Tandem driven dynamic combinatorial resolution *via* Henry–iminolactone rearrangement†

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An unexplored type of tandem reaction is used to kinetically resolve a dynamic combinatorial library resulting in quantitative amplification of an interesting 3-substituted isoindolinone.

Dynamic combinatorial chemistry is an emerging approach for efficient generation of molecular diversity and rapid identification of ligands and receptors for a large variety of target species.[1] This approach relies on constitutional dynamic exchange of kinetically labile entities, where dynamic combinatorial libraries (DCLs) are formed through reversible bonds between participating components. Due to the dynamic nature of DCLs, they can adapt in response to system constraints and selection pressures. To date, applications of DCLs have mainly exploited their potential to adapt to external selection pressures. Molecular targets,[2,3] or external stimuli,[4] have then been used to install secondary processes leading to the amplification of certain library members.

The possibility of controlling a DCL by an internal kinetic selection pressure is a hitherto unexplored approach. In this communication, we demonstrate an example of this sequential approach, where a DCL is influenced and strongly driven by an internal selection pressure. By coupling a thermodynamically controlled DCL to a kinetically controlled sequential intramolecular reaction, a library could be quantitatively resolved into one product. We have recently proposed a dynamic combinatorial resolution process (DCR), where DCLs are kinetically resolved by enzyme-catalyzed reactions,[2a,2b,5] but in the present study, we have taken advantage of the properties of individual library members, creating an internal selection pressure without an external biocatalyst. This represents a highly straightforward one-pot process to selective product formation from a pool of candidates, without the addition of intervening external factors.

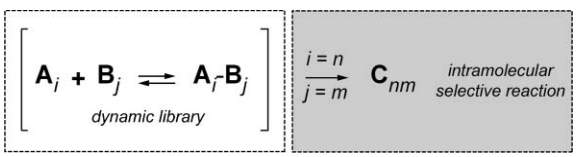

Fig. 1 Concept of tandem driven, internal DCR. A dynamic library is formed from *i* components **A** and *j* components **B**. A specific combination $\mathbf{A}_n$–$\mathbf{B}_m$ subsequently undergoes the selective formation of kinetically stable product $\mathbf{C}_{nm}$.

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The concept is displayed in Fig. 1: a dynamic library from sets of components **A** and **B** is allowed to form by reversible bond formation. A specific constituent can subsequently react further in a consecutive reaction to form a kinetically stable product. The thermodynamically controlled process will simultaneously undergo continuous re-equilibration, and a clear amplification of the coupled tandem reaction product will be observed.

We based our system on the nitroaldol or Henry reaction, a very powerful C–C bond forming reaction with a long history and numerous applications within synthetic organic chemistry.[6–10] Recently, it has also shown great potential in the DCC field where it has been successfully coupled to an enzymatic secondary process.[2a] The robust nature of this transformation, and its potential for handling structural diversity, makes it a good candidate for exploring tandem driven DCLs. Considering these features, a conceptual nitroaldol library was designed (Fig. 2). Five benzaldehyde derivatives (**1**–**5**), all with a unique substitution pattern, were chosen in order to make library generation and analysis clear and simple. A 2-CN substituted benzaldehyde was also included in order to provide a possible candidate for tandem cyclization following dynamic formation of the nitroalcohols (**6**–**10**). A resulting 5-*exo-dig* type cyclization of a hydroxynitrile to the corresponding iminolactone is an expected,[11,12] albeit unexplored,[13–16] intramolecular reaction, and would lead to kinetic resolution of the library. Library generation was initially tested on a reference library (DCL-A), containing one equivalent each of aldehydes **2**–**5** and nitroethane in acetonitrile. To initiate equilibration, triethylamine was added and the mixture was monitored by frequent ^{1}H-NMR analysis. Although catalytic amounts of base proved sufficient, the reaction rate was increased by adding an excess of base. Under these conditions, equilibrium was reached within three hours (Fig. 3a). Following this, a target

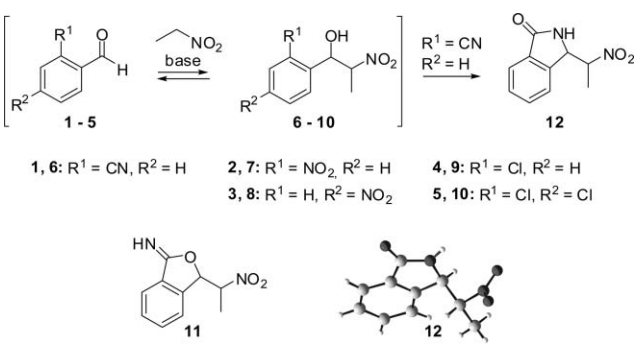

Fig. 2 Tandem driven dynamic nitroaldol library resulting in complete amplification and selection of product **12** (X-ray structure lower right).

