Oxidative Kinetic Self-Sorting of a Dynamic Imine Library

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S *Supporting Information*

ABSTRACT: Dynamic libraries of $[n \times n]$ imine components spontaneously simplify during a slow oxidation reaction to produce only n discrete products. The selectivity of this self-sorting process is a consequence of different oxidation rates for various imines, while the dynamic nature of the library enables self-sorting to proceed with high efficiency.

Scheme 1. Response of an Equilibrating $[2 \times 2]$ Mixture to an Irreversible Removal of One of Its Components


Nature continues to astonish chemists with its complex functional architectures that are constructed with absolute selectivity and without any purification[1] or protecting-group manipulation.[2] Such exquisite control of chemoselectivity[3] is largely enabled by the simultaneous operation of numerous self-sorting processes[4] wherein the components of a metabolic pathway selectively recognize each other within a highly complex cellular environment. Self-sorting spontaneously introduces order into complex systems by reducing them into a set of simpler subsystems that communicate but do not interfere with each other. Chemists are increasingly interested in modeling and replicating the behaviors of biological self-sorting systems through the preparation of their synthetic counterparts.[5]

High-fidelity synthetic self-sorting must have an error-correction mechanism, which is most commonly based on the reversibility of the formation of noncovalent[4a−4d,6] or dynamically covalent[4e,4f,7,8] bonds. Most of the reported self-sorting systems are thermodynamically driven,[4,6a−6f,7] meaning that the resultant assemblies are the most stable state of the system. Far less common are kinetically self-sorting systems,[6g−6i,9] wherein the product formation rates determine the outcome of self-sorting. Kinetically self-sorting systems are arguably more relevant models for biological processes that operate far from equilibrium.[10]

In this communication, we present kinetic self-sorting of a dynamic library of imines[8] that occurs during a slow irreversible oxidation. Our work is based on a hypothesis directly derived from the well-known Curtin–Hammett principle,[11] namely that *a quickly equilibrating mixture will spontaneously simplify (self-sort) if its components react at very different rates in a slow irreversible reaction*. This scenario is illustrated in Scheme 1.

The four compounds **X**, **Y**, **1**, and **2** react in a reversible reaction to establish a mixture of intermediates **X1**, **X2**, **Y1**, and **Y2** (**X** does not react with **Y**, and **1** does not react with **2**). If compound **X1** reacts fastest in an irreversible reaction, the mixture responds to its removal by re-equilibrating to produce more of it. Effectively, **X1** is amplified at the expense of its precursors **X2** and **Y1**; the irreversible removal of **X1** eventually consumes all of **X2** and **Y1**. The nonprecursor compound **Y2** remains unaffected by this process and could react further. Ultimately, only the products derived from **X1** and **Y2** are
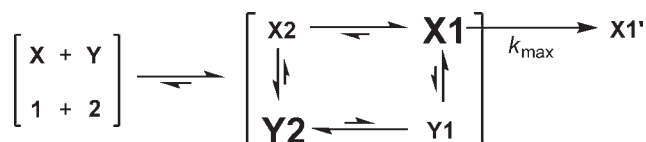
isolated, even though two other compounds with competing reactivity originally existed in the mixture.

We tested this hypothesis on a well-documented synthesis of benzoxazoles and benzimidazoles by oxidative cyclization of aldimines[12] derived from *o*-hydroxy- and *o*-aminoanilines, respectively. We chose this reaction because (a) the intermediate aldimines are formed reversibly, (b) the oxidation step is irreversible, and (c) the rates of oxidation can be modulated by substitution. In an exemplary one-pot reaction (Scheme 2, route A), 1,2-diaminobenzene (**3**) and benzaldehyde (**5**) reacted to first form imine **6**. Addition of I_2 as the oxidant converted the intermediate imine into benzimidazole **8** in 90% yield. The analogous reaction of 2-aminophenol (**4**) gave benzoxazole **9** (86%) without the need to isolate imine **7**.

