ACS Catalysis

pubs.acs.org/acscatalysis Letter

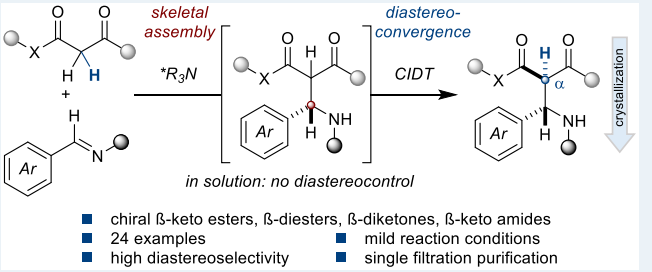
Enantio- and Diastereoselective Mannich Reactions of ß-Dicarbonyls by Second Stage Diastereoconvergent Crystallization

William R. Cassels, Evan T. Crawford, and Jeffrey S. Johnson*

Cite This: ACS Catal. 2023, 13, 6518−6524 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The synthesis of chiral α-monosubstituted-ß-dicarbonyls is a challenging task in asymmetric catalysis due to the rapid, typically uncontrolled, product racemization or epimerization under most reaction conditions. For this reason, diastereoselective additions of unsubstituted ß-dicarbonyls to π-electrophiles are unusual. Herein, we disclose a simple catalytic crystallization-driven enantio- and diastereoselective Mannich reaction for the synthesis of stereodefined α-monosubstituted-ß-keto esters, dissymmetric ß-diesters, dissymmetric ß-diketones, and ß-keto amides that productively leverages product epimerization in solution. Mechanistic studies suggest a scenario where the initial enantioselective, diastereodivergent skeletal assembly is catalyzed by a chiral tertiary amine organocatalyst, which then facilitates second stage crystallization-induced diastereoconvergence to provide the challenging α-stereocenter in excellent stereoselectivity.



KEYWORDS: *asymmetric catalysis, crystallization-induced diastereomer transformation, Mannich reaction, organocatalysis, stereoconvergence*

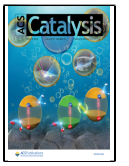
Catalytic reaction platforms that generate multiple stereocenters are desirable in organic synthesis in part due to the trend toward three-dimensional, sp^3-rich carbon frameworks as scaffolds for the next generation of drug candidates.[1] A common paradigm in stereoselective catalysis posits the use of a chiral catalyst to form bonds that concurrently establish one or multiple configurationally static asymmetric centers.[2] A complementary but less explored approach relies on a strategic decision to dissociate skeletal assembly from stereochemical control of configurationally dynamic asymmetric centers.[3−6] Second stage stereoconvergence enables the synthesis of complex small molecules with multiple stereocenters that are challenging to access using alternative methods. Crystallization-induced diastereomer transformation (CIDT) is a powerful stereoconvergent manifold that concurrently alleviates the typical time- and resource-intensive purification methods of catalytic asymmetric reactions (e.g., flash column chromatography).[7] CIDTs are highly desirable in organic synthesis, but general non-auxiliary-based methods that are directly linked to a same-pot catalytic, asymmetric reaction are underexplored.[5,7]

The prototypical examples of base-labile stereocenters are α-monosubstituted-ß-keto esters (pK_a = 13−15, DMSO[8]). Due to their configurational fragility, their asymmetric synthesis remains rare despite the potential for such compounds to provide complementary approaches to the well-established enantioconvergent reactions of chiral racemic ß-keto esters.[9] Select examples of asymmetric α-monosubstituted-ß-keto ester synthesis include Lewis acid-catalyzed formal insertion reactions of diazoacetates and aldehydes[10] and an auxiliary-controlled aldol/oxidation sequence.[11] These reactions established the feasibility of preparing chiral ß-keto esters, but the utility is limited due to the need for cryogenic temperatures and observable product racemization/epimerization during chromatographic purification.[10−12]

An ideal atom efficient manifold for accessing enantioenriched ß-keto esters is the catalytic addition of an unsubstituted ß-keto ester to a π-electrophile. Extant addition reactions of ß-keto esters fall into two principal categories: (a) reactions that form a mixture of diastereomers due to immediate uncontrolled epimerization under the reaction conditions, or (b) reactions that form a fully substituted α-stereocenter that cannot epimerize via keto−enol tautomerization (Scheme 1b).[13,14] A small number of Mannich adducts comprise the notable outliers,[15,16] but general methods have proved elusive and the broader problem remains unsolved to date.

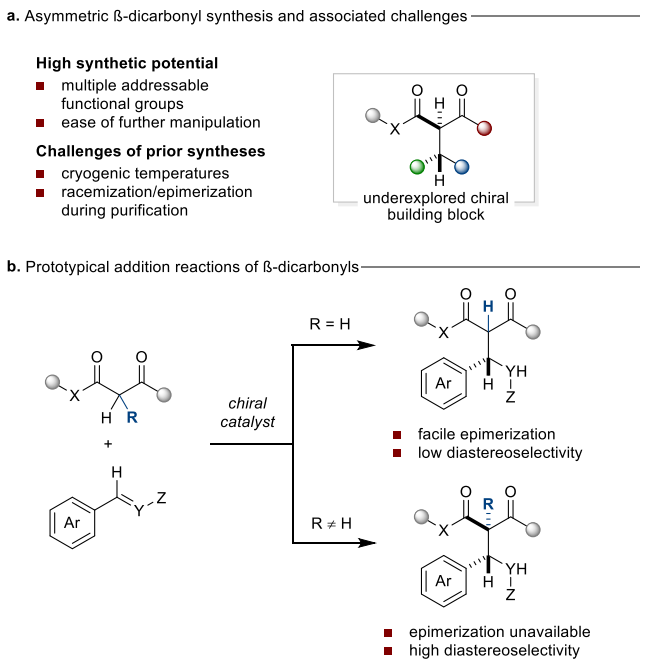
Considering this gap, we proposed that we could overcome the challenges with such addition reactions by applying a merged asymmetric catalysis/CIDT platform.[5] A chiral tertiary amine base could catalyze the key enantioselective carbon−carbon (C−C) bond formation providing the benzylic amine

