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Crystallization-Induced Secondary Selection from a Tandem Driven Dynamic Combinatorial Resolution Process

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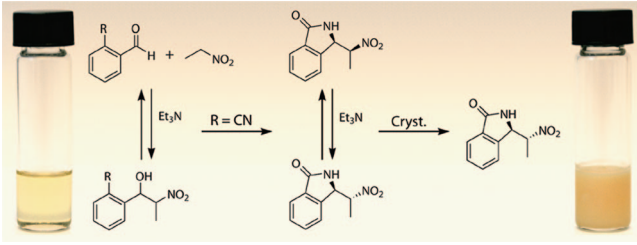

Crystallization-induced secondary selection from a tandem driven dynamic combinatorial library is presented. In a one-pot experiment, an initial nitroaldol equilibrium was kinetically driven by a tandem reaction resulting in a subsequent dynamic library of diastereoisomers. This library was then further driven by a phase change, resulting in amplification and isolation of a highly diastereomerically enriched and synthetically interesting isoindolinone.

Reversibility is a phenomenon that traditionally has troubled the synthetic chemist, forcing the use of excess reagents and limiting reaction yields. With the introduction of dynamic combinatorial chemistry (DCC) in the mid-1990s, reversibility in contrast became increasingly interesting. In this concept, reversible interactions are used to construct dynamic combinatorial libraries (DCLs) of continually interchanging components. The dynamic character of these systems makes them respond to external stimuli and adjust to form the thermodynamically most favorable mixture. This has led to discovery of a range of interesting chemical architectures, good ligands, and effective enzyme inhibitors.[1–12]

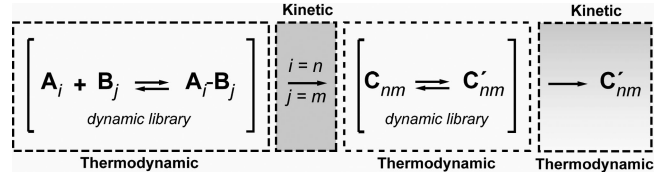

FIGURE 1. Concept of crystallization-induced secondary selection from a tandem driven DCL. A dynamic library is formed from *i* components **A** and *j* components **B**. A specific combination $\mathbf{A}_n-\mathbf{B}_n$ undergoes irreversible formation of **C** and **C′** which are diastereoisomers in equilibrium. **C′** subsequently crystallizes, thereby resolving the library to solely one product.

In the past few years, a range of new, and in some cases fundamentally different uses and approaches to DCC have been reported. We have proposed a dynamic combinatorial resolution process (DCR), where DCLs are kinetically resolved by enzyme-catalyzed reactions.[13–15] In this case, the kinetically controlled second step irreversibly transforms selected components resulting in amplification without the need of stoichiometric amounts of target molecule. We also introduced the concept of tandem driven internal DCR,[16] where internal pressure from a kinetically controlled tandem reaction quantitatively resolved a DCL into one product. This application demonstrates a new tool to prove dynamics in dynamic combinatorial systems and also shows potential for DCC to move into the field of reaction discovery. Another interesting concept involves the use of crystallization to control and drive DCLs. This phenomenon has earlier been described by Lehn and co-workers,[17–19] but has recently been further explored by the groups of Barboiu,[20] Stoddart,[21,22] and Nitschke.[23] Conceptually, the control of a dynamic combinatorial library by a phase change is very interesting and promising but still requires further fundamental and intensive research as suggested by earlier contributors.[21,22]

In this paper, we have combined our approach of tandem driven internal DCR with the crystallization driven approach to create a system of coupled DCLs with coupled selection processes. The concept is displayed in Figure 1: a dynamic

