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Authors: Longle Ma, Anirudra Paul, Martin Breugst, and Daniel Seidel

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

Longle Ma,[a] Anirudra Paul,[a] Martin Breugst,*[b] and Daniel Seidel*[a]

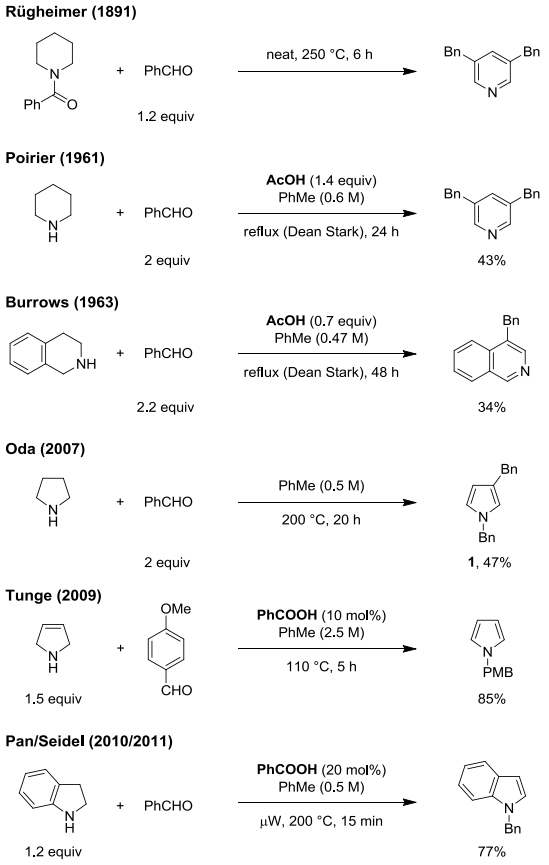
Abstract: Cyclic amines such as pyrrolidine and piperidine are known to undergo condensations with aldehydes to furnish pyrrole and pyridine derivatives, respectively. A combined experimental and computational study provides detailed insights into the mechanism of pyrrole formation. A number of reactive 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.

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 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 t benzaldehyde is thought to initially give rise to *N*,*O*-acetal **2**, species that could exist in equilibrium with iminium ion **3** Elimination of water or carboxylic acid results in the formation c azomethine ylide **4** which could then be captured to form *N*,*C* acetal **5**, possibly via the intermediacy of **6** with which **5** coul also exist in equilibrium. Loss of HOR from **5** or **6** gives enamin **7** which is considered to be a key intermediate of the overa 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



Scheme 1. Examples of redox-neutral amine aromatization.

[a] Dr. Longle Ma, Mr. A. Paul, Prof. Dr. D. Seidel
Department of Chemistry and Chemical Biology
Rutgers, The State University of New Jersey
Piscataway, New Jersey 08854, USA
E-mail: seidel@rutchem.rutgers.edu
Homepage: http://seidel-group.com

[b] Dr. M. Breugst
Department für Chemie
Universität zu Köln
Greinstraße 4, 50939 Köln, Germany
E-mail: mbreugst@uni-koeln.de
Homepage: http://physorg.uni-koeln.de

