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Dynamic Asymmetric Multicomponent Resolution: Lipase-Mediated Amidation of a Double Dynamic Covalent System

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Abstract: The Strecker reaction is one of the most important multicomponent reactions developed, leading to α-aminonitriles that are versatile substrates for many synthetic applications. In the present study, this reaction type has been applied to a double dynamic covalent resolution protocol, leading to efficient C−C- and C−N-bond generation as well as chiral discrimination. The combination of transimination with imine-cyanation enabled the dynamic exchange in more than one direction around a single stereogenic center of restricted structure. This multiple exchange process could generate a vast range of compounds from a low number of starting materials in very short time. The resulting double dynamic covalent systems, created under thermodynamic control, were subsequently coupled in a one-pot process with kinetically controlled lipase-mediated transacylation. This resulted in complete resolution of the dynamic systems, yielding the optimal *N*-acyl-α-aminonitriles for the enzyme, where the individual chemoenzymatic reactions could produce enantiomerically pure acylated *N*-substituted α-aminonitriles in good yields.

Introduction

Dynamic chemistry based on constitutional rearrangement of molecular entities or aggregates forms the basis for a vast range of important processes in chemistry and biology. These processes rely on both molecular − dynamic covalent − and supramolecular interconnections to generate structures of defined geometry, as a consequence of the inherent thermodynamic control of the systems. This is for example the original idea behind the concept of dynamic combinatorial chemistry,[1−6] where fragment reconstitution in the presence of a thermodynamic driving force − often a template or a receptor − results in enrichment of the fittest combination of building blocks.[7] The potential of this concept has for example been underscored in several recent reports.[8−18] However, these dynamic systems may also be kinetically controlled, where kinetically favored pathways may be used to resolve the system. The combined thermodynamic/kinetic events amount to a kinetically controlled dynamic combinatorial resolution (DCR) process,[19] where the lability of the molecules/aggregates is used to generate dynamics and the species experiencing the lowest activation energy is selected from the kinetic process. Both inter- and intramolecular processes can be performed using this concept, resulting in complete resolution and associated amplification of the selected species. When intermolecular processes are resolved using the method, an additional advantage is that only a catalytic amount of selector is required to control the system.

Recently, we proposed and demonstrated such DCR processes.[19−21] Using the dynamic nitroaldol (Henry) reaction to generate dynamic diversity, coupled with lipase-transesterification as a secondary process, not only substrate-specific but also stereospecific amplification of nitroaldol adducts from the dynamic system were shown.[19] Moreover, we also reported a system where a tandem Henry−iminolactone rearrangement was used to drive the DCR process. This resulted in quantitative amplification of single diastereomers of a 3-substituted isoin-

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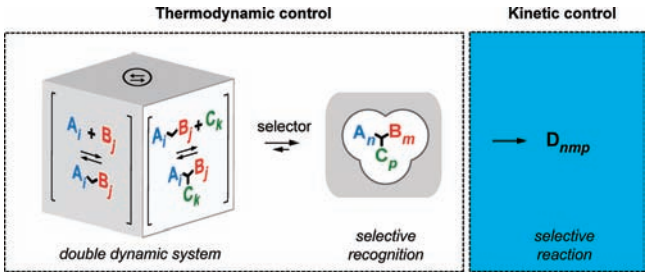

Figure 1. Double dynamic multicomponent resolution. A double dynamic system is formed from *i* components **A** and *j* components **B** followed by *k* components **C**. A specific constituent $\mathbf{A}_n-\mathbf{B}_m-\mathbf{C}_p$ is selectively recognized by a selector (e.g., an enzyme), enabling the formation of specific product $\mathbf{D}_{nmp}$ under kinetic control.

dolinone from the system pool.[22,23] From these studies, dynamically generated chirality, in combination with compact anatomy, play important roles in creating structural diversity and asymmetry. However, in both examples only one moiety, correlated to the chiral center, can be changed due to limitation of the reaction as well as type of the structure. Enhanced diversity of the restricted structural element can conversely be expanded if more than one axis at the same stereogenic center is exchangeable. In this case, the 2D diversity is in principle extended into 3D, more efficiently covering the chemical space.[24] This generates maximum diversity around a minimal point of attachment, resulting in complexity of the highest density. To demonstrate this concept, novel types of reactions and structures have to be investigated, and this has been the objective of the present study (Figure 1).

