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Switchable Enantio- and Diastereoselective Michael Additions of β-Keto Amides to Nitroolefins: Crystallization-Based Inversion of Kinetic Stereocontrol

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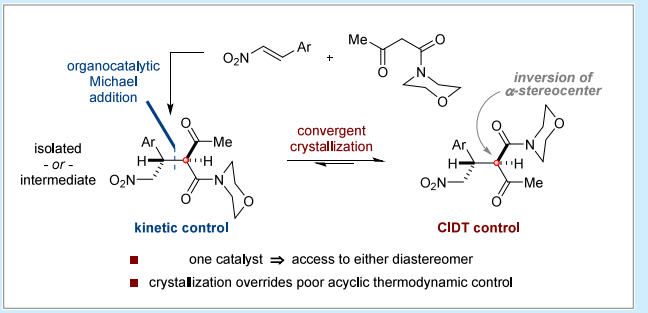
ABSTRACT: Asymmetric catalytic reactions rely on chiral catalysts that induce highly ordered transition states capable of imparting stereoselectivity in the bond-forming step(s). Productive deviations from this paradigm are rare yet hold the potential for accessing different stereoisomers using the same catalyst. Here, we present an enantio- and diastereoselective Michael addition of β-keto amides to nitroolefin electrophiles proceeding via an unusual scenario where the kinetic diastereocontrol imparted by the catalyst may be overridden by crystallization to provide the complementary stereoisomer of the product.



Asymmetric catalysis is a powerful and broadly applied method for the synthesis of new chiral material, a need that is ever-growing with the increased importance of single-enantiomer targets in industry.[1−6] A leading strategy in asymmetric catalytic reaction optimization relies on the fundamental premise that the ideal chiral catalyst induces a single highly ordered transition state to provide high enantio- and potentially diastereoselectivity in the bond-forming step that establishes the new chiral center(s).[7] This process in asymmetric catalysis enables the consistent, reliable preparation of new chiral matter but is inherently limited because only one stereoisomer is obtained. Stereodivergent reactions that allow for the tunable synthesis of multiple complementary stereoisomers have emerged as attractive solutions to address this limitation.[8−12]

Stereodivergent operations typically rely on altering substrates, chiral catalysts, or ligands to achieve divergency.[12] Condition-dependent divergency is more challenging because conventional asymmetric catalysis logic dictates that, when reacting with the same starting materials, a chiral catalyst would need to induce multiple distinct and highly ordered transition states in the bond-forming step solely depending on the reaction conditions. Consequently, such divergent reactivity is underexplored.[13−21] We posit that the simplest platform for stereodivergence would be comprised of a system that provides high *kinetic* (catalyst) diastereoselectivity for one isomer and high thermodynamic selectivity for the other, decoupling the catalyst from stereocontrol in the latter case (Scheme 1a).[13−15] In other words, an initial stereoisomer is prepared in the skeletal assembly and then in a second operation, selectively epimerized to an alternative stereoisomer (stereochemical editing).[22−36] An intramolecular conjugate addition from Jørgensen is a prototypical example of such a stereodivergent reaction pathway (Scheme 1b).[14]

Cyclic systems are usually needed for high diastereocontrol due to the thermodynamic driving force for all substituents to lie in the (pseudo)equatorial position (Scheme 1c, top). Stereoselective epimerization of an acyclic species is more challenging: in solution, ground state energy differences of diastereomeric acyclic species are typically less pronounced and more difficult to predict (Scheme 1c, bottom). The more complicated equilibrium renders stereoconvergent or selective epimerization reactions of acyclic species rare and limited in scope.[28,30,37,38]

The productive merger of asymmetric catalysis with crystallization-induced diastereomer transformations (CIDTs)[39−41] can provide efficient access to stereoenriched acyclic products that show little or no preference in solution (Scheme 2a).[42−45] We hypothesized that CIDT could be an integral component in developing a stereochemically switchable reaction by selecting either kinetic or CIDT control. Any CIDT could in principle produce such stereodivergent reactivity by judicious catalyst design and selection of reaction conditions, and indeed a few single-substrate, crystallization-driven epimerizations have been previously reported,[46−49] but to the best of our knowledge, the phenomenon has not been

