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Three-Way Chemoselectivity Switching through Coupled Equilibria

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ABSTRACT: Controlling the chemoselectivity of reactions operating on complex mixtures, including those found in biological and petrochemical feedstocks or in the primordial soup from which life emerged, is generally challenging. The selectivity of imine oxidation can be controlled in dynamic combinatorial libraries, wherein coupled equilibria of imine exchange and the diaza-Cope rearrangement determine whether and when the oxidizable precursor is made available to the oxidant. Adjusting the rate of oxidant addition allows the isolation of three dominant products.

Control of chemoselectivity is among the central problems of synthetic chemistry.[1] Its ramifications range from solving the mysteries of prebiotic chemistry[2] to improving the efficiencies of separations and functionalizations of feedstocks derived from complex petroleum and biomass sources. For a given set of reactants, the reaction outcome is controlled by thermodynamic and kinetic factors. Often, they work hand-in-hand: the most stable reaction products also form the fastest. Sometimes, they do not, and such reactions can express either their kinetic (fastest formed) or thermodynamic (most stable) products. Are these two extremes the only options? In this Letter,[3] we show that they are not: In a complex mixture of equilibrating precursors, the final reaction product can be switched at will by changing the rate of reagent addition. The key to this behavior is the use of coupled equilibria, in which the products of one reversible reaction act as the substrates for another. Coupled equilibria phenomena[4] have vast relevance to pollution, climate change,[5] ocean acidification,[6] and metabolic pathways.[7] Complex coupled equilibria often give rise to systems-level and emergent phenomena.[8]

Our studies of irreversible reactions operating on imine dynamic combinatorial libraries (DCLs)[9] have shown that such "messy" precursor mixtures can still be chemoselectively functionalized. As one DCL component reacts the fastest in an irreversible reaction, other library members equilibrate to produce more of it. The net result is the high-yielding functionalization of the most reactive DCL member, which is amplified at the expense of the less reactive members.[10] Applied iteratively, such amplification leads to kinetic self-sorting[11] of the DCL into just a handful of fast-reacting components. Self-sorting hinges on the applicability of the Curtin–Hammett principle,[12] which implies a much faster rate of the DCL equilibration compared with the irreversible removal reaction. In such a scenario, relative stabilities of different imines have no bearing on the final reaction products: it is only the relative rates of that irreversible reaction that determine the chemoselectivity. In this study, we manipulated these relative reaction rates, breaking down the Curtin–Hammett selectivity but, in turn, revealing a rich reactivity landscape wherein products can be selected by adjusting the rate of the irreversible removal.

Imines formed from 1,2-phenylenediamine (**3**, Scheme 1) and aromatic aldehydes can be oxidized into corresponding benzimidazoles using iodine (I_2). This oxidation is faster for imines formed from electron-rich aldehydes than for those derived from electron-poor precursors. During our studies of the oxidative self-sorting of imines,[13] we noticed that the product distribution could additionally be influenced by the rate of oxidant addition. The reaction of equimolar amounts of 4-nitrobenzaldehyde (**1**), 4-methoxybenzaldehyde (**2**), and **3** generated a mixture of imines **4** and **5** with some leftover aldehydes. When this mixture was treated with I_2, the imines were oxidized into benzimidazoles **6** and **7**. If I_2 was added very slowly, over 120 h, then the methoxy-substituted **6** constituted 87% of the product mixture. On the contrary, instantaneous

