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Dynamic Covalent Chemistry

Self-Sorting of Dynamic Imine Libraries during Distillation**

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Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 65th birthday

Nature and chemists approach organic synthesis in very different ways. Living systems are grand masters of parallel synthesis: starting with incredibly complex precursor mixtures, highly specialized enzymes operate selectively, simultaneously, and orthogonally to create many different products at once. In contrast, laboratory synthesis typically relies on reagents and catalysts with broad scope and wide functional-group tolerance; in this case, high-purity starting materials are required for the sequential preparation of individual products. Furthermore, undesirable reactivity often has to be blocked by protecting groups.[1] In recent years, self-sorting[2] has emerged as a promising preparative method that can enable the simultaneous synthesis of high-purity products from complex mixtures of starting materials. Self-sorting can be defined as the spontaneous reorganization of a disordered multicomponent system into a set of subsystems with fewer components and greater order.[2d] In the absence of specific enzyme catalysis, high fidelity of synthetic self-sorting is ensured by efficient error-correction mechanisms, which use the reversible formation of noncovalent and dynamic covalent bonds[3] to continuously recycle side products as the system heads towards equilibrium. Self-sorting processes can proceed under thermodynamic[2,4,5] or kinetic[6] control. The former processes are characterized by a self-sorted equilibrium state; the latter are less common and are typically observed when a system is trapped in a self-sorted local energetic minimum. We recently reported[7] a hybrid self-sorting protocol in which components of a dynamic imine mixture freely equilibrate (thermodynamic control), and sort on the basis of the rates of their removal from equilibrium through an irreversible reaction (kinetic control).

The synthetic applicability of self-sorting is frequently limited by the fact that all self-sorted species remain in the same solution. The isolation of individual components requires separation, which can be problematic in the case of fragile supramolecular complexes. Herein, we demonstrate that the self-sorting of dynamic mixtures can occur concurrently with separation to produce multiple products that are not only of high purity, but also mechanically separated. Specifically, we show that vacuum distillation can be used to sort complex libraries of $[n \times n]$ equilibrating imines ($n \leq 5$) into n pure compounds simply on the basis of the volatility of individual imines.

Imines are formed in a reversible reaction of an aldehyde with an amine. When multiple imines are present in a solution, they readily exchange their aldehyde and amine constituents.[8] In any such equilibrating mixture, one imine has the lowest boiling point. If that compound can be distilled away selectively, its removal disturbs the equilibrium of the system and thus forces other imines to reequilibrate and produce more of the compound just removed—as dictated by the Le Châtelier principle. Provided that distillation is sufficiently selective and slower than the imine exchange,[9] the low-boiling imine will extract its constituent aldehyde and amine from all other imines that contained them. In the process, the low-boiling imine is produced in superior yield, and the remaining equilibrating mixture is reduced in complexity through the removal of both the low-boiling imine and all its precursors. If such a sequence is repeated, multiple species can be produced with a single distillation setup.

We assessed the synthetic viability of this proposition in an experiment which examined the behavior of a mixture prepared from two aromatic aldehydes **1** and **2** and two anilines **A** and **B** (Scheme 1). To ensure that the resulting imines had significantly different boiling points, we chose aldehydes and anilines of different molecular masses and assumed that a higher mass would lead to a higher boiling point. The heating of these four reactants under dehydrative conditions produced a mixture of all possible imines: **1A**, **2A**, **1B**, and **2B**.[10] The most volatile of the four was **1A**—the product of the reaction of the lighter aldehyde with the lighter aniline; conversely, the least volatile imine was the product **2B** of the heavy–heavy combination. Vacuum distillation (90–115 °C, 0.10 mmHg) of this mixture began with the selective removal of low-boiling **1A**.[11] With the depletion of **1A**, **2A** and **1B** started decomposing to produce more of **1A**; eventually, these two compounds were completely consumed in the process, and the only imine remaining in the distillation flask was **2B**. Compounds **1A** (most volatile, light distillation fraction) and **2B** (least volatile, heavy distillation fraction) were isolated in virtually quantitative yield (96 and 98%, respectively) and in very high purities, as evidenced by ^{1}H NMR spectroscopy (98 and 99%, respectively; see the Supporting Information for details).[12] Three additional higher-boiling $[2 \times 2]$ combinations (see the Supporting Infor-