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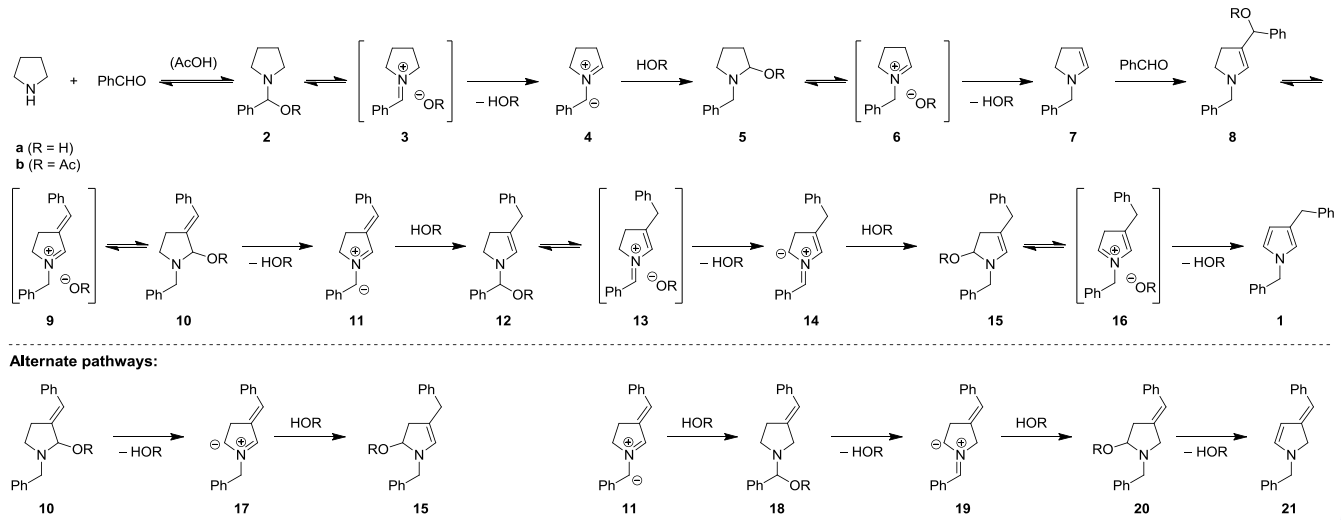
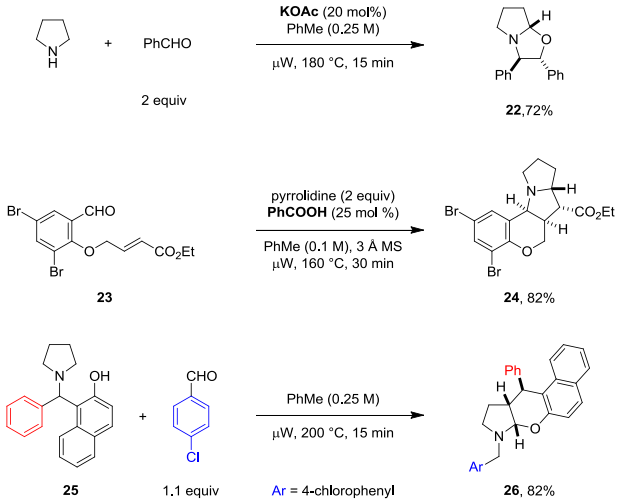


Scheme 2. Potential reaction pathways for pyrrole formation from pyrrolidine.



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

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 azomethin ylides can indeed form from pyrrolidine and benzaldehyde unde conditions known to effect the formation of pyrrole **1** (i.e., unde thermal conditions in the absence of additives).[4a] We reasone that the best indirect evidence for the existence of these high energy intermediates would be to trap azomethine ylides vi intermolecular (3+2) cycloadditions. Due to its high reactivity an well-known propensity to undergo various (3+2) cycloaddition with azomethine ylides, *N*-methyl maleimide was selected as th dipolarophile of choice.[17] Evidence for the formation of not onl azomethine ylide **4** but also the proposed conjugated azomethin ylide **11** was obtained as shown in Scheme 4. Interestingly, b allowing pyrrolidine, benzaldehyde and *N*-methyl maleimide t react under relatively mild conditions (reflux in toluene), (3+2 product **27** was obtained as a 1.5:1 mixture of diastereomers i 18% yield. In addition, products **28a–d** were obtained in 16% overall yield. The relative configuration of the major diastereome **28a** was determined unambiguously by X-ray crystallography Perhaps not surprisingly, conjugate addition product **29** wa obtained as the major product in 64% yield. When the reactio was conducted in the presence of benzoic acid (1.2 equivalents but otherwise identical conditions, the same products wer obtained albeit in substantially different ratios. The yield of **28** increased to 19% at the expense of **27** which was isolated in 6% yield only. The other diastereomers of **28** were also formed i increased amounts (33 % overall yield of **28a–d**). An increase o the amount of benzaldehyde relative to pyrrolidine resulted in th exclusive formation of **28a–d** in an overall yield of 45%, with th main diastereomer **28a** being formed in 29% yield. To rule ou 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%.