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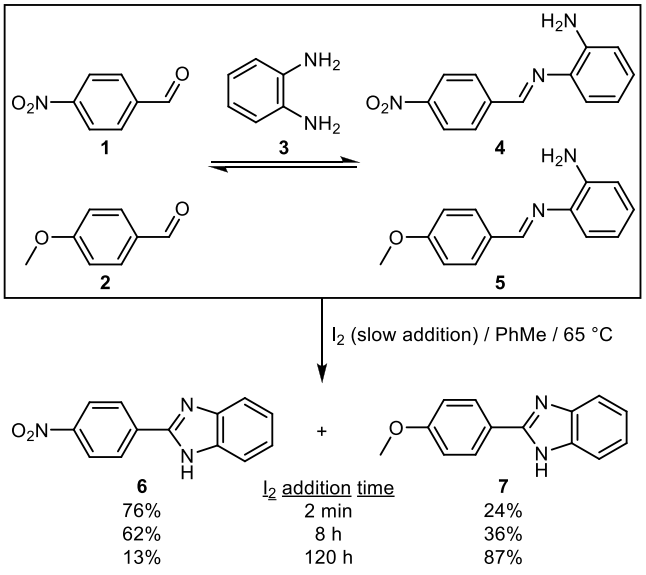
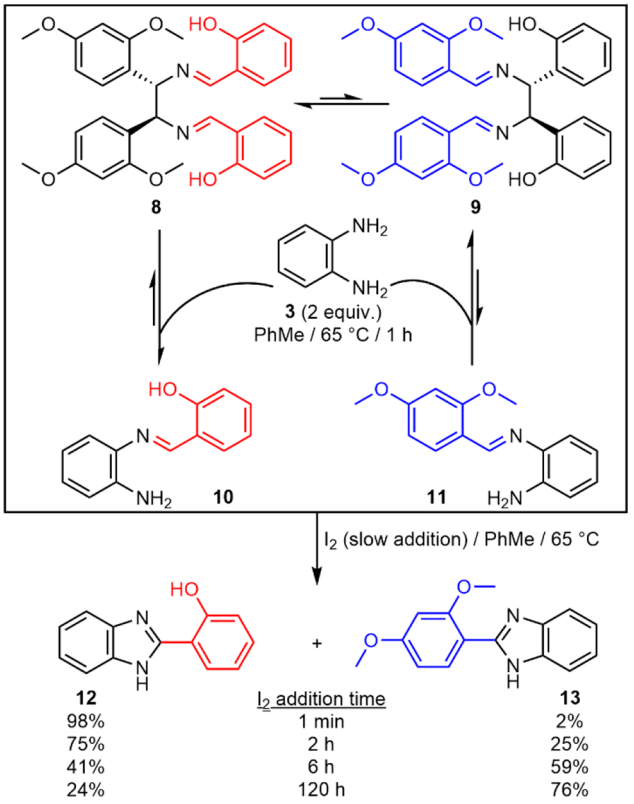
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Oxidation of a Mixture of Imines 4 and 5 Produces 6 and 7 in a Ratio Dependent on the Rate of the I_2 Addition



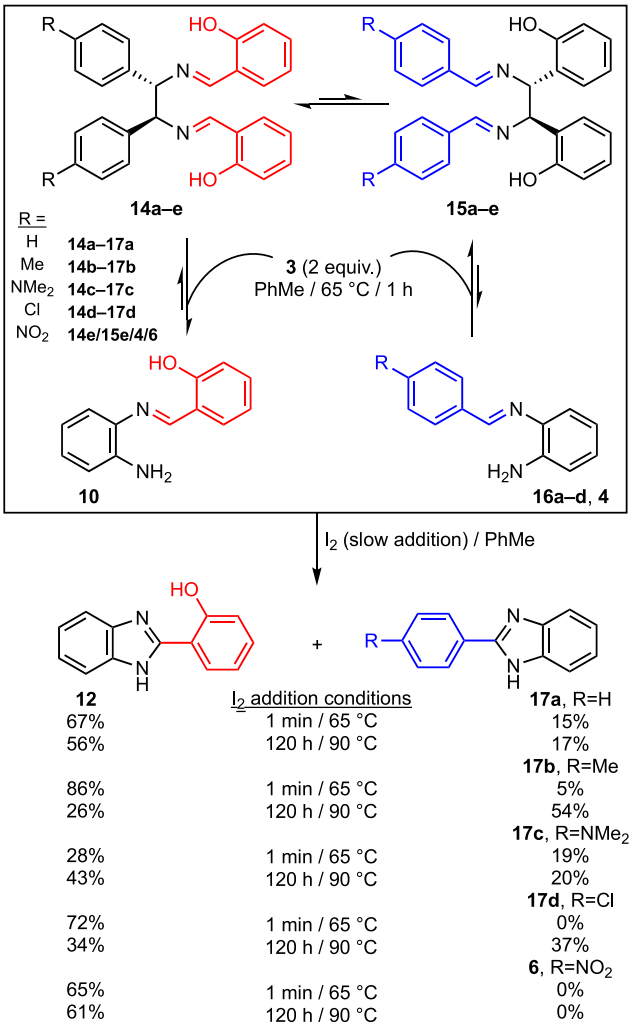
Scheme 2. Oxidation of a Mixture of 3, 8, and 9 Generates 12 and 13 in a Ratio That Is Dependent on the Rate of I_2 Addition[a]



[a]In the top part, the horizontal arrows show the diaza-Cope rearrangement, and the vertical arrows show the imine exchange.