Received: April 3, 2023
Revised: April 21, 2023
Published: April 27, 2023



https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518−6524

Scheme 1. Asymmetric Addition Reactions of ß-Dicarbonyls



stereocenter in high fidelity (Figure 1a left: Asymmetric Catalysis Stage) and then mediate the epimerization of the resulting product. Taking advantage of the different solubility properties of product stereoisomers, dynamic stereoconvergent crystallization of one diastereomer could result in 100% theoretical yield of solid single-stereoisomeric product precipitating from solution (Figure 1a right: Diastereoconvergence Stage). Under this mechanism, the solid ß-keto ester products both are protected from solution-phase epimerization and can be isolated in pure form in a single filtration. In this communication, we disclose the achievement of an enantio- and diastereoselective Mannich reaction of ß-keto esters, dissymmetric ß-diesters, dissymmetric ß-diketones, and ß-keto amides enabled by crystallization.

We began our studies with the reaction of ethyl acetoacetate **1a** and the benzyl carbamate (Cbz) protected imine **2a** using Takemoto's chiral nonracemic tertiary amine catalyst **I** (Figure 1b).[17] In agreement with the prior art, when the reaction was performed in homogeneous conditions (e.g., solvent = DCM), no diastereoselectivity was observed.[15,17b,18] Ethereal solvents proved crucial to the selective crystallization of one diastereomer directly from the reaction mixture (see Supporting Information for reaction optimization).[5] Fine-tuning the carbamate solubility properties by using a mixture of diethyl ether and pentanes (3:1) resulted in good isolated yield while retaining excellent stereoselectivity after a single filtration of the reaction mixture (68% yield, >20:1 dr, 90:10 er).

With optimal reaction conditions in hand, we next explored the allowable parameters of the reaction and found that the transformation exhibited good scope (Table 1). The wide-ranging applicability is compelling considering the high dependence on the physical properties of each individual substrate, standing in contrast to many non-auxiliary-based CIDTs, which commonly are of more limited scope.[7] All reactions were conducted at ambient temperature and diastereoenriched products were isolated by a single filtration of the crude reaction mixture, highlighting the user-friendly nature of the reaction platform.[19] An inherent feature of the method is that in at least some cases, an *in situ* product enantiomeric ratio upgrade is occurring within the crystallization (see Supporting Information for details and further commentary).

p-Halide-substituted aryl imines performed well under the reaction conditions, providing diastereopure amino-ketones **3b−3e** in good yields and enantioselectivities. Electron-deficient (**3f−3h**) and electron-rich (**3i−3j**) carbamates, including lipophilic adducts **3g** and **3j**, were successfully obtained as single diastereomers in good yields and enantioselectivities. *p*-Dimethylaminophenyl amino-ketone **3k** was obtained in excellent yield and diastereoselectivity but poor enantioselectivity, a result that is likely due to aniline-mediated racemic reaction (see Supporting Information for details). *m*-Substituted aryl imines of varying electronic properties successfully delivered carbamates **3l** and **3m**. Piperonal-derived (**3n**) and 2-naphthyl-derived urethanes (**3o**) were also obtained in good yields and high stereoselectivity. *t*-Butyl carbamate (Boc) protected amino-ketone **3p**