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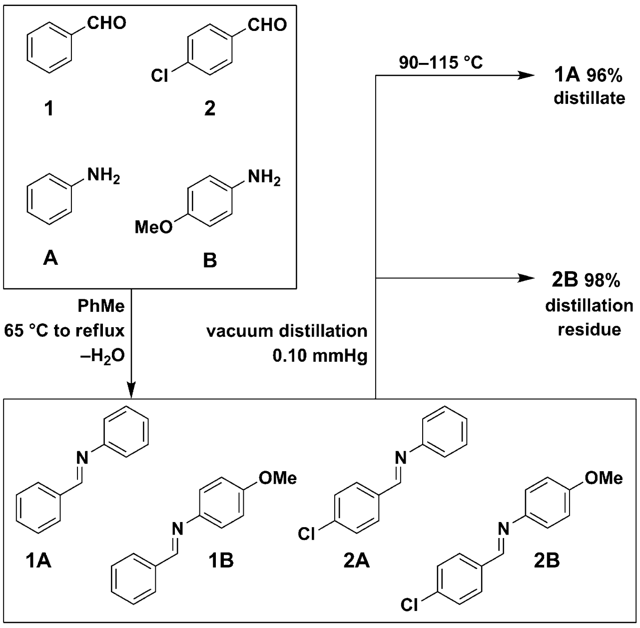
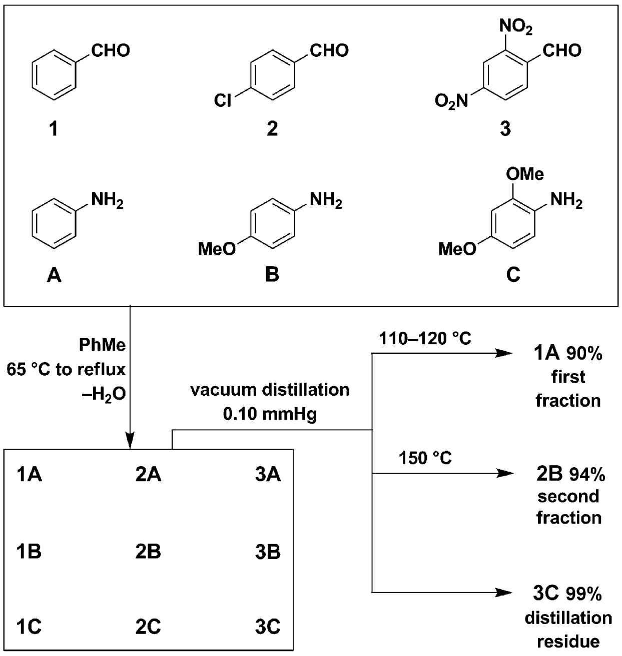


Scheme 1. Simplification of a [2×2] mixture of imines during the course of a vacuum distillation.

