Published in final edited form as:

Chemistry. 2016 December 12; 22(50): 18179–18189. doi:10.1002/chem.201603839.

Redox-Neutral Aromatization of Cyclic Amines: Mechanistic Insights and Harnessing of Reactive Intermediates for Amine α - and β -C–H Functionalization

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Abstract

Cyclic amines such as pyrrolidine and piperidine are known to undergo condensations with aldehydes to furnish pyrrole and pyridine derivatives, respectively. A combined experimental and computational study provides detailed insights into the mechanism of pyrrole formation. A number of reactive intermediates (e.g., azomethine ylides, conjugated azomethine ylides, enamines) were intercepted; outlining strategies for circumventing aromatization as a valuable pathway for amine C–H functionalization.

Graphical abstract

Keywords

C–H functionalization; redox-neutral; azomethine ylides; heterocycles

Introduction

Condensations of fully or partially saturated cyclic amines with aldehydes or ketones can lead to substrate aromatization. These rather unusual transformations are often facilitated by carboxylic acids and are among the oldest reactions that result in the functionalization of relatively unreactive C–H bonds in α -, β -, and γ -position of an amine nitrogen atom (Scheme 1).^[1–7] Reactions in which pyrroles are formed from pyrrolidine or pyrroline, or indole from indoline, represent redox-neutral transformations. No external oxidants are

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required and water is produced as the sole byproduct.^[8] Such reactions are ideal in terms of redox-economy.^[9] If substrate aromatization could be prevented through interception of reactive intermediates with appropriate reaction partners, attractive new pathways for the functionalization of amines would result. Here we report a detailed study that sheds light on the mechanism of pyrrole formation from pyrrolidine and aldehydes. Several strategies are presented that divert aromatization and provide access to new chemical space.

Based on our previous studies on the redox-neutral α -functionalization of amines^[7u, 10] as well as historic insights and recent studies by others,^[2e, 3d, 11, 12] we developed a working hypothesis regarding the mechanism of formation of 1,3-dibenzylpyrrole (**1**) from pyrrolidine and benzaldehyde (Scheme 2). Pyrrole formation could occur in an uncatalyzed fashion or be facilitated by a carboxylic acid. Addition of pyrrolidine to benzaldehyde is thought to initially give rise to *N,O*-acetal **2**, a species that could exist in equilibrium with iminium ion **3**. Elimination of water or carboxylic acid results in the formation of azomethine ylide **4** which could then be captured to form *N,O*-acetal **5**, possibly via the intermediacy of **6** with which **5** could also exist in equilibrium. Loss of HOR from **5** or **6** gives enamine **7** which is considered to be a key intermediate of the overall process. Reaction of **7** with benzaldehyde leads to β -functionalization, possibly involving intermediates **8–10**. Several possibilities exist as to how intermediate **10** could ultimately isomerize to the final pyrrole product **1**. Importantly, all plausible paths linking **7** and **1** appear to require the intermediacy of a conjugated azomethine ylide (either **11** or **17**).

Previous studies on the redox-neutral C–H functionalization of pyrrolidine have pointed at the intermediacy of some of the species thought to be relevant to the formation of **1**. The involvement of **5** and/or **6** can be inferred from the above mentioned studies on amine α -functionalization,^[10, 11d, 11h] although for intramolecular reactions, additional functional groups on the aldehyde often play specific roles.^[10e, 10g, 10i] For intermolecular reactions, specific aldehydes/ketone reaction partners are often required. There is less direct evidence for the formation of azomethine ylides (e.g., **4**) from pyrrolidine and simple aldehydes. As outlined in Scheme 3, Hajra and coworkers reported the formation of (3+2) cycloaddition product **22** via a potassium acetate catalyzed reaction of pyrrolidine and two equivalents of benzaldehyde.^[11e] Our group has reported a related intramolecular (3+2) cycloaddition in which an azomethine ylide intermediate is formed upon benzoic acid catalyzed condensation of pyrrolidine with **23** to ultimately afford product **24**.^[13] The potential of pyrrolidine-derivatives to form enamines such as **7** was indicated in the formation of **26**, in which **25** underwent α,β -difunctionalization upon reaction with *para*-chlorobenzaldehyde.^[14–16] However, more direct evidence for enamines is lacking. To our knowledge, these species have never been isolated from a condensation of pyrrolidine with aldehydes.