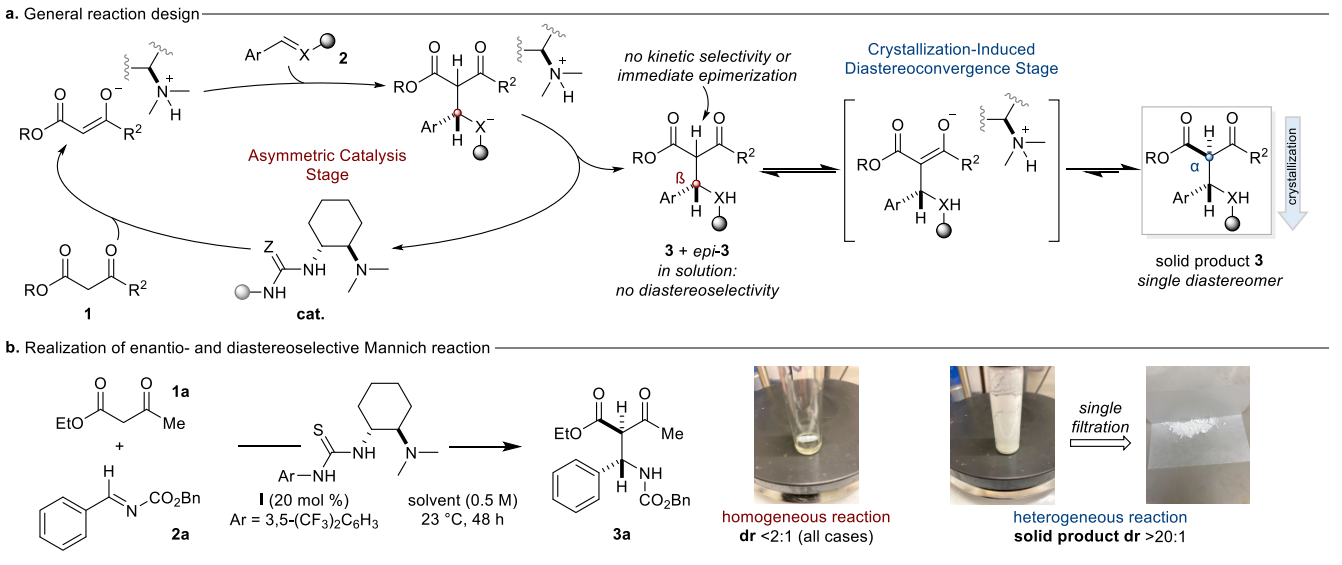
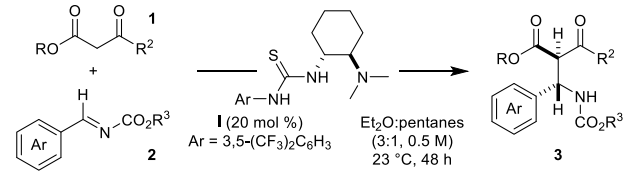
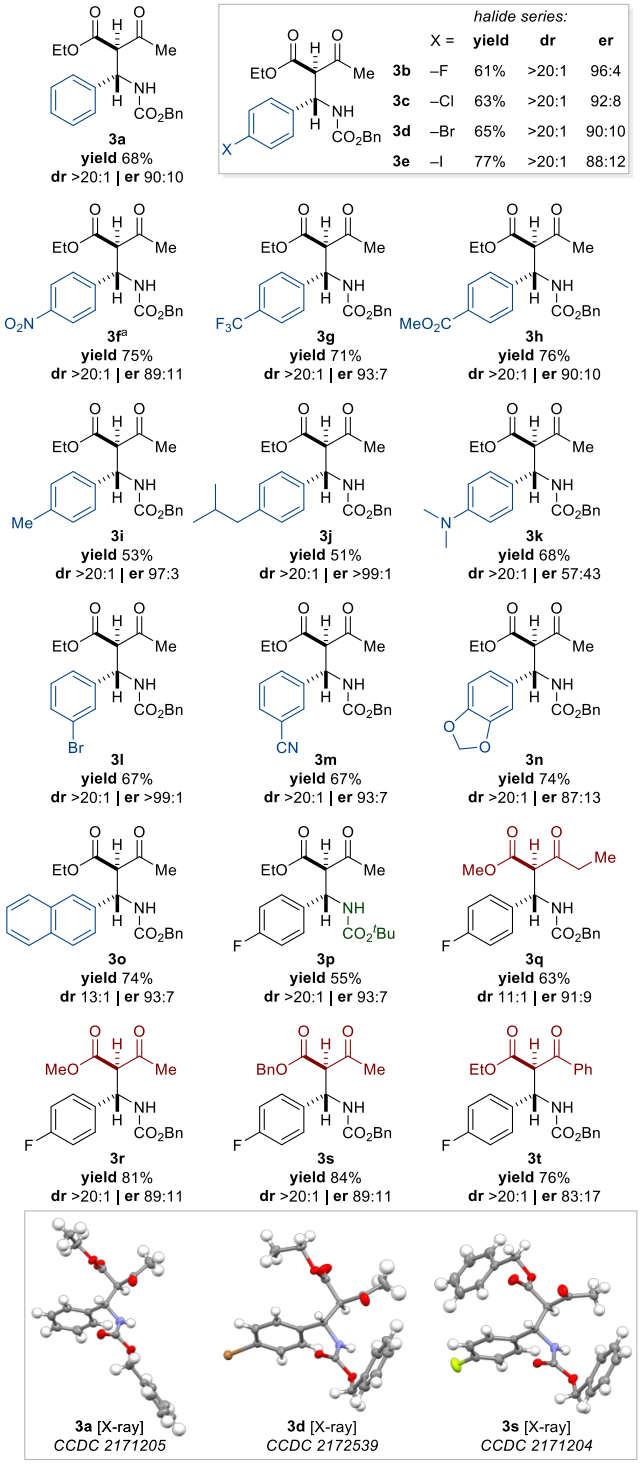


Figure 1. Proposed Reaction Mechanism and Realization of Concept

https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518−6524

Table 1. Scope of Enantio- and Diastereoselective Mannich Reaction of ß-Keto Esters*





*Reaction conditions: ß-keto ester **1** (0.300 mmol, 1.5 equiv), imine **2** (0.200 mmol, 1.0 equiv), catalyst **I** (20 mol %), Et_2O:pentanes solvent (3:1, 0.4 mL, 0.5 M), rt, 48 h. Yields refer to isolated yields. Diastereoselectivity was determined by ^1H NMR spectroscopic analysis of the solid product following filtration. Enantiomeric ratios were determined by HPLC analysis of the solid product following filtration using a chiral stationary phase. For compounds without X-ray crystal structures, the relative stereochemistry of the major diastereomer shown must be considered tentative because of the possibility for thermodynamic crystallization properties to vary depending on the substrate.[5] [a]Reaction solvent = Et_2O.

was obtained in slightly lower yield, but excellent enantio- and diastereoselectivity was retained. Several different unsubstituted ß-keto esters were also viable in the reaction, providing amino-ketones **3q**-**3t** in good yields and stereoselectivities. The absolute and relative stereochemistry of the amino-ketones were determined by single crystal X-ray diffraction analyses of carbamates **3a**, **3d**, and **3s**. At this stage of the optimization, alkyl imines and *o*-substituted aryl imines are not viable in the Mannich reaction due to low conversion and/or poor CIDT.[20] All ß-keto ester products synthesized that did not precipitate out of solution were observed as an approximately 1:1 mixture of diastereomers, emphasizing that crystallization is required for obtaining high diastereoselectivity.