The first imine mixture capable of rudimentary self-sorting was generated by exposing **3** to imine **10** derived from benzylamine (Scheme 2, route B). Equilibration produced a mixture containing **3**, **6**, **10**, and benzylamine (as determined by ^1H NMR spectroscopic analysis). Addition of I_2 initiated the oxidation of **6** into **8**. As **6** was consumed, **3** and **10** re-equilibrated to keep a steady supply of **6** until all of **3** was exhausted. The final product mixture contained only benzylamine and **8**, which was obtained in 90% yield after separation. In a separate experiment, **4** and **10** were converted into **9** in 84% yield. In effect, amines **3** and **4**, which can produce oxidizable imines, extracted benzaldehyde out of its nonoxidizable imine **10**. The yields of this indirect route to **8** and **9** were as high as those obtained in the direct oxidation.

Since imine **10** cannot be oxidized using I_2 as the oxidant, it cannot kinetically compete with **6** and **7**. What happens if two oxidizable imines compete for an oxidant? To answer this question, 1 equiv of **5** was exposed to a 1:1 mixture of **3** and **4** (1.5 equiv of each). As expected, imines **6** and **7** formed after overnight heating in PhMe. The Curtin–Hammett principle stipulates that oxidation of this mixture could have different outcomes depending on its rate. If imines are oxidized faster than they exchange with each other, the final **8/9** ratio should be

Scheme 2. Synthesis of Benzazoles by Oxidative Cyclization of Directly (Route A) and Indirectly (Route B) Prepared Imines

Scheme 4. Amine Selects the Most Electron-Rich Aldehyde
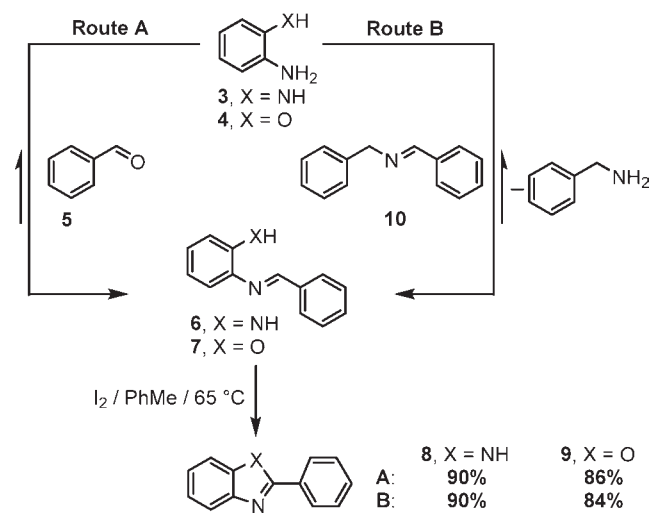
similar to the equilibrium 6/7 ratio.[13] On the other hand, if oxidation is much slower than imine exchange, the more rapidly oxidizing imine (presumably the more electron-rich 6) should slowly "leak out" of the equilibrium mixture, causing the re-equilibration to quickly replenish it. In such a situation, 8 should be obtained in high yield as the product of the faster oxidation, which was more desirable from a synthetic viewpoint. The use of 1 equiv of I_2 as the *weak* oxidant and its slow addition (via syringe pump) ensured that the oxidation indeed proceeded more slowly than imine exchange, and 8 was obtained as the only oxidation product (70%) along with amine 4, which was recovered unchanged (Scheme 3). No 9 was detected by ^{1}H NMR spectroscopy.
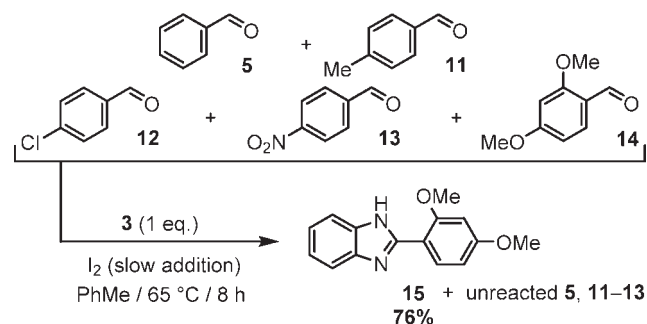
Scheme 3. Aldehyde Selects the More Electron-Rich Amine
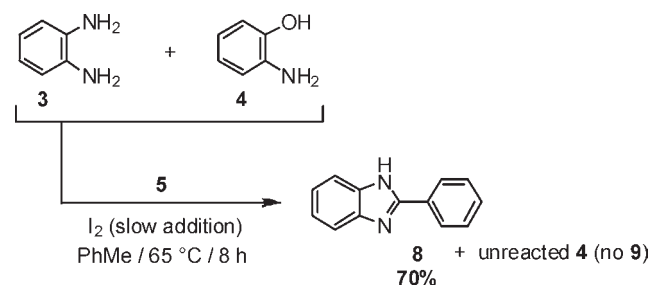
An analogous result was obtained in an experiment in which five aldehydes with various electron densities competed for one amine. Exposure of a mixture of 5 and 11−14 (1 equiv of each) to 1 equiv of 3 (Scheme 4) led to the partial formation of five intermediate imines. The slow oxidation of this mixture exclusively generated (76%) benzimidazole 15 derived from reaction of 3 with 14, the most electron-rich aldehyde in the mixture. Aldehydes 5 and 11−13 were recovered unreacted, even though they all transiently formed imines during the course of the reaction.

