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Crystallization-Enabled Stereoconvergent Michael Additions of β-Keto Esters to Nitroolefins

Emily R. Sherman, William R. Cassels, and Jeffrey S. Johnson*

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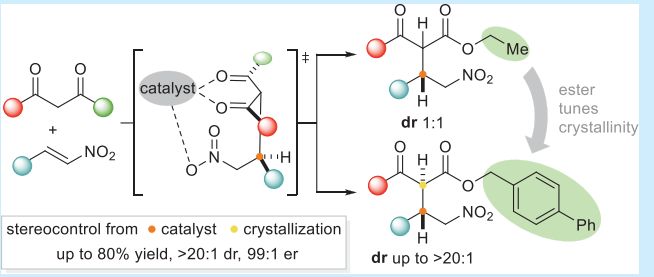
ABSTRACT: Asymmetric Michael additions are powerful tools to meet the growing need for stereochemically complex products. While 1,3-dicarbonyls are common nucleophiles, the successful use of configurationally unstable β-keto esters in diastereoselective variants remains understudied. In this Letter, crystalline β-keto esters were leveraged in a two-phase, one-pot merger of an asymmetric Michael addition with a crystallization-induced diastereomer transformation. Tuning the crystallinity of β-keto ester adducts enabled stereoconvergence of the products, which were isolated by filtration.



Stereochemical complexity is a key feature in many products from agriscience to pharmaceuticals, where a higher number of stereogenic centers has been linked to improvements in environmental safety and outcomes in clinical drug trials.[1−5] To meet the growing demand for stereochemically complex compounds, chemists regularly turn to asymmetric catalysis. Of the wealth of methods available, one of the most powerful is the enantioselective Michael addition,[6−13] an atom-efficient carbon−carbon (C−C) bond forming reaction that produces complex products from simple, inexpensive starting materials.

1,3-Dicarbonyls, whose low pK_a values enable facile deprotonation under mild conditions by a variety of chiral catalysts, are prototypical pronucleophiles in such processes. Symmetrical 1,3-dicarbonyls have been used to synthesize enantioenriched compounds with β-stereogenic centers[14] (orange circle, Figure 1). However, Michael additions with unsymmetrical 1,3-dicarbonyls typically yield mixtures of diastereomers[15−17] since the acidic α-proton results in facile epimerization of the second stereogenic center (gold circle, Figure 1), eroding any kinetic selectivity provided by the chiral catalyst. A small number of diastereoenriched outliers exist,[15,18] but general methods remain rare. A few approaches achieve high diastereoselectivity but must prevent epimerization with cryogenic temperatures,[19,20] careful catalyst tuning,[21] or incorporation of an α-substituent on the 1,3-dicarbonyl nucleophile.[22−24] This prevailing strategy has largely ignored unsubstituted β-keto ester nucleophiles, whose increased acidity poses challenges for approaches relying solely on kinetic selectivity (pK_a = 13−15 in DMSO vs pK_a 18 for related β-keto amide nucleophiles).[21,25] To complement current strategies that seek to avoid epimerization, we sought to productively leverage the acidity of the products to access the Michael adducts as single stereoisomers through crystallization-based stereocontrol.

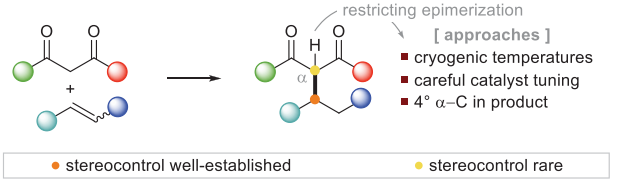


Figure 1. Previous strategies to access diastereoenriched Michael adducts require restricted epimerization.

Crystallization-induced diastereomer transformations (CIDTs) have been successfully merged with asymmetric catalysis in a two-phase approach that achieves excellent stereocontrol and yields complex products.[26−29] In the first phase, a chiral catalyst enables skeletal construction while lowering the activation energy of one enantiodetermining transition state, creating a kinetic preference for one configuration at the new stereogenic center (i.e., β-carbon, Figure 2a). After C−C bond formation, a CIDT enables the thermodynamic driving force of crystallization to funnel an equilibrating mixture of diastereomers into a single crystalline stereoisomer.[30−32] The two phases occur in series in one pot and generate products that can be isolated by the direct filtration of the reaction mixture. By avoiding solvent-intensive