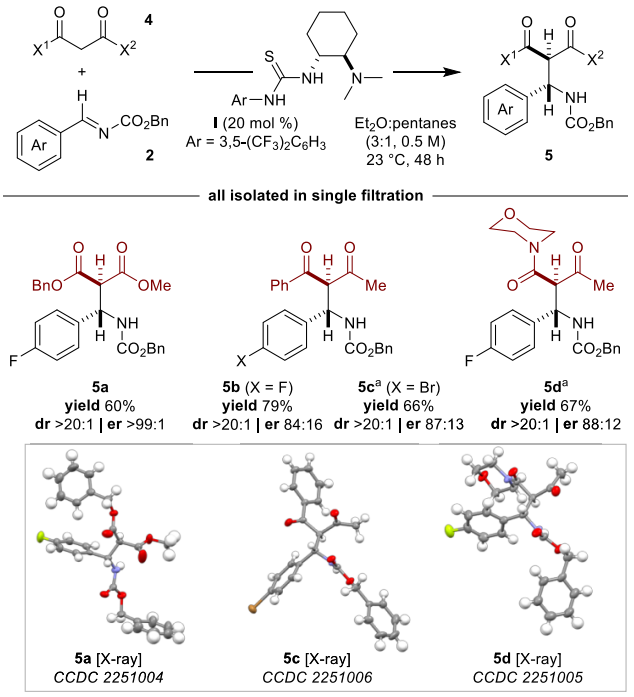
The title Mannich reaction could be extended to the enantio- and diastereoselective synthesis of chiral ß-diester- and ß-diketone-derived carbamates **5a** and **5b**–**c**, respectively (Table 2). Morpholine *β*-keto amide then provided amino-ketone **5d** in good yield and stereoselectivity. The stereoselective Mannich addition could also be expanded to other doubly activated carbon nucleophiles: preliminary studies have revealed that phosphonoacetate and cyanosulfone nucleophiles can also be viable pro-nucleophiles in similar CIDT reactions. Mannich adducts of both were obtained in high diastereoselectivity when mediated by an achiral general base catalyst (Et_3N), but asymmetric variants were unsuccessful under our current optimal conditions (see Supporting Information for further details). Both new transformations are currently under investigation in our laboratory. Similar to the ß-keto ester scope, all reactions were conducted at ambient temperature and diastereoenriched products were isolated in excellent purity after a single filtration of the crude reaction mixture.

A series of experiments was conducted to evaluate the hypothesized merged asymmetric catalysis/CIDT mechanism. A crossover experiment with amino-ketone **3a** and imine **2b** did not show formation of amino-ketone **3b**, providing support that the initial C–C bond formation step is irreversible (Scheme 2a). To demonstrate unambiguously that the major diastereomer was obtained by stereoconvergent crystallization, a 1:1 mixture of diastereomers **3a** and *epi*-**3a** was prepared by catalyst-mediated epimerization in a solvent exhibiting complete homogeneity ($CDCl_3$). Switching the reaction solvent by evaporation of $CDCl_3$ and addition of an Et_2O:pentanes mixture (optimal CIDT conditions) resulted in the reaction rapidly becoming heterogeneous. After 24 h at room temperature, a single filtration of the reaction mixture provided good mass recovery of diastereopure carbamate **3a** (Scheme 2b).

Interested in gaining more information about the rates of epimerization, we next subjected diastereoenriched carbamate **3a** to a variety of different solution-phase conditions.[11a,14] In the presence of catalyst **I** in aprotic solvent ($CDCl_3$), complete equilibration was observed within 15 min (Scheme 2c, blue

https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518–6524

Table 2. Enantio- and Diastereoselective Mannich Reaction of Dissymmetric Malonates, ß-Diketones, and ß-Keto Amides*