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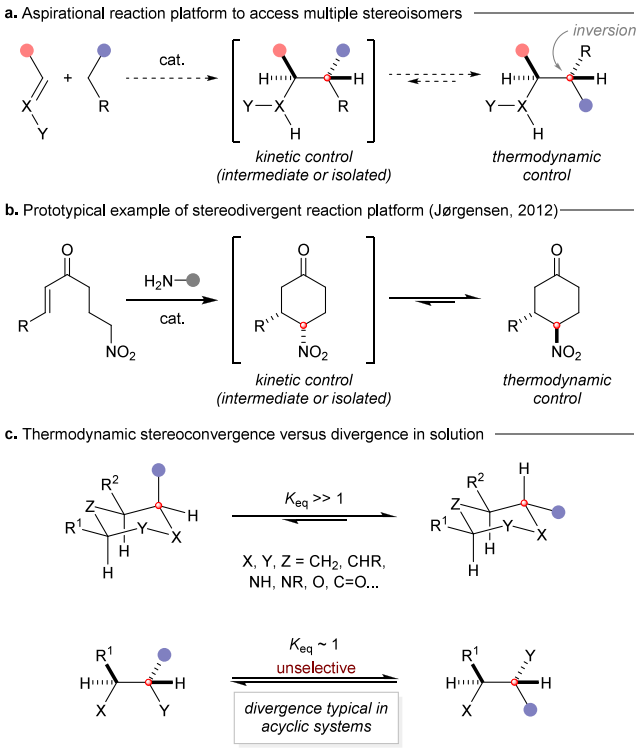
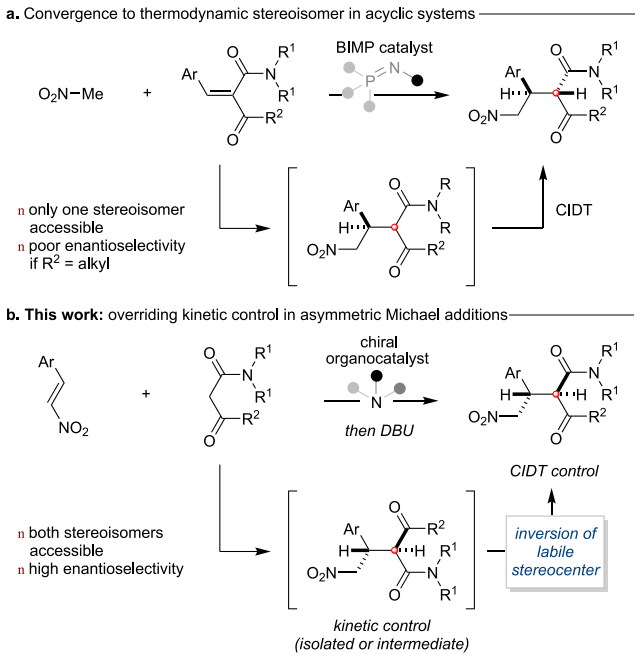
Scheme 1. Leveraging Kinetic and Thermodynamic Control in Addition Reactions



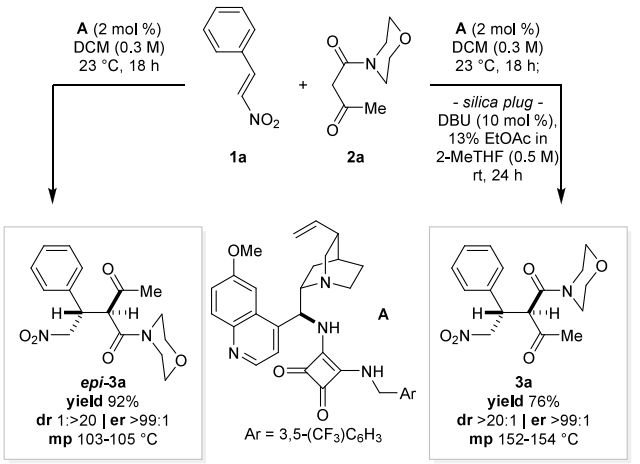
Scheme 2. Crystallization-Induced Stereoconvergent Reactions



used in a general method. In this letter, we disclose an approach where both acyclic product diastereomers of an enantioselective Michael addition can be accessed using the same chiral catalyst by leveraging kinetic or CIDT control, the latter of which arises from a highly selective epimerization of the former (Scheme 2b).