Next, we constructed a [2×2] system by combining amines 3 and 4 with aldehydes 13 and 14 (Scheme 5). In this double-selection mixture, both the amine and aldehyde components
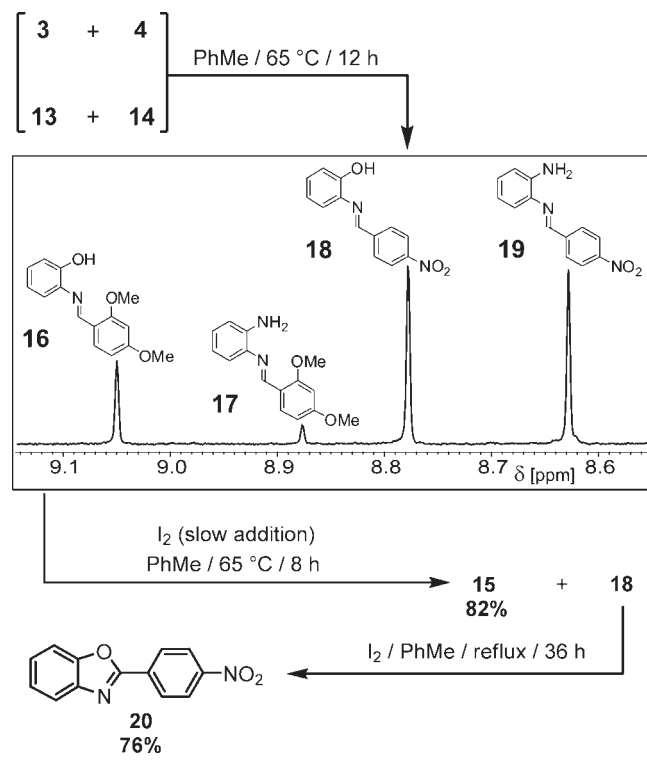
would seek the more electron-rich partner. As anticipated, all four possible imines were formed in appreciable amounts and could be readily identified in the mixture through the diagnostic ^{1}H NMR chemical shifts of their N═C−H protons.[14] As the slow oxidation of this mixture commenced, the most electron-rich imine, 17, was oxidized first, affording benzimidazole 15. In response to the depletion of 17 in the equilibrium mixture, imines 16 and 19 started to disproportionate in order to replenish the lost 17. Eventually, all of 16 and 19 were consumed by this process, and the only species left in solution was the most electron-poor imine, 18. Left to itself, 18 was oxidized after prolonged heating with I_2, generating 20. The final workup of this one-pot reaction isolated only two products: 15 (82%) and 20 (76%). In effect, the [2 × 2] mixture of imines self-sorted during the oxidation, giving only two products that stemmed from the oxidation of the most electron-rich and most electron-poor imines.