Experimental results and discussion

Our first goal was to establish unambiguously that azomethine ylides can indeed form from pyrrolidine and benzaldehyde under conditions known to effect the formation of pyrrole **1** (i.e., under thermal conditions in the absence of additives).^[4a] We reasoned that the best indirect evidence for the existence of these high-energy intermediates would be to trap azomethine ylides via intermolecular (3+2) cycloadditions. Due to its high reactivity and

well-known propensity to undergo various (3+2) cycloadditions with azomethine ylides, *N*-methyl maleimide was selected as the dipolarophile of choice.^[17] Evidence for the formation of not only azomethine ylide **4** but also the proposed conjugated azomethine ylide **11** was obtained as shown in Scheme 4. Interestingly, by allowing pyrrolidine, benzaldehyde and *N*-methyl maleimide to react under relatively mild conditions (reflux in toluene), (3+2) product **27** was obtained as a 1.5:1 mixture of diastereomers in 18% yield. In addition, products **28a–d** were obtained in 16% overall yield. The relative configuration of the major diastereomer **28a** was determined unambiguously by X-ray crystallography. Perhaps not surprisingly, conjugate addition product **29** was obtained as the major product in 64% yield. When the reaction was conducted in the presence of benzoic acid (1.2 equivalents) but otherwise identical conditions, the same products were obtained albeit in substantially different ratios. The yield of **28a** increased to 19% at the expense of **27** which was isolated in 6% yield only. The other diastereomers of **28** were also formed in increased amounts (33 % overall yield of **28a–d**). An increase of the amount of benzaldehyde relative to pyrrolidine resulted in the exclusive formation of **28a–d** in an overall yield of 45%, with the main diastereomer **28a** being formed in 29% yield. To rule out the possibility that **28** could be formed from **27** via an alternate pathway that does not involve conjugated azomethine ylide **11** (e.g., via temporary ring-opening and formation of an intermediate enamine, etc.), **27** was exposed to the reaction conditions in the presence of benzaldehyde. No formation of **28** was observed with **27** being recovered in 90%.

It is of interest to compare the results of Scheme 4 to reactions of pyrrolidine and benzaldehyde that were performed in the absence of *N*-methyl maleimide (Scheme 5). Simple heating of a 1:2 mixture of pyrrolidine and benzaldehyde in toluene under reflux provided 22% of pyrrole **1** and 13% of (3+2) cycloaddition product **22** in addition to polar unidentified byproducts. The reaction remained incomplete as judged by the presence of benzaldehyde. In the presence of benzoic acid, an otherwise identical reaction provided pyrrole **1** in 28% yield. Unreacted benzaldehyde remained and polar unidentified byproducts were observed. However, no **22** was obtained. This suggests that any potential formation of **22** is inconsequential for the synthesis of pyrrole. To provide evidence that **22** can readily undergo retro-(3+2) cycloaddition, this material was exposed to the reaction conditions in the presence of benzoic acid. As a result, **1** was obtained in virtually identical yield as before (27%). Again, polar unidentified byproducts were formed.

Although the intermediacy of enamines is implicated from the results of the experiments described above (formation of **28**), no direct evidence for these transient species was obtained. We rationalized that enamines may become isolable if subsequent reactions of these species could be prevented or at least minimized. Considering that once an enamine forms it will readily attack an aldehyde, it seemed that performing reactions with excess pyrrolidine could reduce the propensity for such subsequent aldol-type reactions. A reduction of the nucleophilicity of the enamine by using a more electrondeficient aldehyde reaction partner appeared to be another promising strategy to stabilize these typically rather reactive intermediates. Based on these considerations and our previous success with 2,6-dichlorobenzaldehyde in bringing about redox-isomerizations with pyrrolidine, this aldehyde was selected for attempts to prepare pyrrolidine enamines (Scheme 6). A reaction of 2,6-