One of the key challenges in dynamic covalent chemistry is the development of efficient reversible reactions. Although several chemistries have been exemplified, imine formation/exchange and thiol−disulfide exchange are most often chosen to form dynamic systems, as these processes have been most developed in the systems studied.[1−6] Nevertheless, one of the most important reactions in organic chemistry, C−C bond formation, is still quite rare in this matter and this is especially the case when generation of chirality is involved in the system.[2,3] Furthermore, dynamic systems based on a single reaction type can in principle be constructed and controlled relatively easily, where the reaction conditions form the constraints of the overall system. When two or more chemistries are combined, this results in additional complications in addressing the chemistries independently.[18,25−30] Thus, not many examples of systems involving the multiple exchange process have been reported so far, and especially examples where multiple exchange reactions are performed simultaneously and continuously communicate with each other during the process.[25]

These challenges prompted us to explore the potential of generating complex dynamic systems using C−C bond-forming reactions, amenable to exchange in more than one dimension around a single chiral center. Furthermore, the use of mild conditions that are compatible with both the selector entities and applicable to a dynamic resolution process were addressed. After surveying different possibilities, we chose the Strecker reaction, in which, originally, α-aminonitriles were formed by mixing an aldehyde, an ammonium salt, and a cyanide source in water.[31] This powerful C−C bond-forming reaction provides chiral α-branched amine structures, which are common substructures in many biologically active entities.[32,33]

Herein, we describe the generation of a multiple dynamic covalent system based on the Strecker reaction, where transimination is combined with imine cyanation, and the reaction is carried out under mild conditions. This multilevel system provided a vast range of substances from a small number of starting compounds, yielding double dynamic covalent systems of *N*-substituted α-aminonitriles. The resulting systems could also be resolved through a coupled process in the form of a kinetically controlled lipase-mediated amidation reaction. Amplification of specific chiral α-aminonitriles could in this case be efficiently achieved in a one-pot process. Benefiting from the self-screening process, high enantiomeric purities of acylated *N*-substituted α-aminonitriles were thus obtained.

Results and Discussion

Thermodynamic Studies of the Strecker Reaction and the Double Dynamic Covalent Systems. The Strecker reaction of preformed, or in situ generated, imines and hydrogen cyanide is arguably the most important method for the synthesis of α-amino acid precursors.[32−36] The products, α-aminonitriles, have furthermore a broad range of synthetic applications through hydrolysis, reduction, or alkylation of the nitrile functionality.[37−49] In addition, these transformations represent one of the simplest and most economical methods on the laboratory scale as well as on the technical scale. In principle, the cyanation reaction is a reversible process but kinetic studies of the reaction in water

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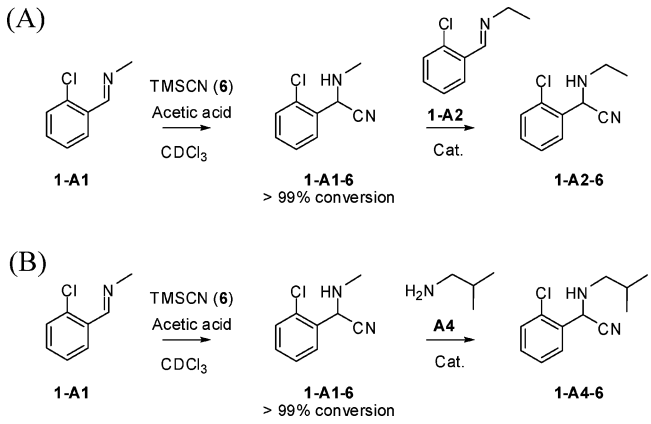
Scheme 1. Model Reactions to Test the Reversibility of the Strecker Reaction and the Double Dynamic Covalent Reaction by Various Catalysts



have shown that the reverse rate is considerably slower (around 10^7 times) than the forward rate, and slightly acidic conditions are required. Activation of the imine is also needed because of poor electrophilic properties.[50] In the present study, water needed to be replaced by typical organic solvents, for example chloroform, acetonitrile, and toluene, improving the solubility of the organic substances as well as being compatible with the selector in the resolution process. Therefore, optimization of the dynamic covalent Strecker system first needed to be addressed.

In initial experiments, 1 equiv each of imine **1-A1**, TMSCN (**6**), and an activator were mixed together in an NMR tube using $CDCl_3$ as a solvent (part A of Scheme 1). According to several reports, alcohols are usually employed as activators of TMSCN but in the present case this proved insufficient.[32,33] This effect may be due to the lower reactivity of the imine used because neither electron withdrawing groups nor electron stabilizing moieties are connected to the nitrogen atom. As an alternative, acetic acid was found to be suitable for this process, and, in three hours, the reaction progressed to completion (>99% conversion) forming α-aminonitrile **1-A1**−**6**, as monitored directly by ^{1}H NMR. Imine **1-A2** was subsequently added to the reaction mixture, and, in absence of any catalyst, reversibility was not observed even for prolonged reaction times (>2 days). Attempts to add different organic acids or bases, for example trifluoroacetic acid, triethylamine, or DBU to reverse the reaction, failed, and none of these agents were satisfactory. Instead, a variety of Lewis acids were examined. Interestingly, zinc halides, scandium triflate, and also gallium(III) triflate were shown to be potentially reactive as catalysts for the *retro*-Strecker reaction, and formation of the α-aminonitrile **1-A2**−**6** could be observed. Moreover, these metal Lewis acids also catalyzed the forward process, which is commonly described in the literature.[32,51−53] To our knowledge, the reversibility of the reaction has however never been reported previously. Zinc bromide proved to be optimal for use in the present system, resulting in the most rapid and stable equilibration observed, and, very importantly, high compatibility of this species with the subsequent enzymatic reaction.