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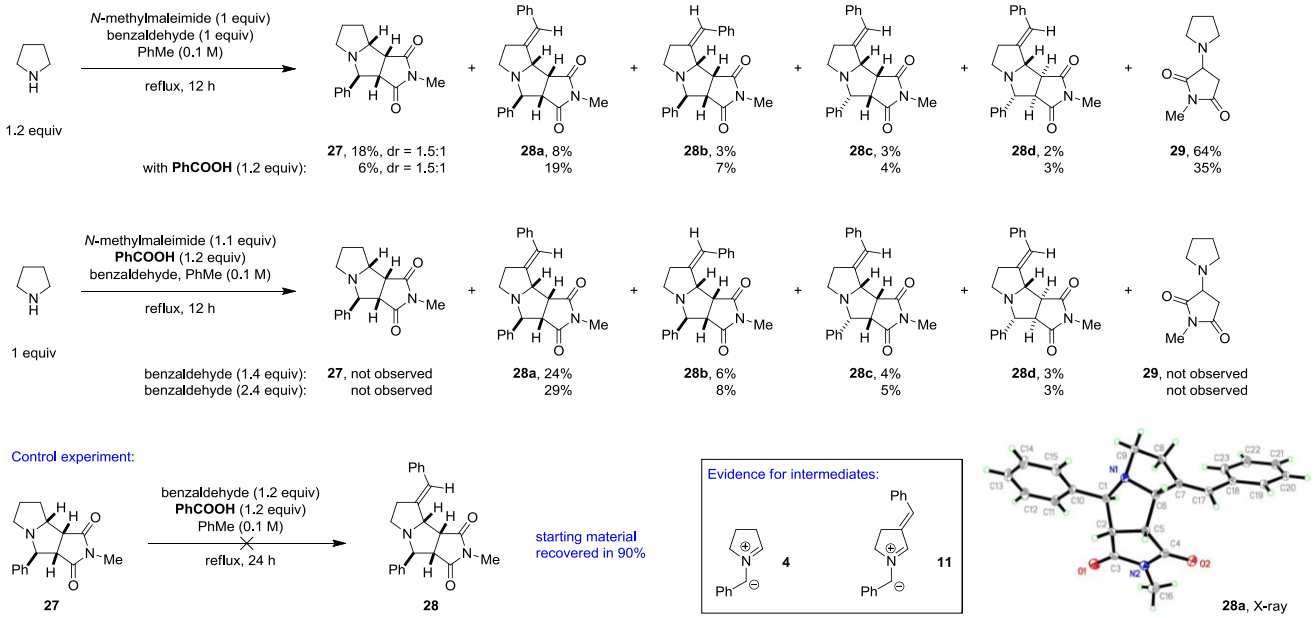
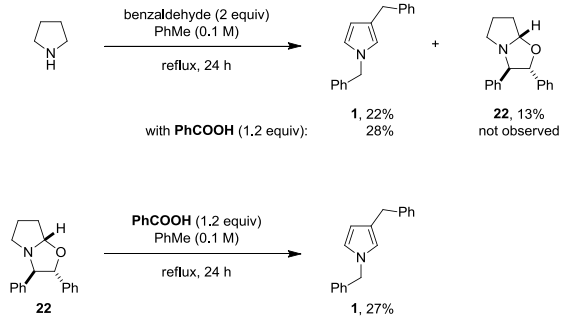


Scheme 4. Evidence for simple and conjugated azomethine ylides.

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.