(<2 min) I_2 addition resulted in **7** as the dominant product (76%). This selectivity switching could be explained as follows. The intermediate imine mixture has more of the nitro-substituted **4**: its push−pull electronic nature means it is both more stable and more quickly formed than **5**. If the oxidation is

Scheme 3. Selectivity Switching in Imine Oxidation as a Function of Substitution and I_2 Addition Rate



quick, then it captures this composition of imine precursor mixture in the ratio of benzimidazole products. However, if the oxidation is very slow, then the dynamic mixture can continuously replenish the electron-rich **5** that is being consumed by its faster oxidation. Slower to oxidize, **4** releases its 1,2-phenylenediamine component to create more of **5**, and the product distribution switches.

Intrigued by this result, we set out to determine whether such selectivity switching could be further controlled. To do so, we devised a dynamic system that operates using two reversible reactions: imine exchange and the diaza-Cope rearrangement of diimines of the general structural type **8** (Scheme 2). Vögtle[14] and others[15] have shown that the diaza-Cope equilibrium favors imines derived from salicylaldehyde (such as **8**) over their rearranged isomers (such as **9**) on account of their greater stabilization by [N···H−O] hydrogen bonding. This equilibrium position means that the salicylaldehyde component (highlighted in red, Scheme 2) can be directly exchanged from its imine **8** by a reaction with **3** to produce the oxidizable imine **10**. The more electron-rich 2,4-dimethoxybenzaldehyde (highlighted in blue) cannot directly engage in an oxidation. Instead, **8** must first undergo diaza-Cope rearrangement into the less favored isomer **9**, and only then can **9** exchange with **3** to produce the oxidizable imine **11**.

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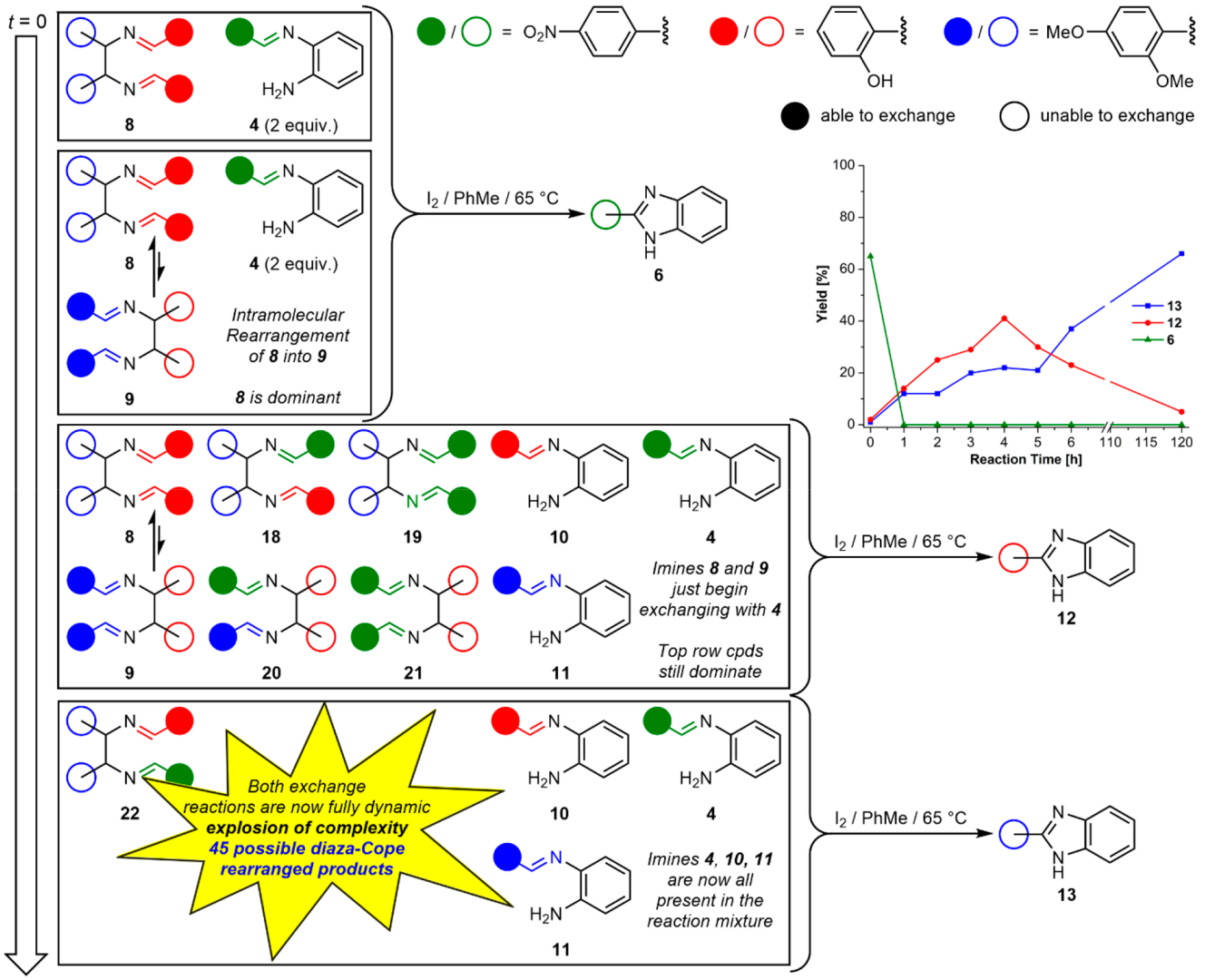
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Three-Way Switching of Chemoselectivity in Imine Oxidation as a Function of I_2 Addition Rate