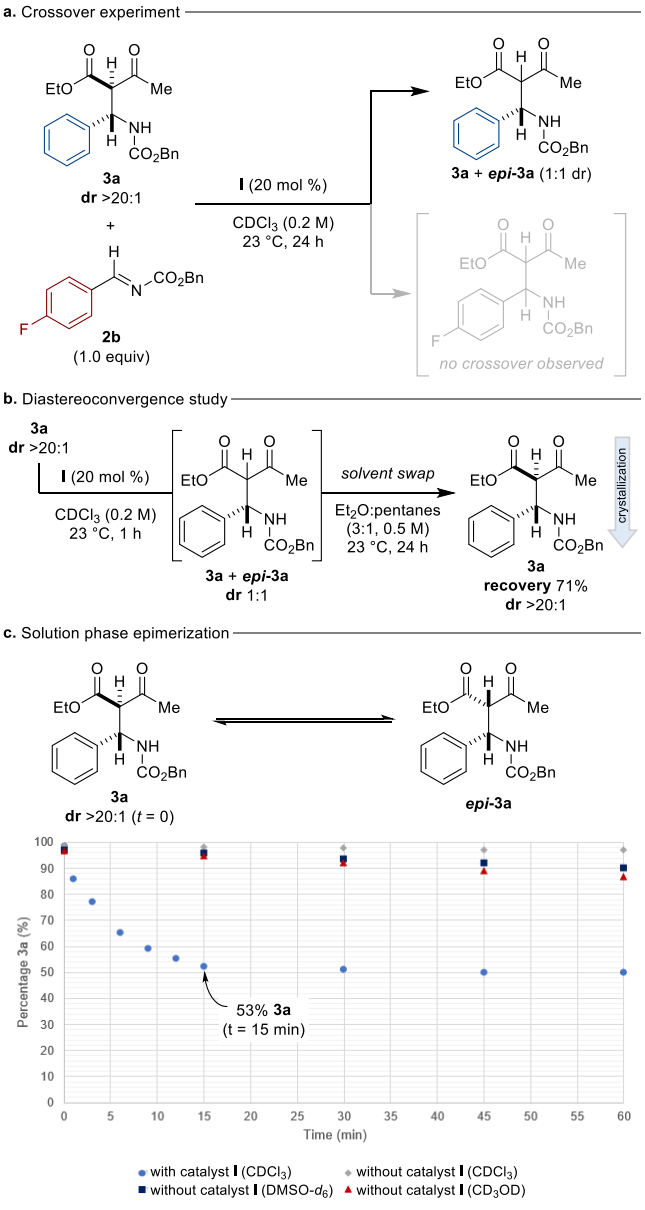


*Reaction conditions: Nucleophile **4** (0.300 mmol, 1.5 equiv), imine **2** (0.200 mmol, 1.0 equiv), catalyst **I** (20 mol %), Et_2O:pentanes solvent (3:1, 0.4 mL, 0.5 M), rt, 48 h. Yields refer to isolated yields. Diastereoselectivity was determined by ^1H NMR spectroscopic analysis of the solid product following filtration. Enantiomeric ratios were determined by HPLC analysis of the solid product following filtration using a chiral stationary phase. For compounds without X-ray crystal structures, the relative stereochemistry of the major diastereomer shown must be considered tentative because of the possibility for thermodynamic crystallization properties to vary depending on the substrate.[5] [a]Reaction solvent = MTBE.

circles). In the absence of catalyst in aprotic solvent ($CDCl_3$), gradual epimerization was still observed (Scheme 2c, gray diamonds; see Supporting Information for complete experimental details). Uncatalyzed epimerization was accelerated in highly polar solvent (DMSO-d_6; Scheme 2c, navy squares) or protic solvent (CD_3OD; Scheme 2c, red triangles). Despite the uncatalyzed epimerization in solution, most diastereoenriched amino-ketones in the solid phase displayed remarkable configurational stability over 1−2 months at room temperature and >6 months in the freezer. These studies underscore the importance of crystallization in maintaining high diastereocontrol: rapid epimerization in solution renders solution-phase conditions, those typically favored for catalytic asymmetric reactions, incompatible for the desired diastereoselective reaction.

With this information in hand, we next explored the synthetic utility of the enantio- and diastereoselective Mannich reaction. The reaction proved readily scalable to 8.50 mmol under identical conditions to provide over 2.7 g of amino-ketone **3a** as a single diastereomer in good yield and enantioselectivity (Scheme 3a). The method benefits from larger scale: the yield was significantly higher in the multigram reaction, suggesting the substantial potential of the approach. Additionally, the crude filtrate containing the catalyst could be