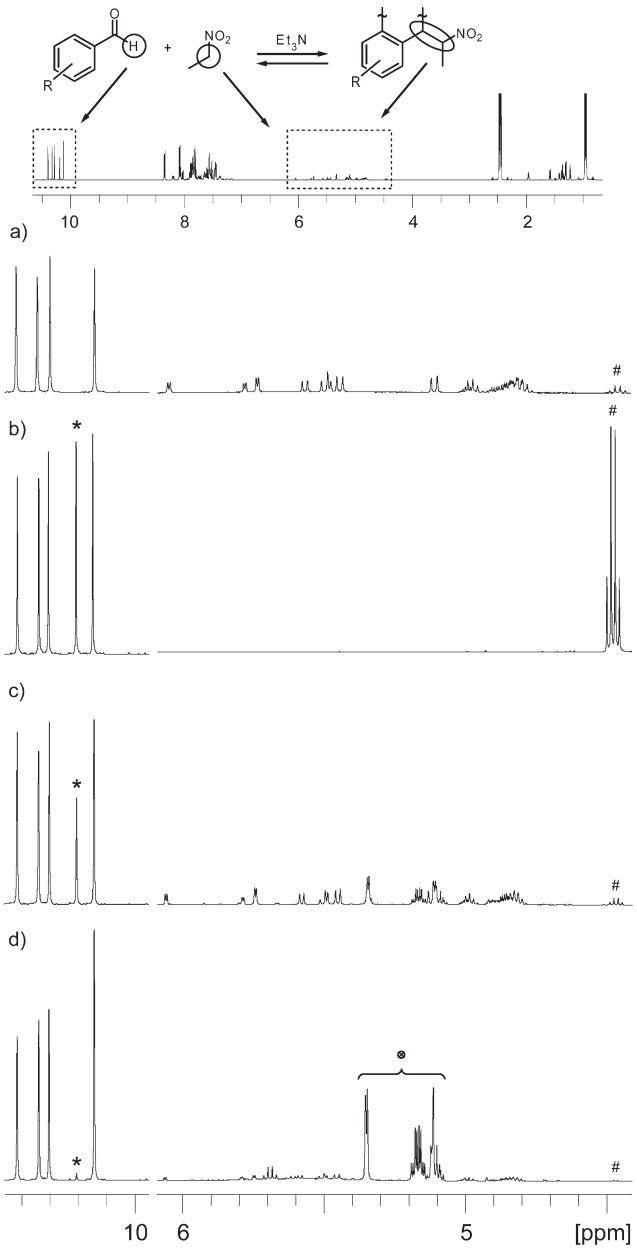

Fig. 3 ^{1}H-NMR spectra for selected DCLs. Enlarged areas display protons marked in the scheme. (a) Reference library DCL-A at equilibrium (t = 24 h). (b) Full compound tandem driven DCL-B at $t = t_0$. (c) DCL-B at t = 30 min. (d) DCL-B after completed tandem reaction (t = 24 h). *, #, and ⊗ indicate the signals of **1**, nitroethane and **12**, respectively.

library (DCL-B) was constructed analogously, this time including aldehyde **1**. Initially, the ^{1}H-NMR analysis displayed a similar pattern, with different nitroalcohols forming competitively. However, as the time approached thirty minutes, an amplification of what was assumed to be the cyclic iminolactone (**11**) was observed (Fig. 3c). This internal amplification process then gradually proceeded until all previously formed nitroalcohols, as well as all nitroethane, had been consumed (Fig. 3d).

Upon successful demonstration of our tandem driven dynamic library, the amplified reaction product was isolated and further characterized. During evaluation of the ^{13}C-NMR spectrum, an unusually high shift for the carbon in the benzylic position was observed, suggesting possible lactam formation. Intrigued by this, single crystals were produced,[17] and subsequent X-ray diffraction analysis proved the compound to be lactam **12** (Fig. 2).‡ Following these surprising results, the literature was probed for similar transformations. Observations where cyanoalcohols were transformed to lactams were found,[18–20] however in all cases requiring a partly different mechanistic route in order to form the final product. These routes also resulted in products that, despite their heterocyclic complexity, are of limited synthetic utility. The 3-substituted isoindoline-1-one represents an interesting motif present in a variety of natural products and drug compounds.[21] Furthermore, compound **12** belongs to a group of synthetic precursors to 1,2-diamines. Reduction of the nitro group and further hydrolysis of the lactam, would lead to these structures which are of broad utility, reaching from antitumor reagents to ligands in stereoselective organic synthesis.[22–24]

More detailed time-dependent NMR-studies of the process with aldehyde **1** were subsequently performed in order to evaluate the tandem reaction (Fig. 4). The experimental data fitted the consecutive reversible/irreversible model well,[25] suggesting that the final rearrangement step is fast compared to the proposed iminolactone formation step. The studies also revealed that the forward nitroaldol formation and the consecutive tandem-cyclization step proceed at comparable rates. The reverse nitroaldol reaction rate was however comparatively low under the present conditions.

In conclusion, we have formulated and demonstrated the concept of intramolecular dynamic combinatorial resolution. From a prototype dynamic nitroaldol library, internal selection pressure from a consecutive intramolecular tandem reaction influenced the thermodynamically controlled process and caused a quantitative amplification effect. Further investigation also showed that the tandem reaction was followed by an unexplored type of intramolecular rearrangement, affording an interesting nitrosubstituted isoindolinone structure. This concept has intriguing potential applications: For example, it provides a possible route to systematization of reaction discovery,[26,27] where novel reactions could be identified from amplification effects due to unexpected coupled reactions occurring in dynamic libraries. Tandem reactions could also be a tool for controlling dynamic combinatorial systems, and to demonstrate dynamics in biased equilibria.[28]

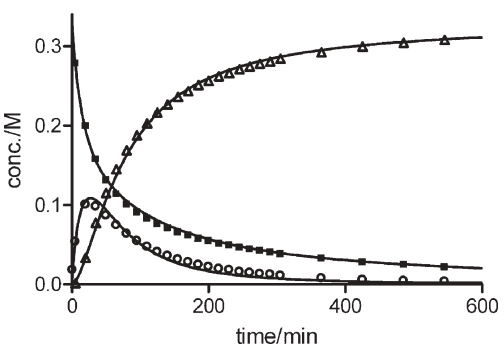

Fig. 4 Reaction composition followed over time (aldehyde **1** (■), nitroalcohol intermediate **6** (○) and product **12** (△)). Lines represent fitted data from kinetic model.[25]

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