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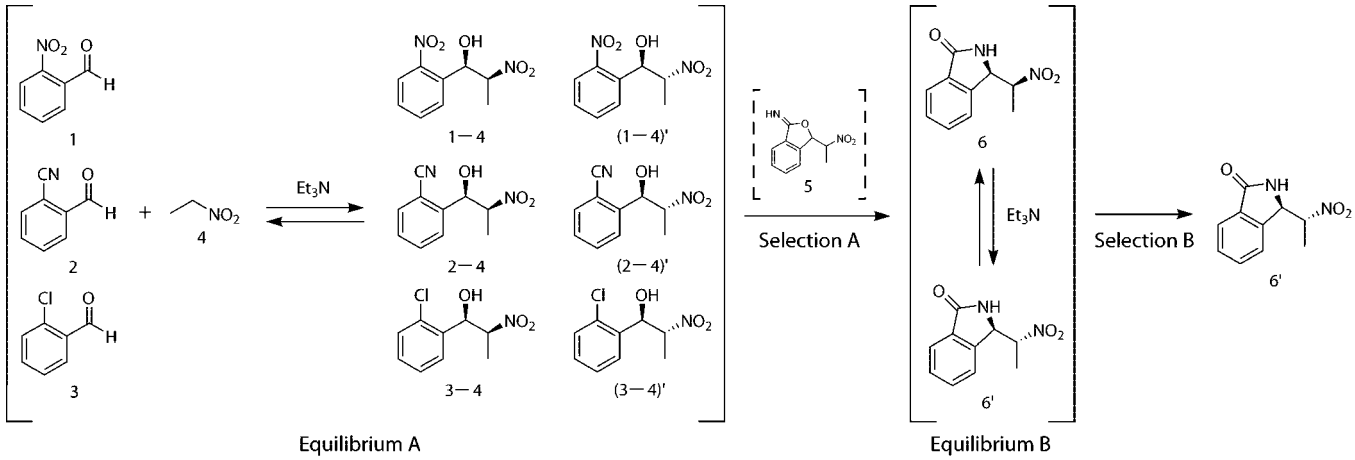
SCHEME 1[a]



[a] Diasteromers in this scheme are graphically displayed in one of the enantiomeric forms. The other form (mirror image) is also present in the mixture.

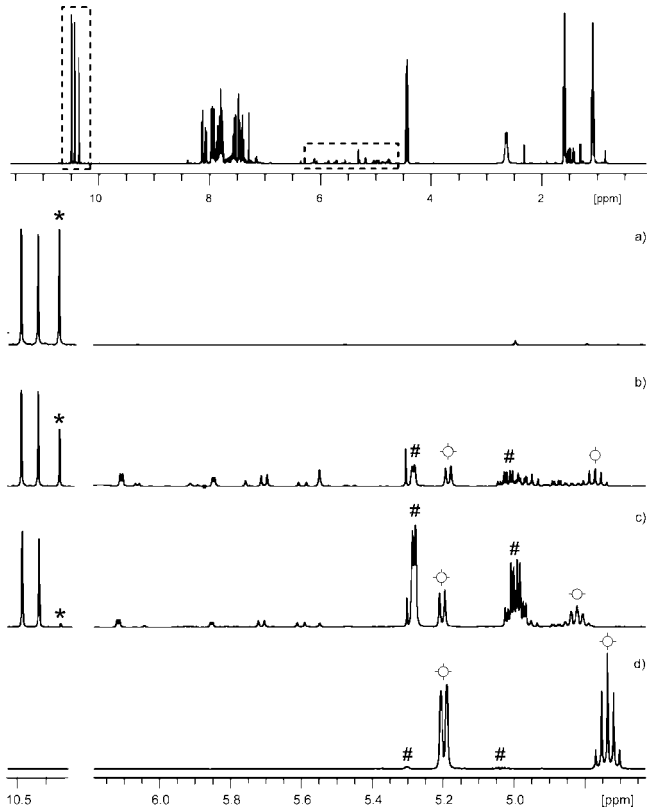


FIGURE 2. Selected ^{1}H NMR spectra. Enlarged areas are marked in the spectrum overview on top. (a) DCL before library generation. (b) DCL at $t = 7$ h. (c) DCL composition at full conversion. (d) Spectrum of filtered precipitate. *, #, and ○ indicate signals of **2**, **6**, and **6′**, respectively.

library from sets of components **A** and **B** is allowed to form by reversible bond formation. A specific component can subsequently react further through a kinetically controlled tandem reaction to form a set of dynamically interchanging diasteroisomers, **C** and **C′**. This smaller subset DCL is then further resolved to one single diasteroisomer, **C′**, due to it crystallizing out of the continuously re-equilibrating solution.

During our most recent work involving dynamic nitroaldol (Henry) systems, we noticed interesting crystalline properties of one of the diastereoisomers of an isolated isoindolinone (**6**,**6′**).[16] We reasoned that this interesting finding could be used to our advantage by demonstrating how a DCL could be directed toward the formation of one or more components, or isomers of components, that are creating a selection pressure by being removed from the equilibrium through a phase change. To test this hypothesis, we designed a system based on the Henry reaction, which we have found to be very effective and tolerant for DCC protocols (Scheme 1).[13,16] Initially, six β-nitroalcohol adducts (equilibrium A) were formed by mixing 1 mmol each of three different 2-substituted benzaldehyde derivatives **1**–**3** with 1 mmol of nitroethane (**4**) and 0.4 mmol of triethylamine in 1 mL of chloroform. 2-Cyanobenzaldehyde (**2**) was included due to its known ability to undergo a subsequent irreversible tandem reaction to form nitrosubstituted isoindolinone **6**,**6′**, proposedly through an intermediate iminolactone (**5**) (selection A).[16] This selection yielded a new DCL composed of the diastereomeric mixture of the formed isoindolinone (equilibrium B). After a few hours, a precipitate started to form in the reaction vessel. Filtration was followed by ^{1}H NMR and analysis, confirming the product to be a highly diastereoenriched (>95:5) mixture of the isoindolinone, which had been diasteromerically amplified through a phase-change driven selection process (selection B).