dichlorobenzaldehyde and pyrrolidine (1:5 ratio), after being heated under reflux in toluene for two hours, provided a mixture of products: the enamine dimer **30** (3% yield), a compound corresponding to the addition product of **7** to **9** (**31**, 17% yield), aminor **32** (27% yield) and recovered aldehyde (18%, not shown). When an identical reaction was performed until the aldehyde was consumed fully,^[18] the yields of **30** and **31** increased to 35% and 26%, respectively. Interestingly, addition of 20 mol% of benzoic acid led to complete consumption of the aldehyde within two hours and allowed for the isolation of enamine dimer **30** in 65% yield.^[19] In this instance, product **31** was not observed. A marked solvent effect was noted. Simply switching the solvent from toluene to methanol afforded **31** as the only isolable product in 45% yield. In a control experiment, aminor **32** was found to convert to **30** under the reaction conditions. It should be noted that the dimerization of endocyclic enamines is a well-known phenomenon^[20] and plays a role in the biosynthesis of certain natural products.^[21] Attempts to generate enamine dimers from reactions of pyrrolidine with parent benzaldehyde led to inferior results. This finding is consistent with the computationally predicted lower stability of the benzaldehyde-derived enamine dimers (vide infra).

In order to probe the reactivity of enamine dimer **30**, this compound was exposed to β -naphthol under a number of conditions (Scheme 7). In the absence of any additive or in the presence of benzoic acid, β -naphthol adds to **30** in a highly efficient manner to provide product **34** as a single diastereomer. A different outcome is observed in the presence of triethylamine. Interestingly partial monomerization of enamine dimer occurs under these conditions, providing product **33**^[10f] in 37% yield in addition to **34** (48%). Given these observations, it appears possible (if not likely) that enamine dimers such as **30** can be intermediates in reactions that result in redox-neutral amine α -functionalization.

It appeared likely that enamine dimers such as **30**, upon monomerization to the corresponding monomeric enamines, could still undergo formation of pyrroles. To test this notion, **30** was exposed to 2,6-dichlorobenzaldehyde in the presence of benzoic acid (Scheme 8). In accord with our hypothesis, pyrrole **35** was formed in 40% yield.

An attractive use for enamine dimers would be their selective β -functionalization, in analogy to the known β -functionalization of more stable, monomeric *N*-aryl enamines.^[16i-k] We speculated that equilibration between enamine dimer and its monomer might be most effective in protic polar solvents. Following some experimentation, this was indeed found to be the case. As outlined in Scheme 9, a reaction of **30** with β -nitrostyrene in methanol gave rise to the desired product **36** in 77% yield.

To test the generality of enamine dimer formation, a number of other amines were exposed to the reaction conditions that allowed for the formation of **30** (Scheme 10). Gratifyingly, piperidine, morpholine and thiomorpholine all underwent the desired reaction to provide the corresponding enamine dimers **37** in good to excellent yields. This finding is quite remarkable, considering that typically much harsher conditions are required to bring about the α -functionalization of these amines. Morpholine-derived enamine dimer **37b** was characterized by X-ray crystallography. In analogy to pyrrolidine-derived enamine dimer **30**,

enamine dimers **37** also underwent facile β -functionalization with β -nitrostyrene (Scheme 11).

In case of azepane, the corresponding enamine dimer proved to be less stable. To circumvent the need for isolation, the crude material was allowed to react with β -nitrostyrene, leading to the synthesis of **39** in 33% yield over two steps (Scheme 12).

Computational results and discussion

As computational investigations not only permit the direct comparison of free-energy profiles of different mechanistic pathways but also allow the characterization of intermediates too unstable to be detected experimentally, we analyzed the mechanisms of the reactions between pyrrolidine and different benzaldehydes with density functional theory. These studies should on the one hand answer why carboxylic acids like acetic or benzoic acids significantly accelerate the reactions. On the other hand, the computational investigations should complement the experimental investigations described above and, as a consequence, should lead to a better understanding of the underlying reaction mechanism.