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

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 wit excess pyrrolidine could reduce the propensity for suc subsequent aldol-type reactions. A reduction of th nucleophilicity of the enamine by using a more electron-deficie aldehyde reaction partner appeared to be another promisin strategy to stabilize these typically rather reactive intermediates Based on these considerations and our previous success wit 2,6-dichlorobenzaldehyde in bringing about redox-isomerization with pyrrolidine, this aldehyde was selected for attempts t prepare pyrrolidine enamines (Scheme 6). A reaction of 2,6 dichlorobenzaldehyde and pyrrolidine (1:5 ratio), after bein heated under reflux in toluene for two hours, provided a mixtur of products: the enamine dimer **30** (3% yield), a compoun corresponding to the addition product of **7** to **9** (**31**, 17% yield aminal **32** (27% yield) and recovered aldehyde (18%, not shown When an identical reaction was performed until the aldehyde wa consumed fully,[18] the yields of **30** and **31** increased to 35% an 26%, respectively. Interestingly, addition of 20 mol% of benzoi acid led to complete consumption of the aldehyde within tw hours and allowed for the isolation of enamine dimer **30** in 65% yield.[19] In this instance, product **31** was not observed. A marke solvent effect was noted. Simply switching the solvent fror toluene to methanol afforded **31** as the only isolable product i 45% yield. In a control experiment, aminal **32** was found t convert to **30** under the reaction conditions. It should be note that the dimerization of endocyclic enamines is a well-know phenomenon[20] and plays a role in the biosynthesis of certai natural products.[21] Attempts to generate enamine dimers fror 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).

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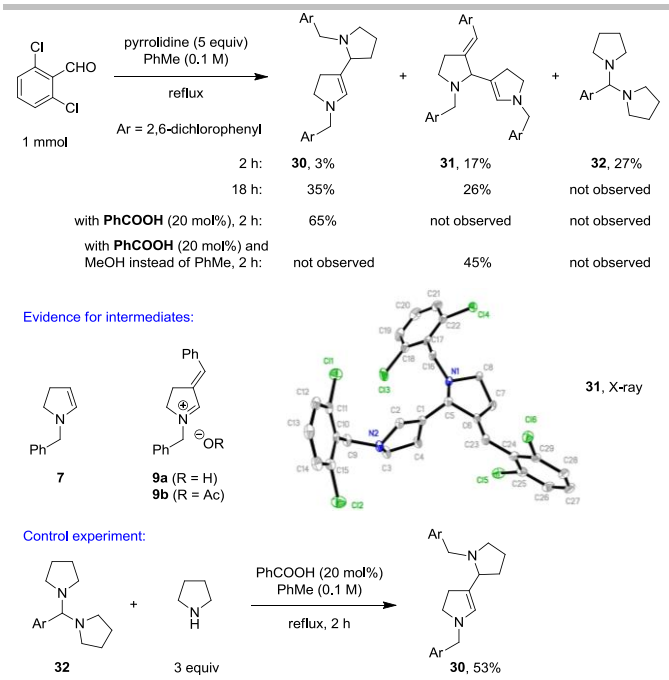
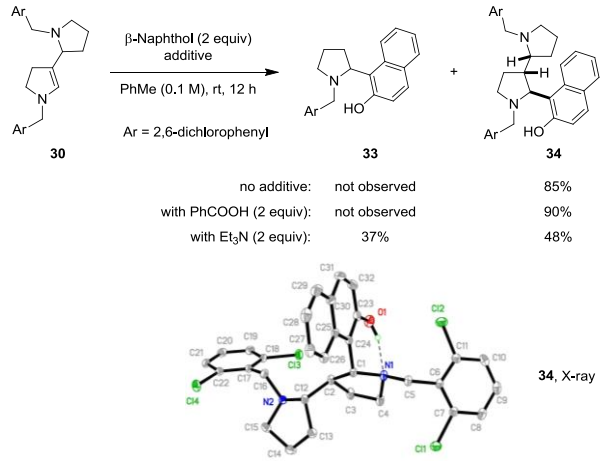


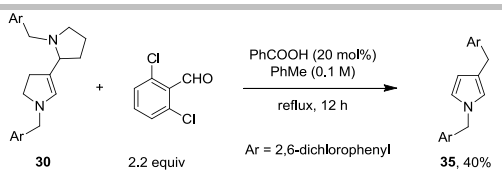
Scheme 6. Evidence for enamine intermediates.