Scheme 2. Mechanistic Investigations

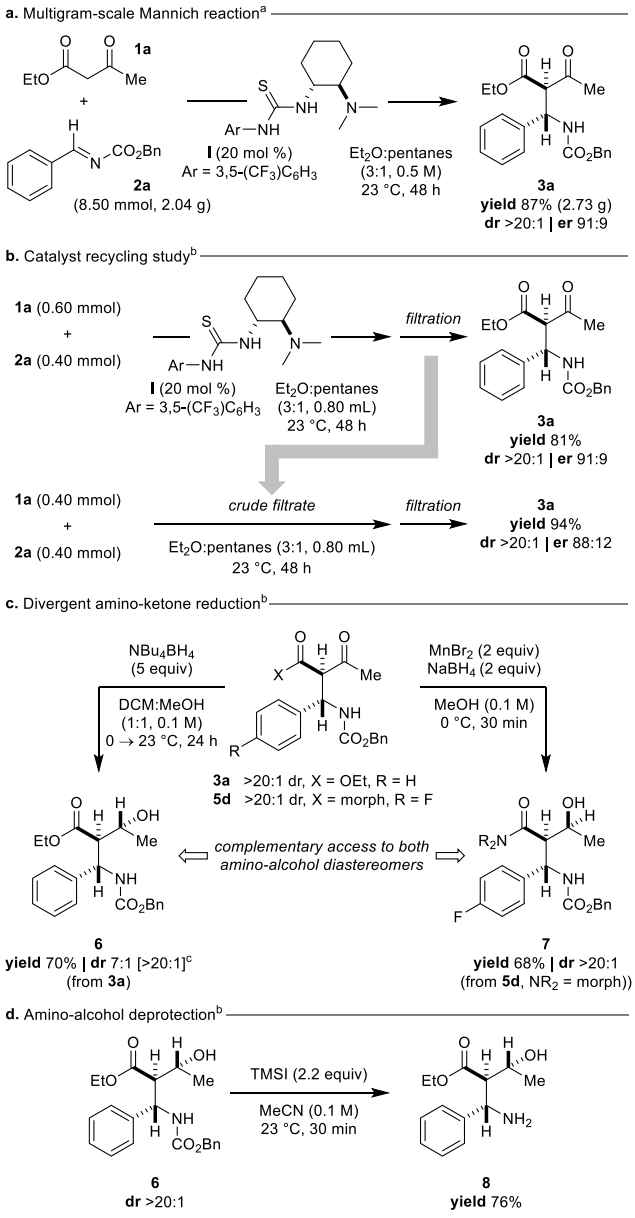


combined with another equivalent of ß-keto ester and imine and resubjected to the CIDT conditions (0.5 M 3:1 Et_2O:pentanes, 48 h), providing a second crop of diastereopure carbamate with just slight loss of enantioinduction (run 1 er: 91:9; run 2 er: 88:12; see Supporting Information for complete experimental details).[5]

Two different methods were used in the reduction of the diastereopure amino-ketones. Substrate-controlled diastereoselective reduction of ß-keto ester product **3a** occurred efficiently using NBu_4BH_4 to provide a good yield of a single diastereomer of amino-alcohol **6** after the minor diastereomer was purged via flash column chromatography (Scheme 3c, left).[21] Although Lewis acid-directed reduction of ß-keto ester products resulted in poor diastereoselectivity (≤2:1 in all cases; see Supporting Information for further details),[22] ß-keto amide product **5d** was reduced using a $MnBr_2/NaBH_4$ combination to provide a single diastereomer of the complementary amino-alcohol **7** (Scheme 3c, right).[23] The relative stereochemistry of amino-alcohols **6** and **7** was

https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518−6524

Scheme 3. Scale-up Reaction and Synthetic Utility



[a]Reaction conditions: Nucleophile **1a** (12.75 mmol, 1.5 equiv), imine **2a** (8.50 mmol, 1.0 equiv), catalyst **I** (20 mol %), Et_2O:pentanes solvent (3:1, 17 mL, 0.5 M), rt, 48 h. Yields refer to isolated yields. Diastereoselectivity was determined by ^1H NMR spectroscopic analysis of the solid product following filtration. Enantiomeric ratio was determined by HPLC analysis of the solid product following filtration using a chiral stationary phase. [b]See Supporting Information for exact experimental details. [c]Number in parentheses represents dr following flash column chromatography.

determined by NOE analysis following conversion to their corresponding cyclic carbamates (see Supporting Information for details). Carbamate deprotection proceeded smoothly on diastereopure amino-alcohol **6** to provide unprotected primary amine **8** (Scheme 3d).[15a]

In summary, we have developed an enantio- and diastereoselective Mannich reaction of unsubstituted ß-keto esters, dissymmetric ß-diesters, dissymmetric ß-diketones, and ß-keto amides. A number of imines and β-dicarbonyls readily undergo the Mannich reaction, and the resulting amino-ketones precipitate from the reaction mixture as a single (or major) diastereomer. Mechanistic studies suggest a scenario where initial asymmetric C−C bond formation delivers the static asymmetric center and provides the platform for diastereoconvergence of the rapidly epimerizing β-dicarbonyl α-stereocenter. The resulting carbamates can then be transformed into useful amino-alcohol products. Ongoing studies in our laboratory are focused on expanding this platform to new asymmetric ß-dicarbonyl addition reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c01515.

Experimental details, materials and methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, and information on X-ray diffraction experiments (PDF)

X-ray crystallographic data for **3a** (CIF)

X-ray crystallographic data for **3d** (CIF)

X-ray crystallographic data for **3s** (CIF)

X-ray crystallographic data for **5a** (CIF)

X-ray crystallographic data for **5c** (CIF)

X-ray crystallographic data for **5d** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Jeffrey S. Johnson − *Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States;* orcid.org/0000-0001-8882-9881; Email: jsj@unc.edu

Authors

William R. Cassels − *Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States*

Evan T. Crawford − *Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.3c01515

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The project described was supported by award no. R35 GM118055 from the National Institute of General Medical Sciences. The X-ray crystallography analysis was supported by instrumentation acquired under the NSF MRI program under grant no. CHE-2117287. We thank Dr. B. Ehrmann and D. Weatherspoon (UNC Dept. of Chemistry Mass Spectrometry Core Laboratory) for their assistance with mass spectrometry analysis. We thank the UNC Dept. of Chemistry NMR Core Laboratory, especially Dr. M. ter Horst, for assistance with NMR analysis.

https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518−6524

REFERENCES

(1) (a) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. Asymmetric Synthesis of Active Pharmaceutical Ingredients. *Chem. Rev.* **2006**, *106*, 2734−2793. (b) Eastgate, M. D.; Schmidt, M. A.; Fandrick, K. R. On the design of complex drug candidate syntheses in the pharmaceutical industry. *Nat. Rev. Chem.* **2017**, *1*, 0016. (c) Méndez-Lucio, O.; Medina-Franco, J. L. The many roles of molecular complexity in drug discovery. *Drug Discovery Today* **2017**, *22*, 120−126. (d) Caille, S.; Cui, S.; Faul, M. M.; Mennen, S. M.; Tedrow, J. S.; Walker, S. D. Molecular Complexity as a Driver for Chemical Process Innovation in the Pharmaceutical Industry. *J. Org. Chem.* **2019**, *84*, 4583−4603. (e) Caille, S. Curbing the costs of chemical manufacturing. *Science* **2019**, *364*, 635.

