SO_4 (142.0 mg, 1 mmol) were added to a flame-dried microwave vial under argon and dissolved in toluene (2.0 mL, 0.5 M). Benzaldehyde (0.102 mL, 1.0 mmol) and propylamine (0.082 mL, 1.0 mmol) were added sequentially, and the vial was sealed shut. The vial was then placed in a silicone oil bath and heated to 115 °C. After 24 h, the reaction mixture was concentrated in vacuo. The crude reaction mixture was purified using gradient flash column chromatography (20−100% EtOAc in hexanes) to afford **27h** (0.185 g, 60%), a single diastereomer, as a white amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.21−8.08 (m, 1H), 7.40 (td, J = 6.9, 4.0 Hz, 2H), 7.22 (d, J = 6.4 Hz, 3H), 7.15−7.08 (m, 1H), 7.08−7.02 (m, 2H), 5.29 (s, 1H), 4.09−3.97 (m, 1H), 3.94 (s, 1H), 2.82 (ddd, J = 14.0, 8.8, 5.8 Hz, 1H), 1.62 (dp, J = 14.6, 7.1 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.5, 164.2, 138.6, 132.1, 131.7, 131.7, 129.4, 129.0, 128.8, 128.5, 128.0, 126.2, 61.1, 51.2, 48.7, 20.8, 11.3; AMM (ESI-TOF) m/z calcd for $C_{19}H_{20}NO_3^+$ $[M + H]^+$ 310.1438, found 310.1437.

*trans-2-Isopropyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27i**).* Homophthalic anhydride (162.0 mg, 1.0 mmol) and Na_2SO_4 (142.0 mg, 1 mmol) were added to a flame-dried microwave vial under argon and dissolved in toluene (2.0 mL, 0.5 M). Benzaldehyde (0.102 mL, 1.0 mmol) and isopropylamine (0.082 mL, 1.0 mmol) were added sequentially, and the vial was sealed shut. The vial was then placed in a silicone oil bath and heated to 115 °C. After 24 h, the reaction mixture was concentrated in vacuo. The crude reaction mixture was purified using gradient flash column chromatography (20−100% EtOAc in hexanes) to afford **27i** (0.261 g, 84%), a single diastereomer, as a white amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.5, 1.6 Hz, 1H), 7.43−7.31 (m, 2H), 7.18 (s, 3H), 7.05 (ddd, J = 12.8, 7.5, 2.0 Hz, 3H), 5.34 (d, J = 1.6 Hz, 1H), 4.98 (hept, J = 7.0 Hz, 1H), 3.88 (d, J = 1.6 Hz, 1H), 1.21 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.6, 164.1, 140.4, 132.1, 131.5, 130.1, 129.1, 128.6, 128.6, 128.0, 127.6, 126.2, 56.6, 52.2, 46.4, 20.3, 20.0; AMM (ESI-TOF) m/z calcd for $C_{19}H_{20}NO_3^+$ $[M + H]^+$ 310.1438, found 310.1438.

*trans-2-Benzyl-3-isopropyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (**27j**).* Homophthalic anhydride (162.0 mg, 1.0 mmol) and Na_2SO_4 (142.0 mg, 1 mmol) were added to a flame-dried microwave vial under argon and dissolved in toluene (2.0 mL, 0.5 M). Isobutyraldehyde (0.091, 1.0 mmol) and benzylamine (0.109 mL, 1.0 mmol) were added sequentially, and the vial was sealed shut. The vial was then placed in a silicone oil bath and heated to 115 °C. After 24 h, the reaction mixture was concentrated in vacuo. The crude reaction mixture was purified using gradient flash column chromatography (20−100% EtOAc in hexanes) to afford **27j** (0.243 g, 75%), a single diastereomer, as a yellow amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 7.4, 1.7 Hz, 1H), 7.53−7.40 (m, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 7.19 (dd, J = 7.2, 1.6 Hz, 1H), 7.11 (t, J = 7.3 Hz,

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2H), 7.05 (t, J = 7.2 Hz, 1H), 5.54 (d, J = 14.5 Hz, 1H), 3.96 (d, J = 14.5 Hz, 1H), 3.75 (s, 1H), 3.71 (dd, J = 7.0, 1.3 Hz, 1H), 1.91 (h, J = 6.8 Hz, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 174.9, 166.0, 138.5, 136.8, 133.5, 130.4, 130.1, 129.5, 129.4, 129.1, 128.5, 128.5, 65.6, 52.1, 45.9, 32.9, 20.2, 19.2; AMM (ESI-TOF) m/z calcd for $C_{20}H_{22}NO_3^+$ $[M + H]^+$ 324.1594, found 324.1595.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01163.

Experimental procedures, characterization details, including ^1H and ^{13}C NMR spectra, and LCMS traces (PDF)

Accession Codes

CCDC 2075126−2075127 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.

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Notes

The authors declare no competing financial interest.

It should be noted that *N,O*-acetal byproducts of the CCR, which are thought to proceed through carboxylate attack on the iminium ion of **4**, have been isolated.[5,39,40] *N,O*-Acetal byproducts have been found to form instantaneously in the case of cyclopentane-fused maleic anhydride, and over the course of 3 days with indolenines, leading exclusively to the aforementioned byproducts with no evidence of the CCR product.[5,40] It is likely that zwitterionic intermediate **4** can be accessed with poor CCR substrates wherein Mannich addition is comparably high in energy.

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