Organocatalytic Michael additions of β-keto amide nucleophiles[50] to nitroolefins[51−54] were selected to assess the feasibility of these research goals. Studies from Constantieux[55] and Dixon[56] provided a platform for the kinetically controlled reaction, and previous studies from our laboratory suggested similar nitro-ketone products could participate in CIDTs.[42] Using Rawal's quinine-derived squaramide catalyst **A**[57] used by Constantieux,[55] morpholine β-keto amide **2a** reacted with (*E*)-β-nitrostyrene **1a** to provide a single kinetic diastereomer of nitro-ketone product *epi*-**3a** (mp 103−105 °C) in excellent yield and enantioselectivity (Scheme 3, left). As a prerequisite

Scheme 3. Stereodivergent Michael Additions



for second-stage stereoconvergence, the rate of diastereomer interconversion was next evaluated. Diastereomerically pure β-keto amide **3a** or *epi*-**3a** was converted to a constant 1:3.3 equilibrium mixture of **3a**:*epi*-**3a** within 10 min in $CDCl_3$ at ambient temperature in the presence of catalytic quantities of DBU (homogeneous conditions, see Supporting Information). With this information, a simple CIDT protocol was developed: following a short silica plug on the kinetic diastereomer *epi*-**3a**, catalytic quantities of DBU in 2-MeTHF induced convergent crystallization and provided a single diastereomer of product **3a** after a filtration of the reaction mixture (Scheme 3, right). Stereoconvergence does not occur in the absence of crystallization; moreover, the NMR studies reveal that more crystalline diastereomer **3a** (mp 152−154 °C) is the minor one in the solution-phase equilibrium. Resubjecting the more crystalline diastereomer to the CIDT reaction conditions over 48 h did not alter the diastereopurity of the sample (see Supporting Information).

We next explored the parameters of the crystallization-induced Michael reaction scope and were pleased to find the concept could be applied to multiple reaction partners. A summary of the reaction scope is provided in Table 1. All reactions were analyzed by ^{1}H NMR spectroscopy following the initial Michael bond formation, and the kinetic diastereoselectivity is provided in brackets. The unpurified mixture after initial analysis was then subjected to the CIDT conditions to provide isolated yields and selectivities (see Supporting Information for exact experimental details). In most cases, the β-keto amide stereocenter is completely inverted to provide the CIDT diastereomer **3** in excellent yield, diastereo- and enatioselectivity. In the synthesis of lower-yielding substrates **3e** and **3g**, the filtrates contained the

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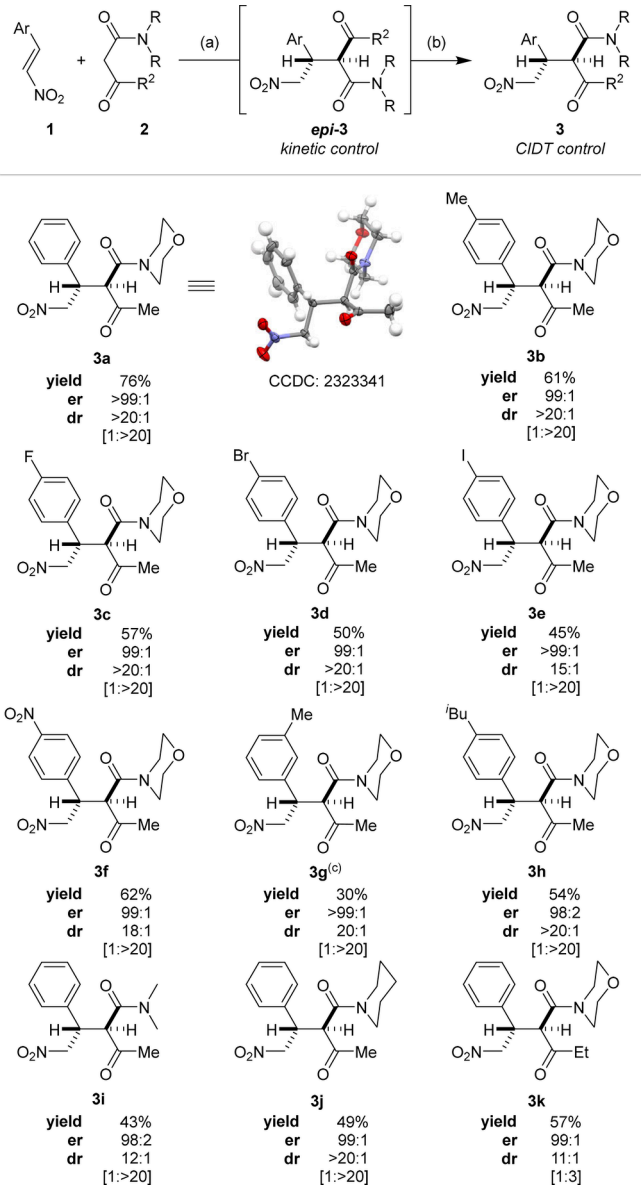
Table 1. Scope of Crystallization-Driven Michael Additions