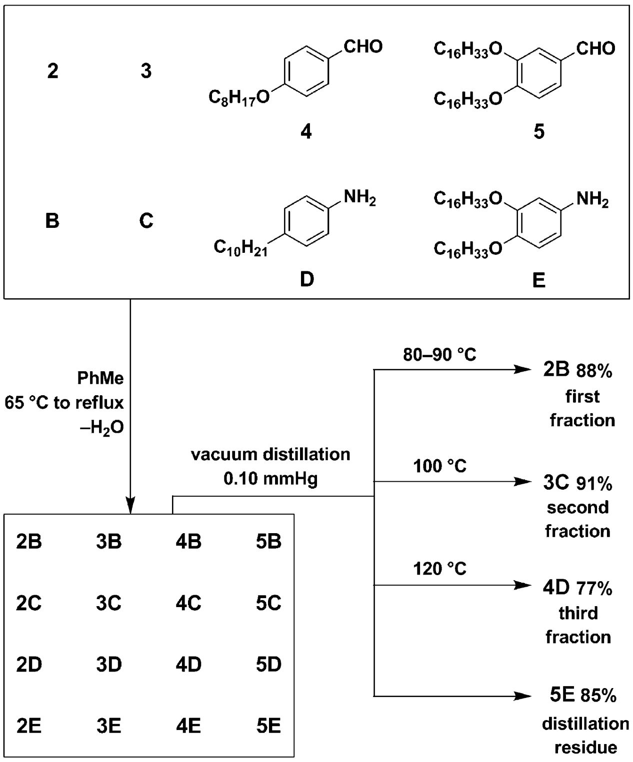
mation) were subjected to similar distillation conditions with analogous results: the high-yielding production of the most volatile and least volatile fractions, with virtually no evidence of "crossed" products.

These encouraging results suggested to us that a more complex mixture could be sorted in an analogous manner during a distillation. A [3×3] imine mixture (Scheme 2) was created from aldehydes **1**–**3** and anilines **A**–**C**. The most volatile of the nine imines formed was **1A**—the combination of the lightest aldehyde and the lightest aniline. Its preferential removal from the mixture by distillation (110–120°C, 0.10 mmHg) caused the decomposition of its precursors **2A**, **3A**, **1B**, and **1C**. Once all of **1A** had been distilled off (90% yield, 98% purity), five imines—**1A**, **2A**, **3A**, **1B**, and **1C**—had been removed from the mixture. In essence, the selective distillation of **1A** extracted the most volatile aldehyde **1** and the most volatile aniline **A** out of all other imines that contained them. Of the four imines that remained (**2B**, **3B**, **2C**, and **3C**), compound **2B** was the next most volatile. An increased distillation temperature (150°C, 0.10 mmHg) enabled its isolation in very high yield (94%, 100% purity) with the concurrent elimination of **3B** and **2C** from the equilibrium mixture. Ultimately, the only compound remaining in the distillation flask was the least volatile imine **3C**, which was isolated in 99% yield (89% purity). Two additional [3×3] experiments were performed (see the Supporting Information).

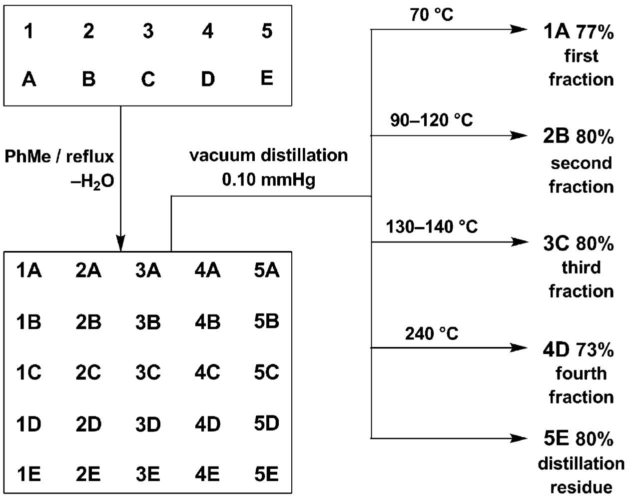
Next, we examined a [4×4] mixture (Scheme 3) produced from aldehydes **2**–**5** and anilines **B**–**E**. ^{1}H NMR spectroscopy revealed the presence of at least 12 imines; overlapping peaks probably obscured the presence of an even larger number of species. According to the logic of the [2×2] and [3×3] experiments, the distillation of this mixture produced, in this order, **2B** (88%), **3C** (91%), **4D** (77%), and **5E** (85%). A



Scheme 2. Simplification of a [3×3] mixture of imines during the course of a vacuum distillation. For simplicity, imine structures are not shown. Imine designators are a combination of the corresponding designators for the constituent aldehyde and aniline; for example, imine **2B** is formed by the dehydrative coupling of **2** and **B**.