To achieve multiaxial variation around a single stereogenic center, the imine cyanation reaction was coupled to another efficient dynamic covalent reaction, aldehyde-free transimination.[54] This process is self-sufficient and the exchange also occurs without disruption of the C═N unit into free amine and carbonyl groups. In addition, the reaction does not involve the mediation of a third constituent (i.e., water), which has to be prevented from the selection process.[54−57] Therefore, experiments were carried out to optimize the double dynamic covalent system. The test reaction was in this case similar to the previous system, where amine **A4** followed by $ZnBr_2$ in DMSO-d_6 (0.7 M, 60 mol %) were added to the mixture instead of another imine after completion (>99% conversion of **1-A1**−**6**) (part B of Scheme 1). Very rapidly, less than 10 min after addition, the newly formed imine **1-A4** and also the released amine **A1** could be observed, and the reaction reached equilibrium in five hours, as verified by the formation of another α-aminonitrile (**1-A4**−**6**) by ^{1}H NMR. According to the literature,[54] scandium triflate has proven to be a good catalyst for transimination processes. However, the combination of this metal salt with zinc bromide in the same reaction vessel resulted in an impaired double dynamic covalent system. Observation of free aldehyde and the formation of a precipitate suggested strong chelation between the metal ion and the amine. Instead, it was found that $ZnBr_2$ is as efficient in catalyzing the transimination process as $Sc(OTf)_3$. From these results, suitable conditions for the rapid and reversible aldehyde-free Strecker reaction in organic solvent could be identified. Furthermore, the combination of two dynamic covalent reactions around the same chiral center generates dynamic diversity in not two, but, in principle, three dimensions.

Thermodynamic Studies Following Expansion of the Dynamic Systems. This new type of double dynamic covalent system prompted us to test the thermodynamic properties and efficiency of the multicomponent reaction while expanding the system with more starting substances. Starting from two imines, **1-A1** and **2-A2**, mixed together in an NMR tube with benzene-d_6 as a solvent, a dynamic system was generated by adding one amine, **A4**, followed by $ZnBr_2$ (60 mol %). This resulted in the formation of six different imines, immediately observed upon mixing. Subsequently, the second dynamic covalent reaction was achieved by the addition of two equivs of TMSCN and acetic acid as activator. Six isomeric Strecker products (12 compounds in total) were in this case clearly observed by ^{1}H NMR. In addition, the Strecker reaction reached equilibrium in 18 h (>99% conversion) in benzene-d_6, slower than in $CDCl_3$ and acetonitrile-d_3. With this method, reversible generation of 12 α-aminonitriles starting from 2 imines and 1 amine, followed by TMSCN, could be achieved (pages S3−S7 of the Supporting Information for more details). Next, 1 equiv of amine **A3** was added to the controlled reaction. The system underwent re-equilibration, and, in 18 h, two more isomeric Strecker products (4 compounds) were formed. On the other hand, when instead 1 equiv of imine **3-A3** was added to the controlled reaction,