Thus being once-removed from the immediate exchange, the 2,4-dimethoxybenzaldehyde component must traverse a longer reaction pathway to engage in an oxidation and may not have enough time to do so if the oxidation is too fast. Indeed, I_2 (2 equiv vs **8**) addition in 1 min effectively generated only the benzimidazole **12** derived from salicylaldehyde (98:2 selectivity over **13** based on NMR yields determined using 1,3,5-trimethoxybenzene as the internal standard). As the I_2 addition was slowed down, 2,4-dimethoxybenzaldehyde had enough time to travel across the shallow energy landscape, and the molar fraction of its oxidation product **13** in the final product mixture increased to 25, 59, and finally 76% if I_2 was added over 2, 6, or 120 h, respectively.

To establish whether this selectivity switching is general, we examined several other diimines analogous to **8** and **9**, which related to each other through diaza-Cope rearrangement (Scheme 3).[16] Salicylaldimines **14a−e** were preferred over their rearranged isomers **15a−e** regardless of the substituents R. The addition of **3** once again initiated the increase in the complexity of this dynamic mixture, as imines **10** and **16a−d**/**4** could now be formed, along with partially exchanged species not shown in Scheme 3. Iodine addition then began (2 equiv relative to **14a−e**). As in the previous experiment, the outcomes of these reactions were dependent on the rate of I_2 addition, but this dependence varied based on the substitution in the starting imines **14**/**15**. In the parent system **14a**/**15a** (R = H), slower addition mildly increased the ratio of product **17a** to product **12**, switching from a relative ratio of 1:4.47 to 1:3.29. Selectivity switching observed in Scheme 2 was replicated with the **14b**/**15b** (R = Me) couple; the benzimidazole obtained from the electron-rich **16b** dominated the product mixture under slow addition conditions, whereas **12** was the main product if I_2 was added instantaneously. In compounds **14c**/**15c**, the result was puzzling: the significantly more electron-rich *para*-*N*,*N*-dimethylamino substituted precursor failed to yield **17c** as the dominant product even at long addition times. A possible explanation for this aberration can be found in the slowdown of the diaza-Cope rearrangement in systems with electron-rich substituents.[15a] This slowing may have effectively shut down the pre-equilibration, making the imine library not dynamic anymore and making the product ratio independent of the I_2 addition rate. The example of **14d**/**15d** (R = Cl) offered another interesting conclusion. As expected, **12** dominated under fast addition conditions, but the switch to **17d** as the major product with slower I_2 addition was

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Org. Lett. XXXX, XXX, XXX−XXX

surprising at first glance. Tentatively, this behavior can be rationalized as follows.