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.



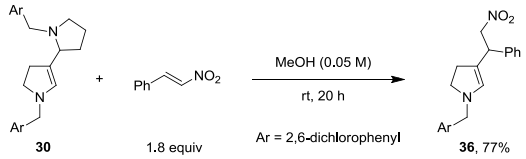
Scheme 7. Reactions of the enamine dimer with β-naphthol.

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.



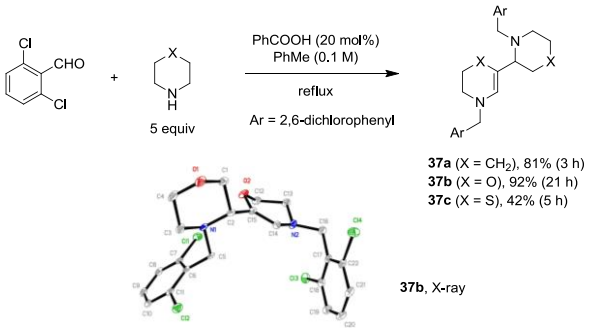
Scheme 8. Pyrrole formation from enamine dimer.

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 i methanol gave rise to the desired product **36** in 77% yield.

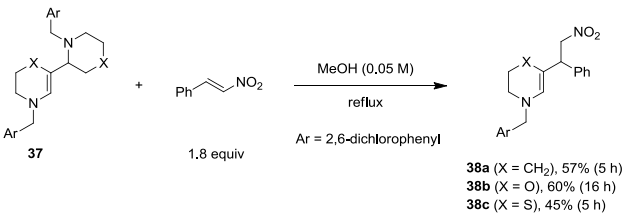


Scheme 9. Enamine dimer monomerization/β-functionalization.

To test the generality of enamine dimer formation, a number o other amines were exposed to the reaction conditions tha allowed for the formation of **30** (Scheme 10). Gratifyingly piperidine, morpholine and thiomorpholine all underwent th desired reaction to provide the corresponding enamine dimers **3** in good to excellent yields. This finding is quite remarkable considering that typically much harsher conditions are required t bring about the α-functionalization of these amines. Morpholine derived enamine dimer **37b** was characterized by X-ra crystallography. In analogy to pyrrolidine-derived enamine dime **30**, enamine dimers **37** also underwent facile β-functionalizatio with β-nitrostyrene (Scheme 11).



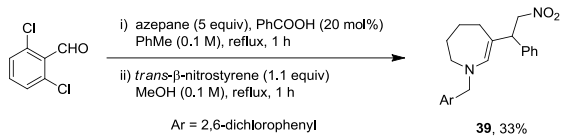
Scheme 10. Synthesis of other enamine dimers.



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

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).