To further investigate this process, samples of much lower concentration were prepared in order for the reaction to stay in solution, thereby eliminating selection phase B. NMR tubes containing deuterated chloroform were used as reaction vessels and the product formation was monitored carefully by ^{1}H NMR (Figure 2). After initiating the process by the addition of triethylamine, ^{1}H NMR immediately started to display peaks in the area between 5 and 6 ppm, originating from the β-nitroalcohols. However, with time, peaks from the amplified isoindolinone (**6**,**6′**) started to appear (Figure 2b). This amplification gradually proceeded until almost all 2-cyanobenzaldehyde (**2**) had been consumed (Figure 2c). Worth noticing is the clear thermodynamic preference for one of the diastereoisomers which is clearly seen when all 2-cyanobenzaldehyde (**2**) has been consumed and the system has been completely shifted to equilibrium B (Figure 2d).

Next, efforts were put into optimizing conditions to maximize the crystallization-induced secondary selection (selection B). Several solvents were screened and although the majority of them would induce crystallization, the process was generally slow and the amount of isolated, amplified material was low. The optimal situation proved to be a mixed solvent system of

chloroform and hexane. Chloroform was a potent solvent for dissolving the starting components which stayed in solution upon subsequent addition of hexane. Precipitation started within 30 min and the mixture was stirred overnight before being filtered, yielding 63% overall yield of a 97:3 diastereomerically enriched mixture. Important to note is that the isolated and amplified diasteroisomer is the opposite isomer of the one being more stable in solution (Figure 2c/d). This further increases the amplification factor.

Finally, the identity of the amplified diastereomer was determined. Crystallization of the isolated precipitate from hot methanol rendered single racemic crystals of the (*R*,*R*)/(*S*,*S*) diastereoisomer (**6′**).[24] These were further compared with a powder X-ray diffractogram of the precipitate, which further confirmed the amplified diastereoisomer to be **6′**.

As we mentioned in our earlier work involving isoindolinone **6**,**6′**, it represents an interesting motif present in a variety of drug compounds and natural products,[25–27] as well as belonging to a group of precursors of the widely utilized 1,2-diamines.[28–31] Considering the simplicity and possible applications of this diastereoselective reaction, we also evaluated the single reaction without any other library components present. This also proved to be very effective, reaching close to full conversion and isolating diastereomerically highly enriched product (**6′**), in high yield (80–85%) with no need of further purification.

(24) Crystallographic data were concordant with previously reported data. See ref 16.

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In conclusion, we have demonstrated how crystallization can be used as a secondary selection process in a tandem driven DCL. Kinetic reaction control selectively formed and amplified one product from a dynamic nitroaldol library, which itself created a new library of dynamically interchanging diastereoisomers. This second library was further amplified through a crystallization-induced phase change, resulting in the complete formation of a single diastereoisomer. This process also proved to work in a single reaction protocol, providing a simple, effective, and purification-free route to a diastereomerically highly enriched and synthetically interesting motif.

Experimental Section

Preparation of the Library for Crystallization-Driven Secondary Selection. Hexane (0.6 mL) was carefully added to a solution of 2-nitrobenzaldehyde (**1**, 151.1 mg, 1 mmol), 2-cyanobenzaldehyde (**2**, 131.1 mg, 1 mmol), 2-chlorobenzaldehyde (**3**, 112.6 μL, 1 mmol) ,and nitroethane (**4**, 71.8 μL, 1 mmol) in 1 mL of $CHCl_3$. The mixture was stirred at room temperature overnight and the formed precipitate was filtered and washed with cold toluene, affording 130 mg of pure isoindolinone **6**,**6′** (63%, dr >93:7 (**6′**:**6**)).

Preparation of the Reference Library. 2-Nitrobenzaldehyde (**1**, 15.1 mg, 0.1 mmol), 2-cyanobenzaldehyde (**2**, 13.1 mg, 0.1 mmol), 2-chlorobenzaldehyde (**3**, 11.3 μL, 0.1 mmol), and nitroethane (**4**, 7.2 μL, 0.1 mmol) were dissolved in 1 mL of $CDCl_3$, and the reaction was carefully monitored by ^{1}H NMR analysis.

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Supporting Information Available: General methods; preparative synthesis of **6**,**6′**; spectra; and powder diffraction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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