The chlorine substituent in the para position is weakly electron-withdrawing, with a Hammett parameter of +0.23. Ortho substituents are generally not used in Hammett correlations because of steric effects, but an OH group in a meta position has a Hammett value close to that of *para*-Cl: +0.12.[17] Stated differently, the OH group influences the electronics of precursor imines by its electron-donating resonance effect but also as an electron-withdrawing inductive acceptor. Finally, the electron-withdrawing NO_2 group in **14e**/**15e** led to identical product mixtures regardless of the I_2 addition rate: **12** was the only product, with no **6** observed in either case. Nitro-substituted **4** oxidizes so much slower than **10** that allowing extra time for pre-equilibration did change the amount of **6** produced.

Encouraged by the apparent ability to switch the product of oxidation, we speculated that a three-way selectivity switching may be possible as well. The experiments aimed at testing this hypothesis exposed the diaza-Cope precursor **8** not to 1,2-phenylenediamine (**3**) but instead to its imine with 4-nitrobenzaldehyde (**4**). Three oxidation products could be obtained from such a DCL (Scheme 4). With very fast oxidant addition, imine **4** had no time to exchange with **8** or with the minor amount of **9** formed by the diaza-Cope rearrangement of **8** and simply oxidized into **6** (top two panels in Scheme 4). If oxidation was slower (1−5 h), then the exchange between **8** and **4** initially generated **10**, **18**, and **19**; imine **10** could then be oxidized into **12** faster than the electron-poor imine **4** (third panel in Scheme 4). The amounts of imines **11**, **20**, and **21** formed under these conditions were still quite small because of the low initial concentration of their precursor **9**, and **12** dominated the product mixture. No **6** was observed under these conditions. Finally, if oxidant addition was slowed down even further (6−120 h), then diaza-Cope rearrangement and imine exchange had enough time to lead to a complete explosion of complexity in this DCL. Starting with just **8** and **4** as starting materials, as many as 45 diaza-Cope rearranged products could be formed, including completely scrambled species such as **22** (bottom panel in Scheme 4). The most electron-rich imine **11** was present in appreciable amounts under these conditions, and its fast oxidation produced the third possible product, benzimidazole **13**. With the oxidant added over 120 h, **13** was the major product, with **12** eventually forming just 7% of the product mixture (graph in Scheme 4, table of yields given in the Supporting Information).

In conclusion, we have shown that the tuning of relative rates of irreversible and reversible transformations in a DCL can express a variety of its members, ranging from electron-rich to electron-poor. This product selection was accomplished in the absence of any enzyme or synthetic catalysts that could impart selectivity, and the only parameter that changed was the rate of oxidant addition. These results may offer insights into processes in prebiotic chemistry: multiple components of the "primordial soup" could have selectively reacted under differing spatiotemporal conditions. We have also shown that the diaza-Cope rearrangement can be used as a well-behaved dynamic reaction, thus expanding the arsenal of dynamic combinatorial chemistry.[18] Our results suggest that in sufficiently complex mixtures there may, in fact, exist a continuum of products ranging from absolute thermodynamic minima to a number of local minima, which can all be addressed by fine-tuning the rates of reagent addition as well as other simple reaction parameters: concentration, pressure, and temperature. We believe that the use of coupled equilibria can allow the virtual dialing-in of reactivity in highly complex libraries.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and copies of ^{1}H NMR spectra (PDF)

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Author Contributions

T.P. performed all experiments and analyzed the results together with O.Š.M. Both authors wrote the manuscript and have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(16) It may seem odd that the slow addition experiments were performed at a higher temperature that the fast addition ones: higher temperature increases the oxidation rate and should erode the selectivity. In optimizing of this process, we found out, however, that the higher temperature ensures that both involved reactions remain dynamic while still maintaining the selectivity of the oxidation.

(17) Some trends seem to suggest that an −OH group in an ortho position has an electron-withdrawing rather than an electron-donating effect. For example, the acidity of hydroxy-substituted benzoic acids is decreased relative to the parent benzoic acid (pK_a = 4.20) when the −OH group is in the para position (pK_a = 4.28) but increased when the same group is meta (pK_a = 3.84) and ortho (pK_a = 2.98) to the −COOH functionality. See also: McDaniel, D. H.; Brown, H. C. An Extended Table of Hammett Substitutent Constants Based on the Ionization of Substituted Benzoic Acids. *J. Org. Chem.* **1958**, *23*, 420−427.

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