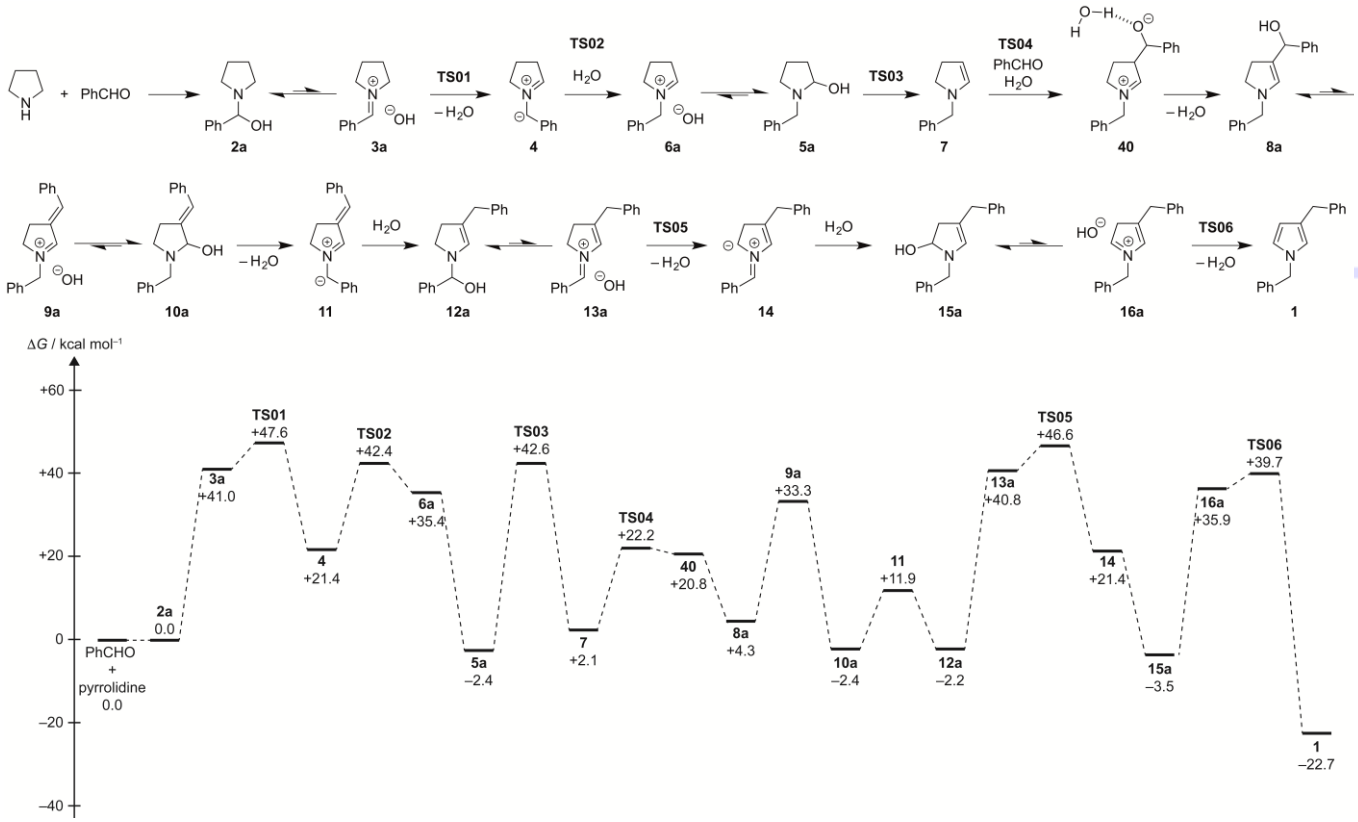


Scheme 12. β-Functionalization of azepane.

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 ($\Delta G \approx 88$ kcal mol^{-1}) which indicate that the deprotonation of the iminium ions (through **TS01**–**TS03** occurs directly from the tight ion pair. Next, the enamin intermediate **7** attacks benzaldehyde through **TS04** and th resulting alkoxide moiety is immediately protonated by water (– **40**). According to our calculations, the free zwitterioni intermediate is unstable under the reaction conditions and revert to the enamine and PhCHO. This implies that both processes nucleophilic attack and protonation, are coupled to each othe After a formal 1,3-OH shift (probably through **9a**), the secon azomethine ylide **11** is formed. A series of elimination, additior and elimination of water eventually leads to the pyrrole product **1**



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].