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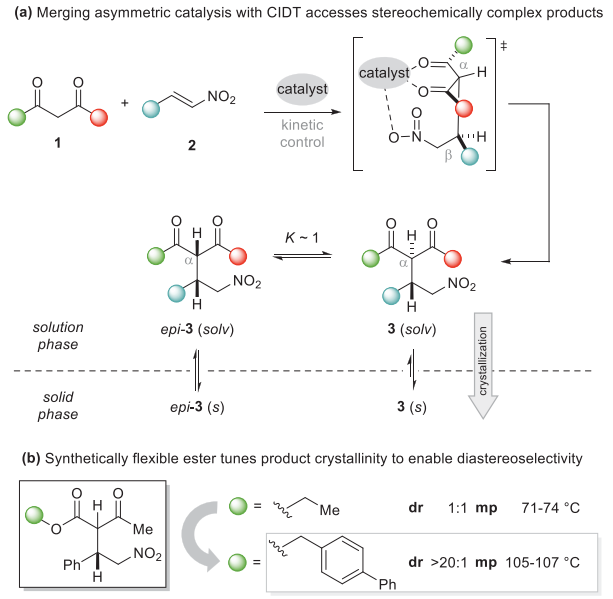


Figure 2. Merging an asymmetric Michael addition with a CIDT and tuning product crystallinity promotes diastereoselectivity.

chromatography, a CIDT can decrease the production cost of stereochemically complex products on industrial scale.[33,34]

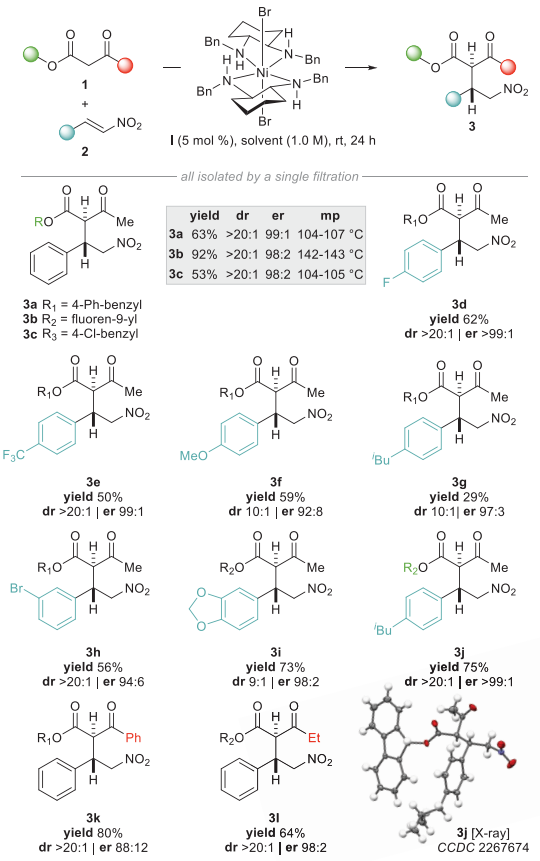
$(Diamine)_2Ni(II)$-catalyzed Michael additions of β-keto esters to nitrostyrenes afforded crystalline products with excellent enantioselectivity but no diastereoselectivity.[17] We wondered if the synthetically flexible β-keto ester[35,36] could be carefully chosen to tune the Michael adducts' crystallinity and promote a CIDT[37] to achieve diastereoselectivity (Figure 2b). In this Letter, we report the asymmetric Michael addition of crystalline β-keto esters to nitroolefins merged with a CIDT to access stereochemically complex products by filtration in up to 88% yield with excellent enantio- and diastereoselectivity.

We began by examining the enantioselective Michael addition of a crystalline β-keto ester **1a** to nitrostyrene, including an aromatic 4,4′-biphenyl ester group to promote crystallinity in product **3a** (biphenyl ester **3a** mp: 105−107 °C vs ethyl ester mp: 71−74 °C, Figure 2b). We were excited to see nickel diamine catalyst **I**[17,38,39] facilitated both the enantioselective C−C bond formation and a CIDT at the resulting α-carbon stereogenic center. After slight modifications to previously successful CIDT conditions,[27,28] which included ethereal solvent and a concentrated reaction mixture ($[nitrostyrene]_0$ = 1.0 M), we obtained crystalline product **3a** in good yield with excellent enantio- and diastereoselectivity upon filtration (see Supporting Information for full optimization).

Next, the method was expanded to include more diverse nitroolefins, requiring only slight modifications to the solvent system across the substrate scope (Scheme 1). Unsubstituted and *para*- substituted nitrostyrenes performed well in this manifold, affording crystalline products in fair to excellent yields with excellent enantio- and diastereoselectivity. Nitrostyrenes with electron-donating (**3f**, **3g**, **3j**) and electron-withdrawing (**3d**, **3e**) substituents were well-tolerated, as was a *meta*- substituted nitrostyrene (**3h**). *Ortho*- substituted, aliphatic, and heteroaromatic nitrostyrenes proved difficult (see Supporting Information for more details).