Encouraged by the successful self-sorting of a [2×2] mixture, we increased the complexity to a [3×3] mixture (Scheme 6). The amines 3, 4, and 4-methoxyaniline (21) were combined with the aldehydes 11, 14, and 2,4-dinitrobenzaldehyde (22). Overnight heating of these six compounds generated all nine possible imine combinations. Among these, six imines (those derived from 3 and 4 but not 21) were oxidizable by I_2. The first equivalent of iodine oxidized the most electron-rich imine, 17, to give 15. The second oxidation proceeded at a slightly higher temperature to provide 23. Finally, the only compound that remained in the mixture was the nonoxidizable imine 24 composed of 21 and the most electron-poor aldehyde, 22. Workup of the reaction mixture isolated only 15 (88%), 23 (76%), and 24 (65%).
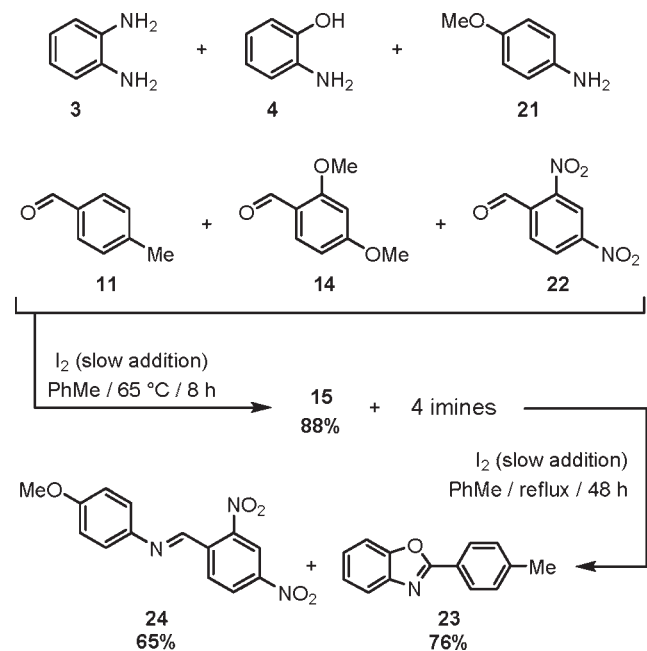
The use of I_2 as a weak oxidant was essential in these self-sorting protocols. Analogous reactions with a stronger oxidant (bromanil or DDQ) led to much poorer selectivities and partial oxidation of electron-rich amines 3 and 4. Iodine also has its limitations, as it cannot oxidize imines that are very electron-poor. Thus, the oxidative self-sorting operates in the region between the extremes of fast (and unselective) oxidation and no oxidation at all.

Finally, to establish the preliminary limitations of the selectivity of the self-sorting process, we performed 17 competition experiments involving different pairs of aldehydes in combination with amine 3 (Table 1). In general, the benzimidazole derived from the more electron-rich aldehyde dominated, but the selectivities were lower than intuitively expected. Most surprisingly, in a competition experiment (marked with a *) involving 13 and 4-methoxybenzaldehyde (25), the major product came from the more electron-poor aldehyde, 13. Oxidation rates depend not only on rate constants but also on the relative

Scheme 5. Oxidative Self-Sorting of a [2 × 2] Mixture of Imines: Shown in the Center Are the Composition and the ^{1}H NMR Spectrum of the Intermediate Mixture of Imines before Oxidation Was Initiated; All Four Possible Imines Were Evident by Their N=C—H Protons