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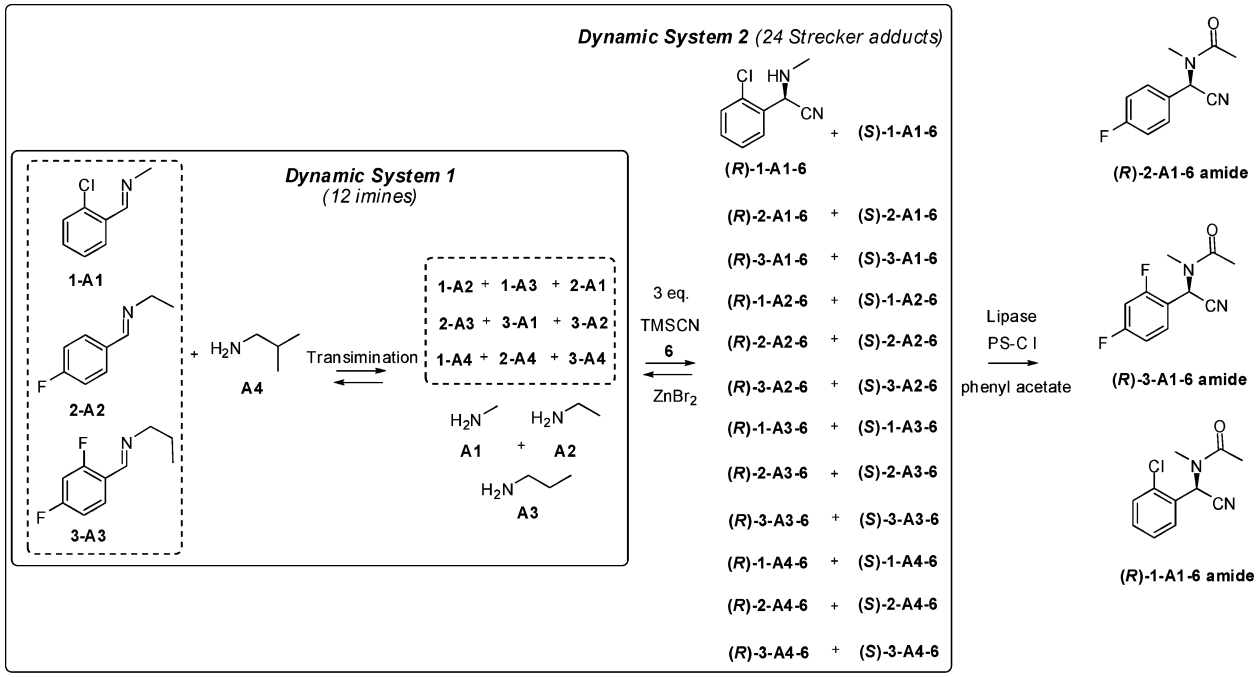
Scheme 2. Double Dynamic Multicomponent Resolution System



1 = 2-chloro phenyl moiety
2 = 4-fuoro phenyl moiety
3 = 2, 4-difuoro phenyl moiety

the double dynamic system re-equilibrated and a total of 24 α-aminonitriles (12 isomers) were formed after 24 h, as confirmed by ESI-MS.[58] This process demonstrated the efficiency of the process as "atom economic synthesis".[59] By adding just one more amine or imine into the double dynamic system, the number of Strecker compounds in the system increased by 33% or 100%, respectively.

Lipase-Mediated Resolution of the Double Dynamic Covalent Systems. Optically active secondary amines are important chiral building blocks in the production of pharmaceuticals and agrochemicals.[60,61] In addition, they play important roles in organic asymmetric synthesis as chiral auxiliaries, catalysts, or resolving agents.[62−64] For these reasons, many chemical processes have been reported for the preparation of this class of compounds. Nevertheless, one of the most efficient methods for the preparation of enantiomerically pure compounds is the kinetic resolution of racemic mixtures by enzymes, especially lipases.[65−68] In addition to their hydrolytic activity toward triglycerides, lipases catalyze (trans)esterification reactions and recognize a broad range of non-natural substrates in both aqueous and nonaqueous media. Moreover, lipases are readily available commercially, they are environmentally friendly catalysts, they do not require expensive cofactors, and they are easily recoverable. For the past few years, lipase-mediated asymmetric acylation of chiral primary amines has become increasingly common.[60,69] Surprisingly, there are however rare examples of the resolution of secondary amines in the literature.[70] Thus, we decided to couple the double dynamic covalent system with lipase catalysis to carry out a DCR process. However, the lipase-catalyzed-amidation of *N*-substituted α-aminonitrile substrates has not been reported. In addition, the undesirable by-reaction between primary amines, emanating from the transimination process, with the acyl donors through both enzymatic and uncatalyzed reactions, had to be prevented. The reaction conditions were optimized by initial screening of a series of enzymes followed by a series of acyl donors. On the basis of these results, the lipase preparation PS-C I from *Pseudomonas cepacia*, together with phenyl acetate, were selected as lipase and acyl donor respectively in the DCR system. The enzyme preparation is very robust and for unstirred systems the activity is well retained over time. For example, the conversion of **2-A1−6** after two months is only reduced by ca. 4% (24 h reaction time), compared to the freshly prepared solution.