Uncatalyzed Reaction

To identify the origin of the catalytic effect of carboxylic acids, we initially calculated the energy profile for the uncatalyzed redox-neutral aromatization of pyrrolidine and benzaldehyde.^[4a] The lowest-energy pathway for the uncatalyzed reaction between pyrrolidine and benzaldehyde is summarized in Scheme 13. This reaction starts with the thermoneutral formation of the hemiaminal **2a** which is converted to the azomethine ylide **4** and subsequently to the enamine intermediate **7**. This process most likely occurs through the formation of the iminium hydroxides **3a** and **6a**. In both cases, the breaking of the C–O bond of the hemiaminals proceeds barrierless and the formed ion pairs are very unstable. According to our calculations, the dissociated ions (i.e., free iminium cations and hydroxide anions) are much higher in energy ($G \approx 88 \text{ kcal mol}^{-1}$) which indicates that the deprotonation of the iminium ions (through **TS01–TS03**) occurs directly from the tight ion pair. Next, the enamine intermediate **7** attacks benzaldehyde through **TS04** and the resulting alkoxide moiety is immediately protonated by water ($\rightarrow$ **40**). According to our calculations, the free zwitterionic intermediate is unstable under the reaction conditions and reverts to the enamine and PhCHO. This implies that both processes, nucleophilic attack and protonation, are coupled to each other. After a formal 1,3-OH shift (probably through **9a**), the second azomethine ylide **11** is formed. A series of elimination, addition, and elimination of water eventually leads to the pyrrole product **1**.

In general, our calculations predict very unfavorable transition states and iminium-hydroxide intermediates for the uncatalyzed reaction. However, the accurate description of these species in toluene solution is problematic because of the probability of specific solvent-solute interactions which are not considered in continuum models. Although the activation barriers are probably slightly overestimated, the rate-limiting step for the uncatalyzed reaction should be a deprotonation of an iminium hydroxide (e.g., **TS01–03**, **TS05**). The calculated high barriers are also reflected in the harsh experimental conditions and the moderate yield obtained in the synthesis of pyrrole **1** (Scheme 1). Obviously, the high

exergonicity of the overall reaction ($\Delta G = -22.7 \text{ kcal mol}^{-1}$) is the thermodynamic driving force and partially compensates the high activation barrier under these conditions.

Carboxylic-acid-catalyzed reaction

After establishing the reaction mechanism for the uncatalyzed reaction, we investigated the role of acetic acid as a model carboxylic acid in these transformations. In previous investigations, the catalytic efficiency of AcOH was traced back to either proton-shuttle mechanisms^[10g,i] or the formation of acetylated *N,O*-acetals,^[3d,10j] and both effects could also play an important role in these transformations. Scheme 14 summarizes the lowest-energy pathway for the acetic-acid-catalyzed reaction.

Similar to the uncatalyzed reaction, the first step of the acid-catalyzed pathway is the formation of an acetylated *N,O*-acetal (**2b**) in a slightly endergonic step. However, we were unable to calculate any transition states for the formation of **2b**, as the addition of acetate to the corresponding iminium ion occurs barrierless. A reaction involving a concerted proton transfer and substitution between the hemiaminal **2a** (Scheme 13) and acetic acid did not result in any transition states either, probably due to the unfavorable alignment of the acetate as a hydrogen-bond acceptor and the attacking nucleophile. In contrast to the reaction in the absence of AcOH, no iminium acetates are formed in this process. These species are either unstable and collapse to the corresponding *N,O*-acetals or are significantly higher in energy. Instead, a concerted elimination of acetic acid through **TS07** (Scheme 14) takes place forming the azomethine ylide **4** from the *N,O*-acetal **2b**. Similar transition states have been described for comparable transformations in the past.^[3d, 10j] Within **TS07**, the C-O bond is already completely broken (3.39 Å) while the proton transfer is still in progress. Addition of AcOH in the other orientation through **TS08** leads to the regioisomeric, slightly more stable hemiaminal **5b**. After 1,2-elimination of acetic acid, enamine **7** is formed and subsequently attacks benzaldehyde to give the hydrogen-bonded complex **41**. Acetylation leads to **8b** and an isomerization to **10b** occurs. This process can either take place in a concerted fashion through **TS11** ($\Delta G^\ddagger = 32.3 \text{ kcal mol}^{-1}$) or stepwise via **9b**. According to our calculations, both breaking and forming the C-OAc bonds occur without significant barriers which renders the concerted pathway via **TS11** less likely.