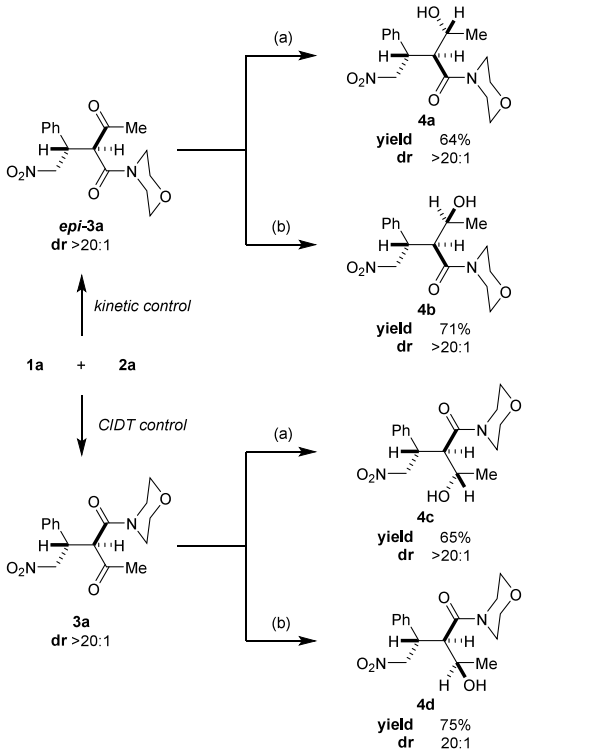


(a) Nucleophile (1.0 equiv), nitroolefin (1.0 equiv), squaramide **A** (2 mol %), DCM (0.3 M), 18 h. (b) DBU (10 mol %), ethereal solvent (0.25−1.0 M), 18 h; (c) 7.5 mol % squaramide **A** was used. Yields refer to isolated yields. The diastereomer ratios are reported as the ratio of **3**:*epi*-**3** and were determined by ^{1}H NMR spectroscopic analysis of the solid obtained by filtration of the reaction mixture; the ratio in brackets is the kinetic ratio. The er values of the solids after filtration were determined by high-performance liquid chromatographic analysis using a chiral stationary phase.

remaining mass balance as a mixture of adduct epimers and unreacted starting materials in approximately equal measure (see Supporting Information). To demonstrate the scalability, the reaction to form nitro-ketone **3a** was accomplished on 1.00 mmol scale without any loss in efficiency. An X-ray diffraction study was carried out to establish the relative and absolute stereochemistry for *β*-keto amide **3a**.

The nitro-ketone products proved to be versatile intermediates in the synthesis of chiral building blocks. Both **3a** and *epi*-**3a** readily participate in two different reductions (Scheme 4). Directed reductions by borane dimethyl sulfide complex

Scheme 4. Diastereoselective Reductions of Nitro-Ketone Products



(a) $TiCl_4$ (1.0 equiv), $Me_2S{\bullet}BH_3$ (5.0 equiv), MeOH (0.10 M), −78 °C, 18 h. (b) Bu_4NBH_4 (1.5 equiv), DCM (0.10 M), 0 °C, 18 h; rt, 4 h.

mediated by titanium tetrachloride[42,58] (A) or undirected reductions by tetrabutylammonium borohydride[43,55,59] (B) provide four complementary amido-alcohol stereoisomers. All the amido-alcohols are derived from nitro-ketones arising from the same *β*-keto amide and nitrostyrene starting materials made using the same chiral catalyst.

In conclusion, we have developed a crystallization-driven Michael addition of *β*-keto amide nucleophiles and nitroolefin electrophiles. Studies reveal an unusual scenario where kinetic diastereocontrol is completely overridden by a crystallization-induced diastereomer transformation (CIDT) to provide the solid complementary stereoisomer. This work serves as an exciting proof-of-concept manifold for unlocking contra-kinetic products with CIDT using the same chiral catalyst. Current work in our laboratory is underway seeking to identify other reaction manifolds that allow for crystallization-enabled stereodivergency.

■ 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.4c02617.

Synthesis of *β*-keto amides; synthesis of nitroolefins; synthesis of quinine squaramide catalyst; enantio- and diastereoselective Michael additions of *β*-keto amides to nitroolefins; X-ray crystallographic data (PDF)

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Accession Codes

CCDC 2323341 contains 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.

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