Next, the double dynamic resolution process was addressed (Scheme 2). A dynamic set of 24 α-aminonitriles (12 enantiomer pairs) was originally constructed from equimolar amounts of three imines **1-A1**, **2-A2**, and **3-A3**, together with 1 equiv of isopropylamine (**A4**), followed by 3 equivs of TMSCN (**6**) and

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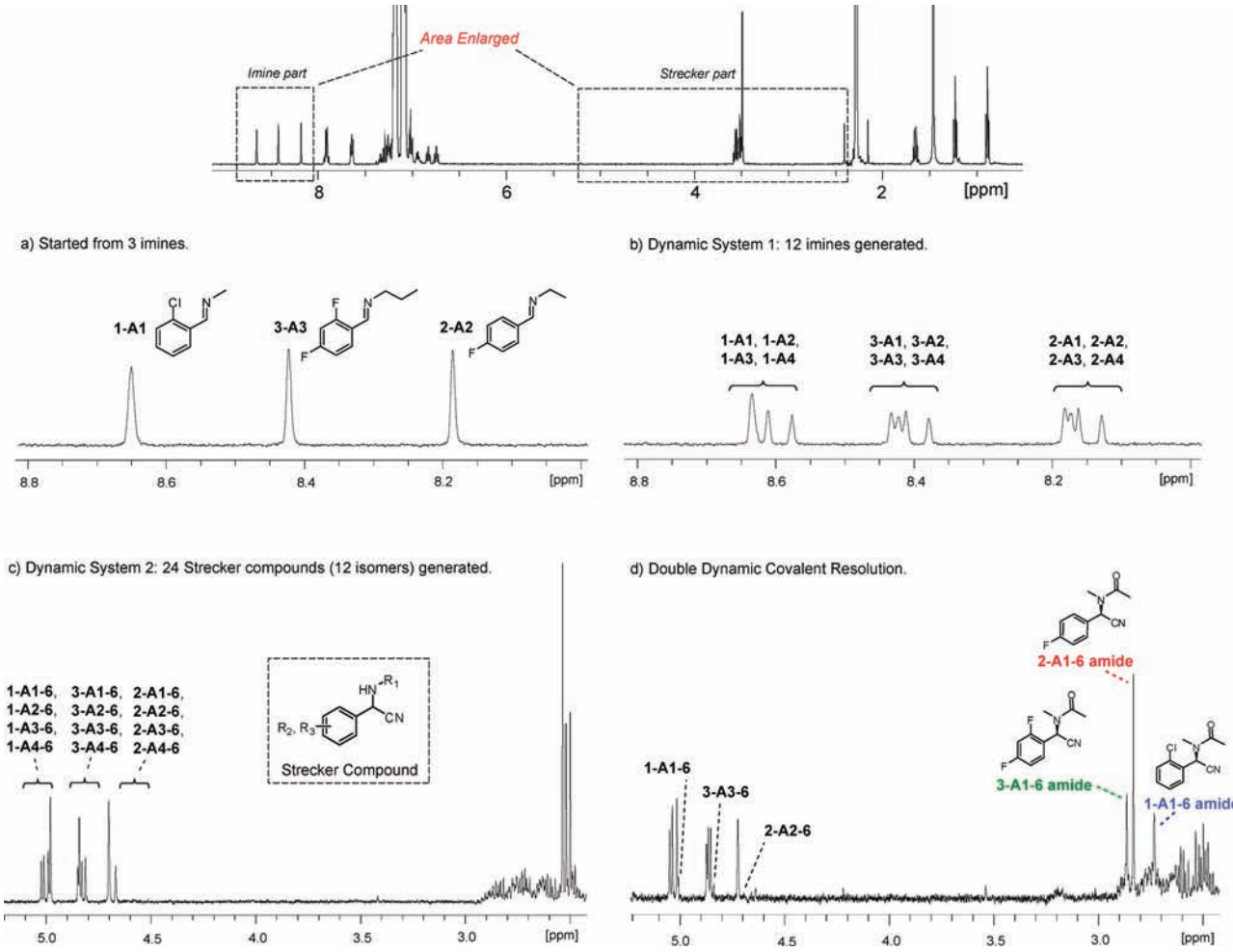

Figure 2. ^{1}H NMR spectra of the reaction mixture at various stages of the double dynamic resolution process: a) imine signals before equilibration; b), equilibrium imine signals of dynamic system 1; c) equilibrium signals of Strecker compounds (α-protons) of dynamic system 2 in the absence of PS-C I and phenyl acetate; d) signals of acylated Strecker compounds (*N*-alkyl protons) and remaining Strecker compounds (α-protons) of the dynamic system 2 in the presence of PS-C I and phenyl acetate (t = 40 d).

acetic acid as an activator. These aldimines and the amine were chosen in view of their similar individual reactivity not only in the transimination process but also in the imine cyanation reaction, with close to isoenergetic behavior in the double dynamic system produced. In addition, variations of the amine size from one carbon up to four carbons, and the substitution position of the aromatic moiety were chosen in view of the enzymatic screening of various types of Strecker compound structures. Figure 2 shows the ^{1}H NMR spectroscopic analysis of the generation and further reaction of the α-aminonitrile double dynamic system. The ^{1}H NMR spectrum of the initial components before library generation is displayed in part a of Figure 2. The generation of the first dynamic system, transimination, was subsequently initiated by addition of amine **A4** and equilibration between the initial components and all 12 aldimines were followed (part b of Figure 2), also confirmed by ESI-MS. Then the cyanide source TMSCN was added together with acetic acid and $ZnBr_2$ (60 mol %) to the first dynamic system. The Strecker compounds were instantly formed, and, in the absence of the selector, the second dynamic system reached equilibrium within hours (part c of Figure 2).