(2) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books, 2009; pp 114−164.

(3) DeHovitz, J. S.; Loh, Y. Y.; Kautzky, J. A.; Nagao, K.; Meichan, A. J.; Yamauchi, M.; MacMillan, D. W. C.; Hyster, T. K. Static to inducibly dynamic stereocontrol: The convergent use of racemic β-substituted ketones. *Science* **2020**, *369*, 1113−1118.

(4) For select examples of stereochemical editing by selective epimerization, see: (a) Wang, Y.; Hu, X.; Morales-Rivera, C. A.; Li, G.-X.; Huang, X.; He, G.; Liu, P.; Chen, G. Epimerization of Tertiary Carbon Centers via Reversible Radical Cleavage of Unactivated C(sp^3)−H Bonds. *J. Am. Chem. Soc.* **2018**, *140*, 9678−9684. (b) Wang, Y.; Carder, H. M.; Wendlandt, A. E. Synthesis of Rare Sugar Isomers through Site-Selective Epimerization. *Nature* **2020**, *578*, 403−408. (c) Walker, M. M.; Koronkiewicz, B.; Chen, S.; Houk, K. N.; Mayer, J. M.; Ellman, J. A. Highly Diastereoselective Functionalization of Piperidines by Photoredox-Catalyzed α-Amino C−H Arylation and Epimerization. *J. Am. Chem. Soc.* **2020**, *142*, 8194−8202. (d) Zhang, Y.-A.; Gu, X.; Wendlandt, A. E. A Change from Kinetic to Thermodynamic Control Enables Trans- Selective Stereochemical Editing of Vicinal Diols. *J. Am. Chem. Soc.* **2022**, *144*, 599−605. (e) Oswood, C. J.; MacMillan, D. W. C. Selective Isomerization via Transient Thermodynamic Control: Dynamic Epimerization of trans to cis Diols. *J. Am. Chem. Soc.* **2022**, *144*, 93−98. (f) Shen, Z.; Walker, M. M.; Chen, S.; Parada, G. A.; Chu, D. M.; Dongbang, S.; Mayer, J. M.; Houk, K. N.; Ellman, J. A. General Light-Mediated, Highly Diastereoselective Piperidine Epimerization: From Most Accessible to Most Stable Stereoisomer. *J. Am. Chem. Soc.* **2021**, *143*, 126−131. (g) Li, X.; Wu, J.; Tang, W. General Strategy for the Synthesis of Rare Sugars via Ru(II)-Catalyzed and Boron-Mediated Selective Epimerization of 1,2- Trans -Diols to 1,2- Cis -Diols. *J. Am. Chem. Soc.* **2022**, *144*, 3727−3736. (h) Kazerouni, A. M.; Brandes, D. S.; Davies, C. C.; Cotter, L. F.; Mayer, J. M.; Chen, S.; Ellman, J. A. Visible Light-Mediated, Highly Diastereoselective Epimerization of Lactams from the Most Accessible to the More Stable Stereoisomer. *ACS Catal.* **2022**, *12*, 7798−7803. (i) Carder, H. M.; Wang, Y.; Wendlandt, A. E. Selective Axial-to-Equatorial Epimerization of Carbohydrates. *J. Am. Chem. Soc.* **2022**, *144*, 11870−11877. (j) Shen, Z.; Vargas-Rivera, M. A.; Rigby, E. L.; Chen, S.; Ellman, J. A. Visible Light-Mediated, Diastereoselective Epimerization of Morpholines and Piperazines to More Stable Isomers. *ACS Catal.* **2022**, *12*, 12860−12868. (k) Zhang, Y.-A.; Palani, V.; Seim, A.; Wang, Y.; Wang, K. J.; Wendlandt, A. E. Stereochemical Editing Logic Powered by the Epimerization of Unactivated Tertiary Stereocenters. *Science* **2022**, *378*, 383−390.

(5) de Jesús Cruz, P.; Cassels, W. R.; Chen, C. H.; Johnson, J. S. Doubly stereoconvergent crystallization enabled by asymmetric catalysis. *Science* **2022**, *376*, 1224−1230.

(6) de Jesús Cruz, P.; Johnson, J. S. Crystallization-Enabled Henry Reactions: Stereoconvergent Construction of Fully Substituted [*N*]-Asymmetric Centers. *J. Am. Chem. Soc.* **2022**, *144*, 15803−15811.

(7) (a) Anderson, N. G. Developing Processes for Crystallization-Induced Asymmetric Transformation. *Org. Process Res. Dev.* **2005**, *9*, 800−813. (b) Brands, K. M. J.; Davies, A. J. Crystallization-Induced Diastereomer Transformations. *Chem. Rev.* **2006**, *106*, 2711−2733. (c) Kolarovič, A.; Jakubec, P. State of the Art in Crystallization-Induced Diastereomer Transformations. *Adv. Synth. Catal.* **2021**, *363*, 4110−4158.

(8) Bordwell, F. G. Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(9) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. Stereoselective hydrogenation via dynamic kinetic resolution. *J. Am. Chem. Soc.* **1989**, *111*, 9134−9135. (b) Rachwalski, M.; Vermue, N.; Rutjes, F. P. J. T. Recent advances in enzymatic and chemical deracemisation of racemic compounds. *Chem. Soc. Rev.* **2013**, *42*, 9268−9282. (c) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations. *Chem. Rev.* **2017**, *117*, 4528−4561.