Scheme 3. Simplification of a [4×4] mixture of imines during the course of a vacuum distillation. Imine designators are a combination of the corresponding designators for the constituent aldehyde and aniline.



Scheme 4. Simplification of a [5×5] mixture of imines during the course of a vacuum distillation. Imine designators are a combination of the corresponding designators for the constituent aldehyde and aniline.

second [4×4] experiment is described in the Supporting Information.

In our most complex experiment, we constructed a [5×5] library of presumably 25 imines (Scheme 4; the exact number of imines could not be confirmed by ^{1}H NMR spectroscopy because of overlapping peaks) from aldehydes **1**–**5** and anilines **A**–**E**. Again, imine **1A** was distilled first (77% yield, 96% purity as determined by NMR spectroscopy); in the process, imines **2A**, **3A**, **4A**, **5A**, and **1B**–**E** were all eliminated from the equilibrium mixture. The second step of the distillation saw the isolation of **2B** (80% yield, 96% purity) at the expense of **3B**, **4B**, **5B**, and **2C**–**E**. Imine **3C** was isolated third (80% yield, 99% purity), with the removal of **4C**, **5C**, **3D**, and **3E**. In the final step of the distillation, imine **4D** (73% yield, 99% purity) was formed and distilled at the expense of **5D** and **4E**. The residue in the distillation flask was identified as **5E** (80% yield, 83% purity). Effectively, one reaction enabled us to access five compounds simultaneously, all in yields greater than 70%!

Figure 1 illustrates the typical purities of products obtained from the distillative self-sorting of an exemplary [4×4] mixture (discussed in Scheme 3): four isolated fractions are essentially pure compounds, as evidenced by the segments of their ^{1}H NMR spectra in the bottom panel of Figure 1. As could be expected, the final distillation residue (lowermost spectrum, compound **5E**) is the least pure fraction.

In this hybrid self-sorting protocol, both kinetic and thermodynamic factors play a role in the outcome of self-sorting. Although evaporation rates determine which imines will be isolated as the exclusive products, the underlying thermodynamic equilibration is required to maximize the yields of these products. In that respect, this distillative self-sorting is conceptually similar to our recently reported self-sorting of an imine mixture through an irreversible oxidation.[7] The chief difference is in the method used to irreversibly disturb the equilibrium and initiate a self-sorting sequence: in the current study, a physical transformation (evaporation) is used, whereas we used a chemical stimulus (oxidation) in our previous study. Taken together, these results suggest that hybrid self-sorting should be very broadly applicable.