After another elimination of AcOH through **TS12**, the same azomethine ylide (**11**) is obtained that has been discussed above for the uncatalyzed reaction. Next, acetic acid is added ($\rightarrow$ **12b**) and no transition states could be located for this process. It is likely that this process occurs in a stepwise manner, as the corresponding iminium acetate (not shown in Scheme 14) was located only 3 kcal mol⁻¹ above **11**. Another cascade of elimination and re-addition of acetic acid via **TS13** and **TS14** (Scheme 14) yields the *N,O*-acetal **15b**. A final 1,2-elimination of AcOH (**TS15**) then leads to pyrrole **1**.

Intermediate **15b** can also be formed in a different pathway starting from the *N,O*-acetal **10b** (Scheme 15). Regioisomeric elimination of acetic acid in **10b** (via **TS16**) yields the azomethine ylide **17**, which is less stable than its exocyclic isomer **11**. This ylide can again add acetic acid (via the second resonance formula) and form **15b** and no transition states could be located for either protonation or C-O bond formation.

Another series of addition/elimination sequences is also conceivable for the formation of pyrrole **1** and was also included into our computational study (Scheme 16). Starting from the azomethine ylide **11**, an isomerization to the less stable azomethine ylide **19** occurs through addition and elimination of acetic acid (**TS17** and **TS18**). Transformation to the *N,O*-acetal **20b** (via **TS19**) and 1,2-elimination (**TS20**) affords the dienamine intermediate **21** which can isomerize to the final product **1**. Based on our computational results, this alternate pathway has to be considered less likely, as **TS18** is approximately 4 kcal mol⁻¹ higher in energy than the transition states of Scheme 14.

Several transition states (**TS07**, **TS13**, and **TS14**) fall within a very small range of less than 0.5 kcal mol⁻¹ and could all be the rate-limiting step of this transformation. In general, the calculated activation free energy of ca 26–27 kcal mol⁻¹ is also in reasonable agreement with the experimental conditions (elevated temperatures, prolonged reaction times) for this transformation.

2,6-Dichlorobenzaldehyde

In the course of the experimental investigations, we realized that the replacement of benzaldehyde with 2,6-dichlorobenzaldehyde allowed the isolation of different side products that provided valuable insights into important intermediates. Therefore, we decided to additionally investigate the reaction involving 2,6-dichlorobenzaldehyde before focusing on reactions that trap these intermediates. A complete mechanistic analysis is presented in the supporting information and Scheme 17 summarizes the lowest-energy pathway. According to our calculations, the reactions of both aldehydes proceed through the same reaction mechanism and the free-energy profile for benzaldehyde (Scheme 14) and 2,6-dichlorobenzaldehyde (Scheme 17) are qualitatively similar. In general, the additional chlorine substituents stabilize most species involved in the transition state and the largest effects were calculated for the zwitterionic azomethine ylides (e.g., **43**, **50**, **52**). However, this stabilization effect is not paralleled in the transition states to the same extent. As a consequence, the transition-state energies for the crucial steps increase for chlorine substituents [e.g., +26.4 vs. +27.5 kcal mol⁻¹ (for **TS07** and **TS24**), or 26.6 vs. 30.2 kcal mol⁻¹ (for **TS13** and **TS29**)]. Therefore, the activation free energy for the rate-limiting step (**TS24**) in the dichlorobenzaldehyde series was found to be 3.6 kcal mol⁻¹ higher in energy than in the corresponding benzaldehyde series (Scheme 14). These higher transition state energies calculated for the reaction involving 2,6-dichlorobenzaldehyde also provide a rationalization for why it is easier to trap reactive intermediates compared to the unsubstituted benzaldehyde.