(10) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. Catalytic Asymmetric Roskamp Reaction of α-Alkyl-α-diazoesters with Aromatic Aldehydes: Highly Enantioselective Synthesis of α-Alkyl-β-keto Esters. *J. Am. Chem. Soc.* **2010**, *132*, 8532−8533.

(11) (a) Wu, W. J.; Li, M. M.; Liu, B.; Wu, Y. Racemization of α-Alkyl-β-Keto Esters and Enantioselective Total Synthesis of Two C-2‴Epimers of Plant Glycerolipid Santinol C. *Eur. J. Org. Chem.* **2019**, *2019*, 3169−3173. (b) Xiong, X.; Wu, Y.; Liu, B. Enantioselective Synthesis of the Proposed Structure of Santinol D. *Eur. J. Org. Chem.* **2020**, *2020*, 948−960.

(12) Gao, L.; Kang, B. C.; Hwang, G. S.; Ryu, D. H. Enantioselective Synthesis of α-Alkyl-β-ketoesters: Asymmetric Roskamp Reaction Catalyzed by an Oxazaborolidinium Ion. *Angew. Chem., Int. Ed.* **2012**, *51*, 8322−8325.

(13) (a) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. Mastering ß-Keto Esters. *Chem. Rev.* **1995**, *95*, 1065−1114. (b) Palomo, C.; Oiarbide, M.; López, R. Asymmetric organocatalysis by chiral Brønsted bases: implications and applications. *Chem. Soc. Rev.* **2009**, *38*, 632−653. (c) Das, J. P.; Marek, I. Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems. *Chem. Commun.* **2011**, *47*, 4593−4623. (d) Kotsuki, H.; Sasakura, N. Asymmetric Organocatalysis for the Construction of Quaternary Carbon Stereogenic Centers. *New and Future Developments in Catalysis: Catalysis for Remediation and Environmental Concerns*; Elsevier, 2013; pp 563−603. (e) Govender, T.; Arvidsson, P. I.; Maguire, G. E. M.; Kruger, H. G.; Naicker, T. Enantioselective Organocatalyzed Transformations of β-Ketoesters. *Chem. Rev.* **2016**, *116*, 9375−9437. (f) Wright, T. B.; Evans, P. A. Catalytic Enantioselective Alkylation of Prochiral Enolates. *Chem. Rev.* **2021**, *121*, 9196−9242.

(14) Du, H.; Rodriguez, J.; Bugaut, X.; Constantieux, T. Organocatalytic Enantio- and Diastereoselective Conjugate Addition to Nitroolefins: When β-Ketoamides Surpass β-Ketoesters. *Chem.—Eur. J.* **2014**, *20*, 8458−8466.

(15) (a) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. Asymmetric Mannich Reactions of β-Keto Esters with Acyl Imines Catalyzed by Cinchona Alkaloids. *J. Am. Chem. Soc.* **2005**, *127*, 11256−11257. (b) Hatano, M.; Horibe, T.; Ishihara, K. Chiral Lithium(I) Binaphtholate Salts for the Enantioselective Direct Mannich-Type Reaction with a Change of Syn/Anti and Absolute Stereochemistry. *J. Am. Chem. Soc.* **2010**, *132*, 56−57.

(16) It is mechanistically possible that a handful of Mannich adducts in the literature were unrecognized products of CIDTs. In our laboratory, we independently reproduced Schaus's cinchonine catalyzed Mannich reaction (ref 15a) and did observe the reaction as heterogeneous, but the filtration did not provide diastereoenriched product. This observation provided support that they were likely not unknowingly accomplishing a CIDT in the reaction vessel (what we propose is occurring in our system). See Supporting Information for further details and commentary.

(17) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672−

https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518−6524

12673. (b) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. Chiral-Thiourea-Catalyzed Direct Mannich Reaction. *Synthesis* **2007**, *2007*, 2571−2575.
(18) (a) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. Organocatalysed asymmetric Mannich reactions. *Chem. Soc. Rev.* **2008**, *37*, 29−41. (b) Bagheri, I.; Mohammadi, L.; Zadsirjan, V.; Heravi, M. M. Organocatalyzed Asymmetric Mannich Reaction: An Update. *ChemistrySelect* **2021**, *6*, 1008−1066.
(19) Anderson, N. G. Assessing the Benefits of Direct Isolation Processes. *Org. Process Res. Dev.* **2004**, *8*, 260−265.
(20) In this context, "poor CIDT" refers to at least one of three scenarios: (1) no or minimal solid product precipitating out of the reaction mixture; (2) poor dr of solid product; or (3) solid product is contaminated with significant impurities.
(21) Raber, D. J.; Guida, W. C. Tetrabutylammonium borohydride. Borohydride reductions in dichloromethane. *J. Org. Chem.* **1976**, *41*, 690−696.
(22) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. Compounds Related to Podophyllotoxin. XII. Podophyllotoxone, Picropodophyllone and Dehydropodophyllotoxin. *J. Am. Chem. Soc.* **1960**, *82*, 6074−6081.
(23) Fujii, H.; Oshima, K.; Utimoto, K. A practical and stereoselective reduction of 3-keto-2-methyl esters or 3-keto-2-methyl amides into erythro-3-hydroxy-2-methyl esters or erythro-3-hydroxy-2-methyl amides with $NaBH_4$ catalyzed by $MnCl_2$. *Tetrahedron Lett.* **1991**, *32*, 6147−6150.

https://doi.org/10.1021/acscatal.3c01515
ACS Catal. 2023, 13, 6518−6524