Both aromatic and branched aliphatic ketone groups were also tolerated (**3k** and **3l**, respectively), as were various

Scheme 1. Scope of the Enantio- and Diastereoselective Michael Addition[a]



[a]Reaction conditions: Nucleophile **1** (0.300 mmol, 1.5 equiv), nitroolefin **2** (0.200 mmol, 1.0 equiv), catalyst **I** (5 mol %), rt, 24 h. Solvent (Et_2O, MTBE, toluene, etc.) and concentration were adjusted by substrate. Yields refer to isolated yields. Diastereoselectivity was determined by ^1H NMR spectroscopic analysis of the solid product following filtration. Enantiomeric ratios were determined by chiral HPLC analysis of the solid product. 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.[27] X-ray structure of adduct **3j** is shown at 50% thermal ellipsoids.

aromatic ester groups (**3a**, **3b**, **3c**). The crystallinity of the product could be tuned by altering the keto ester. Using fluorenol-derived keto ester **1b** in place of keto ester **1a** increased the yield and diastereoselectivity of the Michael addition to a lipophilic nitrostyrene (cf. adducts **3g** vs **3j**). This difference in crystallinity was reflected in their respective melting points (biphenyl methyl ester **3g**, mp 109−112 °C; fluoren-9-yl ester **3j**, mp 133−135 °C). An X-ray diffraction study of keto ester **3j** revealed the absolute stereochemistry to be (2*R*,3*S*), and together with the X-ray structure of hydroxy ester **4** derived from keto ester **3a** (*vide infra*), the configurations of the other Michael adducts were assigned by analogy. An improved yield and excellent selectivity were realized on larger scale: the synthesis of adduct **3a** on gram scale afforded the desired product in 88% yield, >20:1 dr, and >99:1 er (see Supporting Information for more details).

To investigate if the reaction was indeed operating by a CIDT, we analyzed by ^1H NMR spectroscopy the reaction

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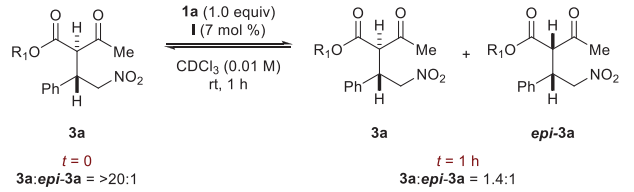
Org. Lett. 2023, 25, 6779−6783

filtrate from the synthesis of adduct **3a**. The filtrate was revealed to contain a mixture of adduct **3a** and its epimer as a 1:1 mixture of diastereomers in solution, indicating any kinetic selectivity during C−C bond formation was removed by epimerization and that the enrichment was not simply a consequence of selective nondynamic crystallization. A second ^{1}H NMR spectroscopic analysis revealed that a single stereoisomer (>20:1 dr) of **3a** was converted to a 1.4:1 mixture of **3a**:*epi*-**3a** in 1 h by catalyst **I** (7 mol %) in the presence of an equivalent of keto ester **1a**, highlighting the catalyst's role in epimerizing the Michael adducts to establish the equilibrium required for a CIDT (Scheme 2). Finally,

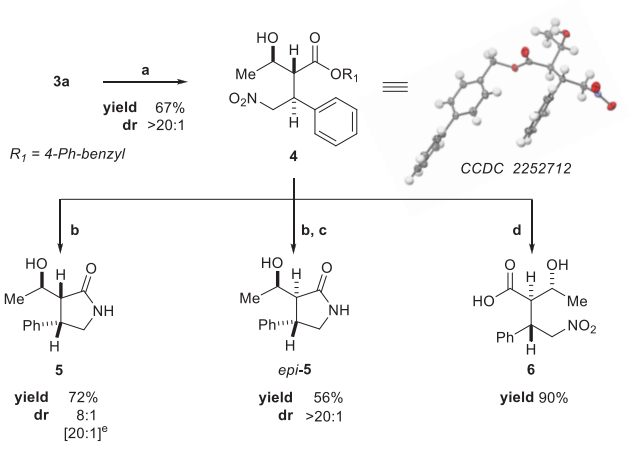
Scheme 2. Ni(II) Catalyst I Rapidly Epimerizes the Michael Adduct To Facilitate a CIDT



under homogeneous conditions, adduct **3a** was synthesized with an er of 95:5 relative to the 99:1 er obtained under CIDT conditions, indicating that the latter provides a concurrent upgrade to the enantioselectivity during crystallization (see Supporting Information for more details).