Alternate Products

The computational studies have so far shown why carboxylic acids are required for an efficient transformation and that the redox-neutral aromatization is less favorable for dichlorobenzaldehyde. The experimental investigations additionally provided strong evidence for the presence of azomethine ylides (e.g., **4** or **11**) in the reaction mixture, and these species could be trapped in different (3+2) cycloaddition reactions with either benzaldehyde (→ **22**, Scheme 3) or *N*-methylmaleimide (→ **27** and **28**, Scheme 4). In addition, intermediately formed enamines (e.g., **7**) could be detected and higher enamine

aggregates could be isolated. Accordingly, we have included these pathways in our DFT analysis and compare them with the energy profiles of Schemes 13 and 14.

Based on our findings, all (3+2) trapping reactions proceed in an exergonic fashion (Figure 1, for more details see the Supporting Information). Combinations of azomethine ylides with *N*-methyl maleimide occur rapidly with small activation free energies (**TS33** and **TS34**) that are significantly lower than the rate-limiting step of Scheme 14. A small energy difference ($G = 1.3$ kcal mol⁻¹) between **4** and **TS33** has been calculated on the M06-L potential energy surface, while a negative barrier was obtained from M06-2X-D3 single-point calculations, which indicates a barrierless reaction. In contrast, the (3+2) cycloaddition between **4** and benzaldehyde requires a higher activation energy (**TS32**). These computational results match the experimental observations that the (3+2) cycloadducts are formed preferentially in the presence of *N*-methyl maleimide and indicate that one of the later transition states (**TS13** or **TS14**, Scheme 14) is the rate-limiting step for the carboxylic-acid-catalyzed pathway. Furthermore, the calculated high barriers for the (3+2) reaction with benzaldehyde also explain why cycloadduct **22** is not formed under acid catalysis.

Besides azomethine ylides, the experimental investigations also revealed that the formation of enamine di- and trimers (e.g., **30** and **31**) can become the major reaction pathway under carefully optimized conditions. As these species can be formed in many different reactions, we only investigate the thermodynamic stabilities of these products. As shown in Scheme 18, both alternatives **30** and **31** (as well as **54** and **55**) are formed in exergonic reactions. However, the chlorine substituents have a large impact on the thermodynamic stability and significantly lower the energies of the formed enamines. This is also reflected in the experimental observations as these enamine species were isolated predominantly from reactions involving 2,6-dichlorobenzaldehyde. In terms of thermodynamic stabilities, product **31** is almost comparable to the pyrrole **35**. This particularly large thermodynamic driving force together with the higher transition state energies for the chlorine-substitution also explain why these enamine products were predominantly isolated in reactions involving dichlorobenzaldehyde.

Computational Details

For the computational investigations, the conformational space for each structure was explored using the OPLS-2005 force field^[22] and a modified Monte Carlo search algorithm implemented in MacroModel 10.6.^[23] An energy cut-off of 20 kcal mol⁻¹ was employed for the conformational analysis, and structures with heavyatom root-meansquare deviations (RMSD) less than 2 Å after the initial force field optimizations were considered to be the same conformer. The remaining structures were subsequently optimized with the dispersion-corrected M06-L functional^[24] with Grimme's dispersioncorrection D3^[25] and the double- ζ basis set 6-31+G(d,p). Solvation by toluene was taken into account by using the integral equation formalism polarizable continuum model (IEFPCM)^[26] for all calculations. Vibrational analysis verified that each structure was a minimum or transition state. Following the intrinsic reaction coordinates (IRC) confirmed that all transition states connected the corresponding reactants and products on the potential energy surface. Thermal corrections were obtained from unscaled harmonic vibrational frequencies at the same level