Table 1. Selectivity in Imine Oxidations Evaluated by Pairwise Comparisons of Different Aldehydes[a]
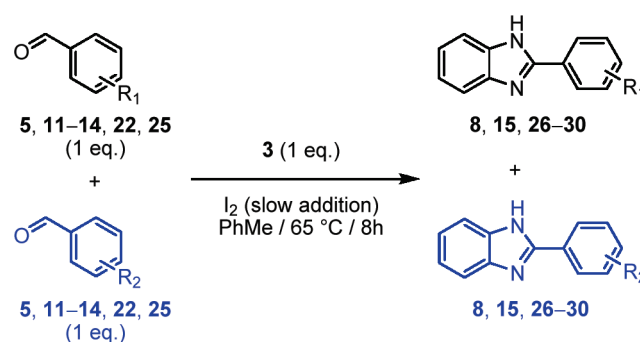
R2 ▼ \ R1 ▶	2,4-(OMe)2 15 (14)	2,4-(NO2)2 30 (22)	4-NO2 29 (13)	4-OMe 28 (25)	4-Cl 27 (12)	4-Me 26 (11)
4-H 8 (5)	74 : 26	0 : 100	—	—	36 : 64	40 : 60
4-Me 26 (11)	86 : 14	0 : 100	40 : 60	37 : 63	—	
4-Cl 27 (12)	86 : 14	7 : 93	54 : 46	—		
4-OMe 28 (25)	82 : 18	15 : 85	62 : 38*			
4-NO2 29 (13)	80 : 20	28 : 72				
2,4-(NO2)2 30 (22)	100 : 0					

[a] The table shows ratios of the relative ^{1}H NMR yields of the benzimidazole substituted with R1 (first number, black) to the benzimidazole substituted with R2 (second number, blue). For each benzimidazole in the table, the number in parentheses indicates the precursor aldehyde. The * indicates the competition experiment involving **13** and **25** that was mentioned in the text.

indicated by ^{1}H NMR spectroscopic analysis), its oxidation proceeded faster despite the presumably lower rate constant.[15] This thermodynamic preference for certain imines and the fact that imines form and exchange at rates that strongly depend on their structures add two further levels of complexity to the phenomenon of oxidative kinetic self-sorting of imines. We are currently exploring the possibility of sequential self-sorting based on these additional facets of imine reactivity.

In conclusion, we have demonstrated an example of self-sorting of a dynamic imine mixture during the course of a slow irreversible oxidation. The self-sorting is *kinetically driven* in that the final product ratios are determined by the corresponding rates of formation, and it is *thermodynamically enabled* because high-yielding formation of individual benzazoles would not have occurred were it not for the free equilibration of the underlying mixture of imine precursors. The phenomenon of kinetic self-sorting should be general for all slow irreversible reactions of imines as well as other dynamic covalent systems. We are presently working on demonstrating kinetic self-sorting in imine reductions and Diels—Alder reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Synthetic details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 6. Oxidative Self-Sorting of a [3 × 3] Mixture of Imines

concentrations of the two competing imines: as the imine derived from **13** was favored at equilibrium to the tune of ~20:1 (as

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(13) In fact, a fast irreversible reaction is often used to "trap" an equilibrating mixture before analysis without disturbing the component ratios.

(14) The situation is slightly more complex than suggested by the ^{1}H NMR spectrum in Scheme 5. Amine **3** is capable of forming double imines with either of the aldehydes, and some imines exist in their closed benzimidazoline and benzoxazoline forms (not shown).

(15) The opposing influences of imine stability (which favors donor–acceptor combinations of constituent amines and aldehydes) and rate of oxidation (which favors donor–donor combinations) suggest that the outcome of oxidation should depend on the rate of addition of I_2. Indeed, when I_2 was added very slowly (over 120 h), the **29**/**28** ratio shifted to 17:83. On the other hand, when addition of I_2 was instantaneous, the **29**/**28** ratio was 76:24. Details of these and related investigations will be reported elsewhere.

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