Having developed a highly diastereo- and enantioselective reaction platform, we sought to exploit the polyfunctional nature of the products in a variety of secondary transformations (Scheme 3). The ketone was reduced with a noncoordinating borohydride to yield β-hydroxy ester **4** in good yield and excellent dr.[40] An X-ray diffraction study of alcohol **4** was conducted to assign the absolute stereochemistry as (1*R*,2*R*,3*S*). The nitro group of alcohol **4** was further reduced to the amine,[41] which spontaneously cyclized to form

Scheme 3. Reactions of Michael Adducts



[a](a) Bu_4NBH_4 (3 equiv), DCM:MeOH (1:1, 0.05 M), −50 °C, 9 h. (b) Fe (10 equiv), HCl (10 equiv), EtOH (0.05 M), reflux, 1 h. (c) NaOH (33 equiv), MeOH (0.03 M), 40 °C, 2.5 h. (d) Pd/C (10 wt %), EtOH:EtOAc:MeOH (1:1.4:3, 0.03 M), H_2 (2 atm), 20 min. (e) Number in parentheses represents dr following flash column chromatography. X-ray structure of alcohol **4** is shown at 50% thermal ellipsoids.

β-hydroxy lactam **5**. The latter could be epimerized to a second diastereomer, *epi*-**5**, under basic conditions. Hydrogenolysis of benzyl ester **4** allowed for simple functional group interconversion, revealing β-hydroxy acid **6**.

The precise molecular drivers for selectivity remain to be determined; however, a closer examination of the X-ray structures of Michael adduct **3j** and alcohol **4** revealed possible clues involving the aromatic ester groups and their intramolecular interactions that possibly enhance the crystal packing[42] of the major diastereomer. The *iso*-butyl group of Michael adduct **3j** exhibited a contrasteric conformation, possibly due to attractive London dispersion interactions with the fluorenol ester group. The biphenyl ester of alcohol **4** was found to have a C−H π interaction between the biphenyl ester and the phenyl ring (Figure 3). How important (or incidental) such interactions are and the extent to which they can be integrated into designed CIDTs are topics of ongoing investigation.

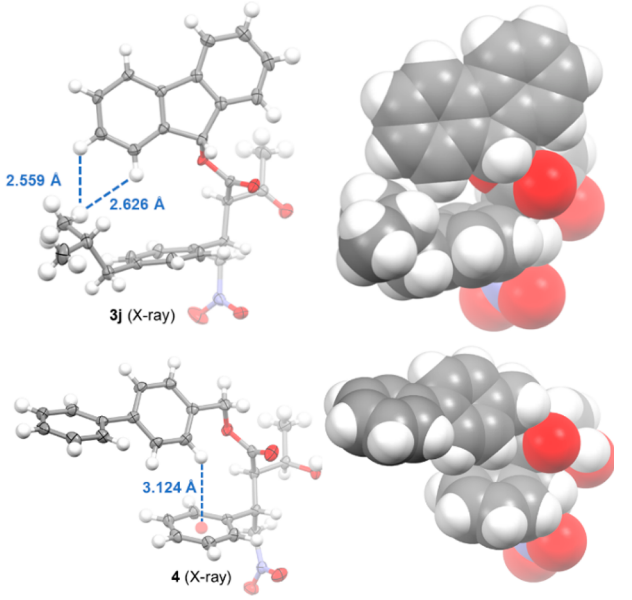


Figure 3. Intramolecular interactions for keto ester **3j** and biphenyl ester **4** in the solid state.

In summary, we have developed a method that merges a CIDT with the asymmetric Michael addition of unsubstituted β-keto esters to nitroolefins, affording complex products as single (or major) diastereomers that can be isolated by direct filtration of the reaction mixture. Three crystalline β-keto esters promoted the product crystallinity required for a CIDT and could be tuned to improve the reaction's yield and diastereoselectivity. ^{1}H NMR spectroscopy studies indicate the dual role of nickel diamine catalyst **I** in forming the key C−C bond and epimerizing the resulting α-carbon stereogenic center to promote a CIDT. The stereochemically complex Michael adducts were then diversified to access useful products, including a γ-lactam and β-keto acid. Our laboratory continues to investigate the potential of this merged manifold in other asymmetric Michael additions.

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Org. Lett. 2023, 25, 6779−6783

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02799.

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

Accession Codes

CCDC 2252712 and 2267674 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

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

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

William R. Cassels − *Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States;* orcid.org/0009-0006-3375-3545

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c02799

Notes

The authors declare no competing financial interest.

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