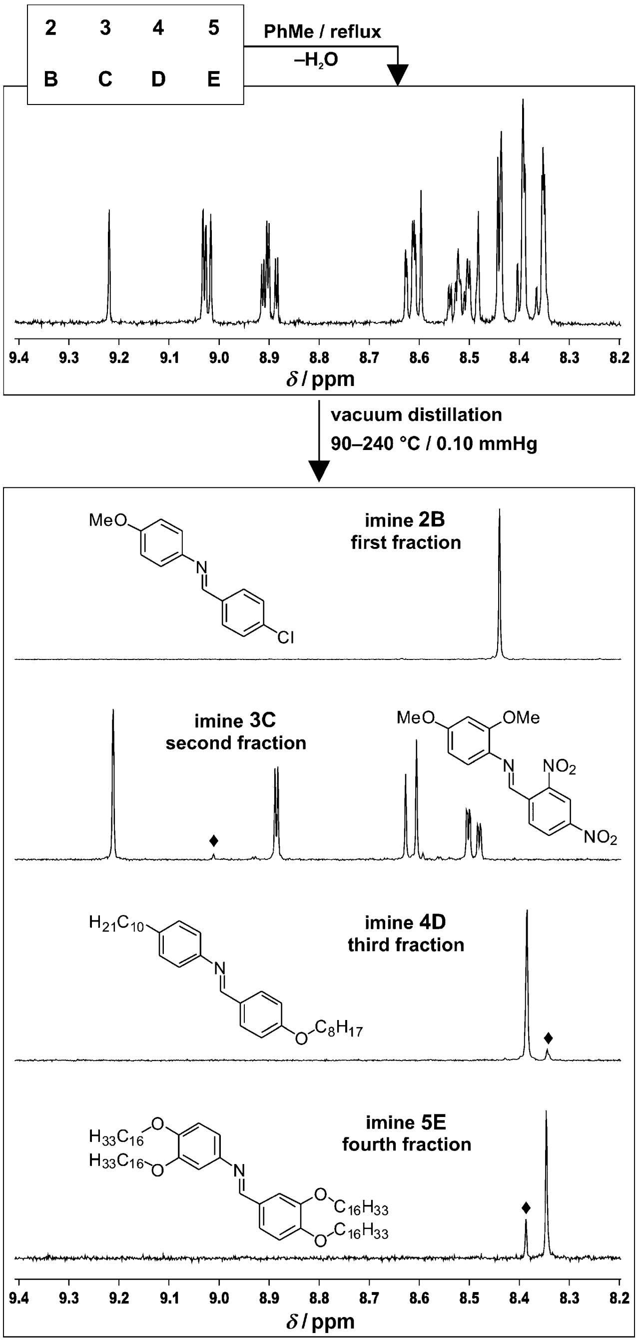


Figure 1. Top: Imine-diagnostic segment of the ^{1}H NMR spectrum of the crude mixture of imines obtained by the dehydrative heating of aldehydes **2**–**5** with anilines **B**–**E** (Scheme 3). Bottom: The same segment of the ^{1}H NMR spectra of individual distillation fractions; each spectrum indicates almost the exclusive presence of a single imine. "♦" denotes minor imine impurities.

The success of this self-sorting method sounds a cautionary note about the use of separation techniques in the analysis of dynamic combinatorial libraries (DCLs). Distillation is clearly able to profoundly affect the composition of a dynamic library.[13] Our experiments were designed to maximize these effects, but changes in composition probably occur during all separations of DCLs, as any separation creates an open system that begins to move away from the established equilibrium. Thus, the use of HPLC, GC/MS, and other separation-coupled analysis techniques should be accompanied by the independent verification of library composition through, for example, purely spectroscopic techniques, which are unlikely to significantly affect product distribution.

We believe that our study may have industrial relevance. Within the past two decades, some of the most significant reductions in construction and energy costs in the chemical industry have been achieved through *reactive distillation plants*,[14] which use distillation both as a separation technique and as an equilibrium-driving force that ensures full conversion of precursors. Esters are among the hundreds of chemicals produced by this method;[14b] reactive distillation drives their formation from carboxylic acid and alcohol precursors. Since transesterification is a dynamic reaction,[5k] largely parallel to imine exchange, our protocol should enable the equilibration and distillative self-sorting of a mixture of esters. Could a mixture of several carboxylic acids and alcohols be used for the production of many different esters in a single reactor and their self-sorting by distillation into a handful of high-purity products? Current studies in our group are focused on answering this question and on the combination of chemical and physical self-sorting methods into sequences which could exponentially simplify complex precursor mixtures.

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[10] Imine mixtures were preformed in toluene at reflux. Water removal (with a Dean–Stark trap) is critical, because it prevents the hydrolysis of imines into an aniline and an aldehyde—both of which would be more volatile than the corresponding imine. After dehydration, the only dynamic reaction is imine exchange.

[11] Imine distillation should be understood conditionally. Virtually all imines investigated in this study are solids. Upon heating, they melt and then evaporate, and solidify at various points along the distillation apparatus, from where they can be extracted by careful scratching and washing. See the Supporting Information for details.

[12] In all distillation experiments, the major impurities were other imines—typically the "crossed" light–heavy combinations; no NMR spectroscopic evidence of other side products was found. Purity was thus estimated by comparing the integral of the N=C–**H** peak of the desired imine to the sum of the integrals of the corresponding peak for all other imines.

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