In a first attempt, the combination of the double dynamic system with the enzymatic reaction to screen *N*-substituted α-aminonitrile substrates was performed at room temperature. Mainly *N*-methylacetamide was however observed as a product from the process, likely due to the by-reaction between the primary amine and the acyl donor. To avoid this by-reaction, several conditions were tested and a better result was seen when the reaction was run at 0 °C. Under these conditions, the byproduct could be avoided even with a reaction time for 14 days (less than 5% conversion). Unfortunately, the desired final product could also not be observed under these conditions. It was however hypothesized that the $ZnBr_2$ solution could be the cause of the result, binding to polar amino acid residues on the protein surface. This coordination would block the active site or decrease the protein flexibility that is essential to the catalytic activity.[71] Fortunately, by serendipity, it was found that solid-state $ZnBr_2$ could be employed as a heterogeneous catalyst for the double dynamic system at 0 °C. This enabled the enzymatic process in the screening of the *N*-substituted α-aminonitrile substrates from the double dynamic system in a one-pot reaction (part d of Figure 2). It could be proposed that the solid-state catalyst interfere considerably less or not at all to the chemoenzymatic reaction because the two processes are separated from each other. Moreover, the rate of the by-reaction was reduced due to strong chelation between the amine and the $ZnBr_2$ in the heterogeneous system.

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HPLC was also used to analyze the data because some overlaps of significant peaks (α-protons) of the final products were observed in the ^{1}H NMR spectrum. Using the integration of an achiral (Zorbax) and a chiral (OD-H) column for the HPLC analyses, all of the final products could be distinguished. This technique allowed the determination of not only the conversions but also the enantiomeric excesses directly from the crude reaction mixture. According to both analyses, the first major product was found to be the **2-A1−6** *amide*, produced from aldimine **2-A1**, obtained via transimination, and TMSCN (**6**). The relative concentration of the **2-A1−6** α-aminonitrile, the corresponding substrate for the lipase reaction, was however not among the highest in the double dynamic system in the absence of the enzyme. Nevertheless, **2-A1−6** was the main structure selected as a substrate for the amidation. Interestingly, the other final products were found to be the **3-A1−6** *amide* and the **1-A1−6** *amide*, formed at the second and the third highest conversion, respectively. From our experiences with *β*-nitroalcohols, the lipase enzyme will not prefer a substrate that possesses an ortho-substituted phenyl moiety, not even a small entity such as fluoride.[11] However, in the present study, ortho-substituted aromatic α-aminonitrile substrates, not only fluoride but also chloride showed the highest accessibility to the lipase active site to undergo amidation. Moreover, at another axis of the stereogenic center, the result also demonstrated that only a methyl group at the *N*-substituted moiety can fit the enzymatic reaction. All of the final products were obtained in a combined approximate overall yield of 5% after two days. Better yields were observed after longer reaction times and the products were obtained in over 39% and 65% yield after 18 and 40 days (part d of Figure 2), respectively. Longer reaction times (48 days) resulted in ^{1}H NMR trace peaks of remaining target intermediates in the double dynamic system, and a slightly increased overall conversion (69%). The slower conversion at longer reaction times may be due to slow evaporization of methylamine, a major component in all three final products, from the reaction mixture. Attempts to perform the reaction at −18 °C, resulted in stable dynamic systems, but no reactivity of the biocatalyst, even for 30 days reaction time. The equilibration of the double dynamic covalent system could be efficiently followed by ^{1}H NMR, not only by decreasing signals of the best substrate, that is, the para-substituted fluorophenyl species, but also by increasing signals of the nonselected entities. In addition, a significant amplification effect was recorded from the HPLC analyses (Figure 3). At two days reaction time, similar ratios of the final products, **2-A1−6** *amide* (2%) and **1-A1−6** *amide* (2%) were observed (part a of Figure 3), whereas lower formation of the **3-A1−6** *amide* (1%) was observed. For longer reaction times (18 days, part b of Figure 3), the ratios changed to 22% (**2-A1−6** *amide*), 8% (**3-A1−6** *amide*), and 9% (**1-A1−6** *amide*), clearly indicating that **2-A1−6** is the best partner in the system. At 40 days reaction time (part c of Figure 3), **3-A1−6** proved to be the second best partner because the ratios changed to 37% (**2-A1−6** *amide*), 15% (**3-A1−6** *amide*), and 13% (**1-A1−6** *amide*). These results demonstrate that the enzymatic system plays an essential role for dictating the outcome of the double dynamic covalent process, forcing the system to re-equilibrate, the reactions to continuously communicate, and select for the better substrates, **2-A1−6** and **3-A1−6**. The third possibility, **1-A1−6**, was essentially rejected by the enzyme, although it was the most abundant compound in the double dynamic system.