of theory for a standard state of 1 mol L⁻¹ and 298.15 K. Entropic contributions to the reported free energies were derived from partition functions evaluated with the quasiharmonic approximation by Truhlar and coworkers.^[27] Electronic energies were subsequently obtained from single point calculations of the M06-L-D3 geometries employing the meta-hybrid M06-2X functional,^[28] Grimme's dispersion-correction D3 (zero-damping),^[25] the large quadruple- ζ basis set def2-QZVP,^[29] and IEFPCM for toluene, a level expected to give accurate energies.^[30] An ultrafine grid was used throughout this study for numerical integration of the density. All density functional theory calculations were performed with Gaussian 09.^[31]

Conclusions

The combination of experimental and computational studies enabled the elucidation of the likely reaction mechanism of the redox-neutral formation of pyrroles from pyrrolidine and aromatic aldehydes. Enamines and a variety of azomethine ylides were identified as key intermediates in this process. The computational investigations revealed that carboxylic acids facilitate the redox-neutral aromatization through the formation of acetylated *N,O*-acetals and a series of addition/elimination steps of acetic acid. Several protocols were developed that allow interception of reactive intermediates as a valuable path to rapidly access new chemical space.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support from the NIH–NIGMS (R01GM101389), the Fonds der chemischen Industrie (Liebig scholarship to M.B.), and the University of Cologne within the excellence initiative is gratefully acknowledged. We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis and the Regional Computing Center of the University of Cologne (RRZK) for providing computing time on the DFG-funded High Performance Computing (HPC) system CHEOPS as well as for their support.

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32. CCDC 1491711–1491714 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Figure 1. Calculated activation and reaction free energies and transition states for the trapping of the azomethine ylides **4** and **11** [in kcal mol⁻¹ and Å, M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].

Rügheimer (1891) **Poirier (1961)** **Burrows (1963)** **Oda (2007)** **Tunge (2009)** **Pan/Seidel (2010/2011)** **Scheme 1.**

Examples of redox-neutral amine aromatization.

Scheme 2.

Potential reaction pathways for pyrrole formation from pyrrolidine.

Scheme 3.
Support for azomethine ylide/enamine formation from pyrrolidine.

Scheme 4.
Evidence for simple and conjugated azomethine ylides.

Scheme 5.
Pyrrole formation and (3+2) cycloaddition.

Evidence for intermediates:

Control experiment:

Scheme 6.
Evidence for enamine intermediates.

no additive:	not observed	85%
with PhCOOH (2 equiv):	not observed	90%
with Et ₃ N (2 equiv):	37%	48%

34, X-ray

Scheme 7.
 Reactions of the enamine dimer with β -naphthol.

Scheme 8.
Pyrrole formation from enamine dimer.

Scheme 9.
Enamine dimer monomerization/ β -functionalization.

Scheme 11.
Reactions of enamine dimers with β -nitrostyrene.

Scheme 12.
 β -Functionalization of azepane.

Scheme 13.

Calculated free energy profile for the lowest-energy pathway for the uncatalyzed reaction between benzaldehyde and pyrrolidine [in kcal mol⁻¹; M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].

Scheme 14.

Calculated free energy profile and selected transition state structures for the lowest-energy pathway for the acetic-acid-catalyzed reaction between benzaldehyde and pyrrolidine [in kcal mol⁻¹ and Å; M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].

Scheme 15. Alternate pathway for the acetic-acid-catalyzed conversion of **10b** to **15b** [in kcal mol⁻¹].

Scheme 16. Alternate pathway for the acetic-acid-catalyzed conversion of **11** to **1** [in kcal mol^{−1}].

Scheme 17.

Calculated free energy profile for the lowest-energy pathway for the acetic-acid-catalyzed reaction between 2,6-dichlorobenzaldehyde and pyrrolidine [in kcal mol⁻¹; M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].

Scheme 18.

Calculated thermodynamics for the formation enamine intermediates [in kcal mol^{-1} ;
 M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d, p)/IE FPCM].