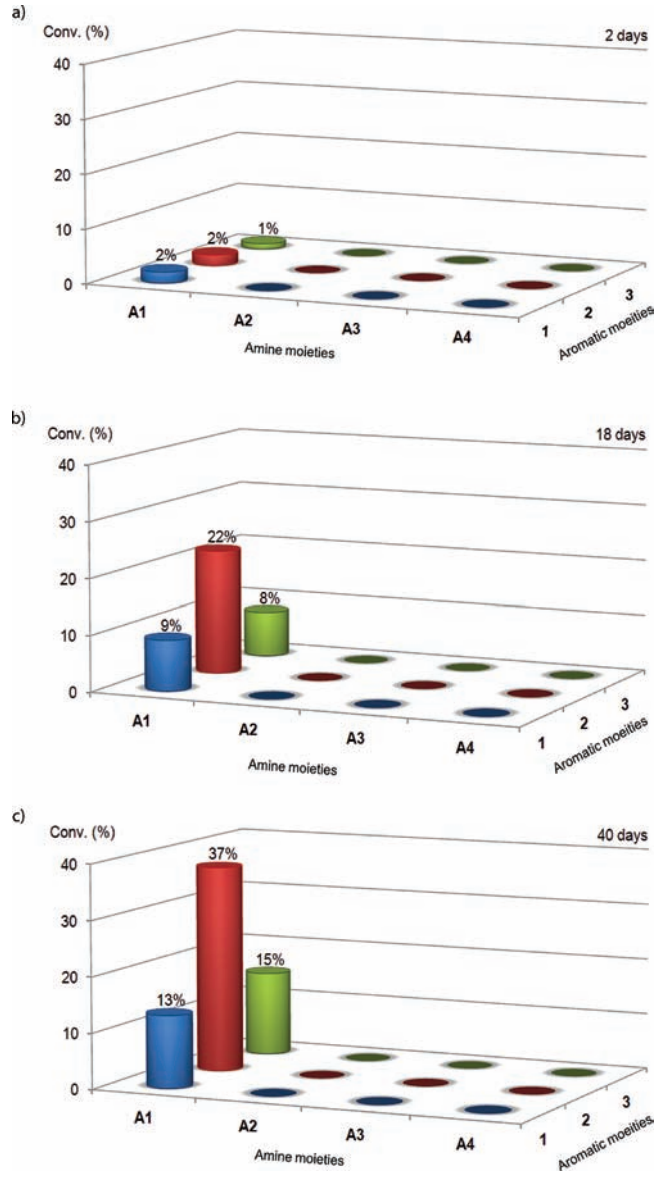

Figure 3. Conversion (%) of acylated *N*-substituted α-aminonitriles from the double dynamic resolution process at a) 2 d, b) 18 d, and c) 40 d.

The *N*-substituted α-aminonitrile-lipase DCR process did not only amplify specific α-aminonitriles derivatives, but asymmetric discrimination was also observed. HPLC analysis of the total DCR process, showed that the highest enantioselectivity was around 5−10% ee, for the **2-A1−6** *amide* and **1-A1−6** *amide*, respectively. These results prompted us to examine the stability of the α-protons of the final products at various conditions. The final compound, *rac* **2-A1−6** *amide*, was thus tested with a variety of organic acids or bases related to the DCR process, together with D_2O, to record the exchange of the α-proton.[58] As expected, relatively fast racemization was observed at basic conditions, especially for primary amines. Moreover, the exchange reaction could also be detected at diluted conditions, or from the action of the Strecker compounds themselves, at a slower rate. Thus, these results clearly explained that the low enantioselectivity in the DCR process is due to slow, but significant, amine-induced racemization during the DCR process. However, substitution of the solvent for *tert*-butyl methyl ether (TBME), commonly used for lipases, resulted in prevention of the racemization process, and hence, these

improved conditions were subsequently applied to the DCR process. As expected, high enantioselectivity was observed for all three final products, 90% ee (**2-A1−6** *amide*), 92% ee (**1-A1−6** *amide*), and 73% ee (**3-A1−6** *amide*) with approximately 14% conversion in 18 days (Figures S5 an S7 of the Supporting Information for more detail). The rate of the resolution process was in this case lower than in toluene. Avoiding racemization, these results strongly confirmed the efficiency of the dynamic resolution process by selecting 3 compounds from a pool of 24. Moreover, the important information from the DCR process; substrate selectivity and stereoselectivity, prompted the further development of a practical chemoenzymatic route for the preparation of optically active *N*-methyl α-aminonitrile derivatives through lipase-mediated amidation. The final product, the **2-A1−6** *amide*, was thus obtained in high enantiomeric excess (92%) and good yield (48%) from **2-A1−6** in a kinetic resolution (KR) process.

Conclusions

In conclusion, we have developed the Strecker reaction as a new and efficient asymmetric C−C bond-forming and also nitrogen-containing route to complex dynamic system generation, catalyzed by Lewis acids. Furthermore, we have demonstrated that the combination of two dynamic covalent systems, aldehyde-free transimination and imine cyanation, allowed the multiple exchange in 3D around a single stereogenic center of restricted structure. This multiple exchange process also demonstrated the vast expansion of the system by addition of just one component, an amine or imine. The primary double dynamic systems generated under thermodynamic control could also be successfully coupled to a secondary synthetic process mediated by a lipase under kinetic control. This dynamic multicomponent resolution process was used to generate a collection of potential enzyme substrates and to identify the best substrates for the lipase PS-C I from *Pseudomonas cepacia*. The resolution system is a significant screening method because the diversity of Strecker compounds can be evaluated at the same time in one pot. Furthermore, the reduced need for purification as well as the low amount used of the toxic cyanide compound is advantageous and environmentally friendly. On the basis of the results from the DCR process, efficient asymmetric resolutions of *N*-methyl α-aminonitriles through chemoenzymatic amidation could be achieved. At optimal conditions, high enantiomeric purities of acylated *N*-methyl α-aminonitriles were obtained, with up to 92% ee in excellent yields in a kinetic resolution process. These results indicate that double dynamic systems can be applied to various types of lipases and other enzymes, to efficiently screen the substrate selectivity.

Experimental Section

All reagents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR data were recorded on a Bruker Avance 400 spectrometer at 400 (100) MHz and/or a Bruker Avance DMX 500 at 500 (125) MHz, respectively. Chemical shifts are reported as δ values (ppm) with $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0) as an internal standard. *J* values are given in Hertz (Hz). Analytical high performance liquid chromatography (HPLC) with achiral and/or chiral stationary phase was performed on HP-Agilent 1110 Series controller and photodiode array detector, using Zorbax Rx-SIL (46 × 250 mm, 5 μm) and Daicel Chiralpak OD-H columns (46 × 250 mm, 5 μm). Solvents for HPLC use were spectrometric grade.

Generation of Double Dynamic Covalent Systems and Lipase-Mediated Screening. Initially, the first dynamic system, transimination, was generated by using three different aldimines (**1-A1**, **2-A2**, and **3-A3**, 0.09 mmol each), together with 1 equiv of isobutylamine (6.6 mg, 0.09 mmol) in dry toluene (0.6 mL) at −78 °C. The reaction mixture was performed at 0 °C to equilibrium (∼2 h). Then TMSCN (26.8 mg, 0.27 mmol) and acetic acid (16.2 mg, 0.27 mg) were added to the first dynamic system at −78 °C. The second dynamic covalent system was initiated by transferring the reaction mixture directly to a 1.5 mL sealed-cap vial which contained *Pseudomonas cepacia* lipase (PS-C I, immobilized on ceramic, Sigma-Aldrich EC 3.1.1.3, 200 mg) together with 0.6 equivs of $ZnBr_2$ solid (12.2 mg, 0.054 mmol) under argon atmosphere. The dynamic systems were generated at 0 °C, and followed by ^{1}H NMR at 298 K by addition of aliquots (10 μL) from the reaction mixture to $CDCl_3$ (0.6 mL). For the lipase-mediate screening, 3 equivs of phenyl acetate (36.8 mg, 0.27 mmol) was added to the double dynamic covalent systems and the reaction carried out at 0 °C without stirring under argon atmosphere.

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Supporting Information Available: Preparation procedures, full characterization, ^{1}H NMR and Mass spectra of thermodynamic studies, HPLC analyses of the double asymmetric multicomponent resolution process, racemization test of **2-A1−6** *amide*, determination of absolute configuration of final product and kinetic resolution method. This material is available free of charge via the Internet at http://pubs.acs.org.

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