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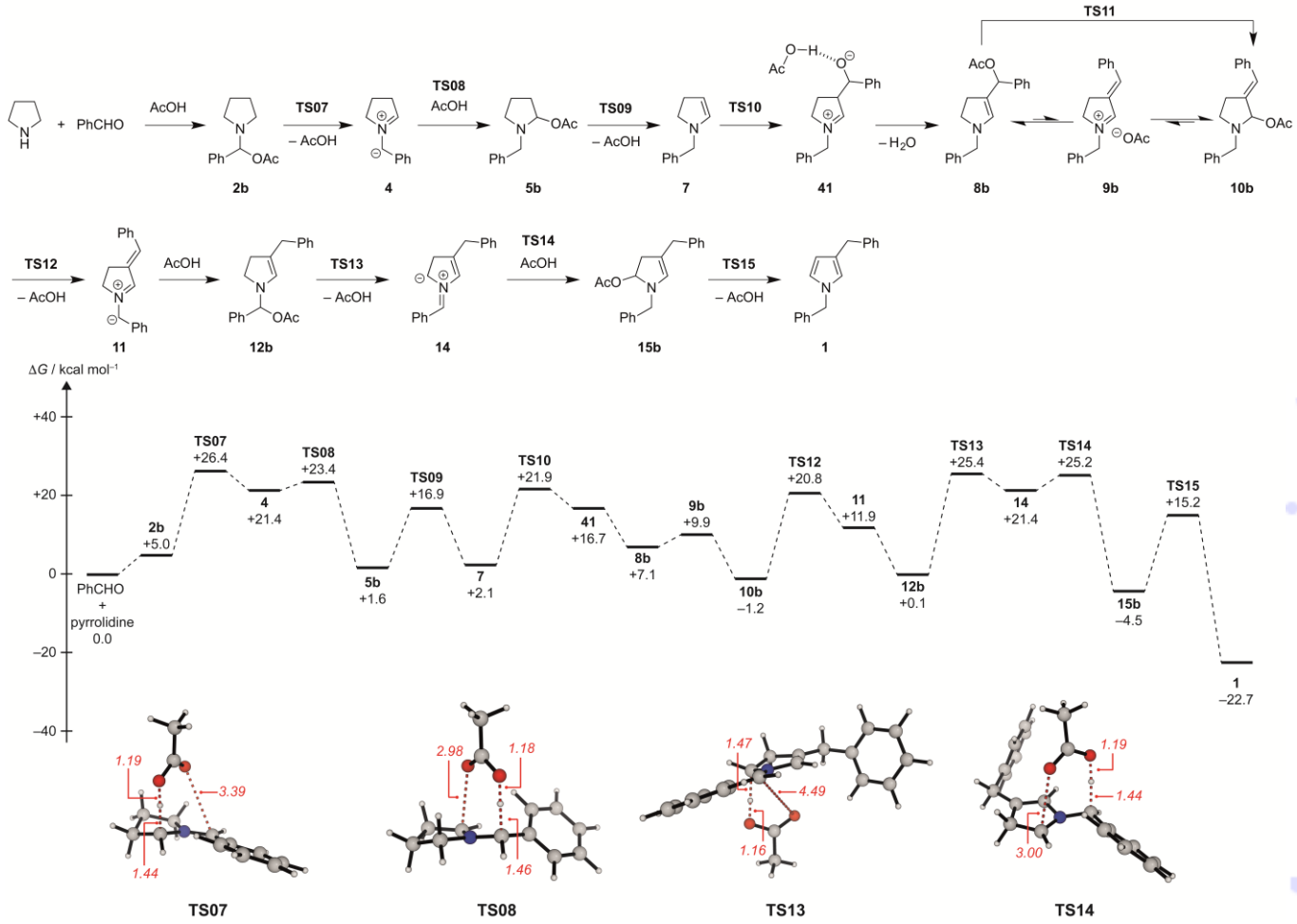


Scheme 14. Calculated free energy profile and selected transition state structures for the lowest-energy pathway for the acetic-acid-catalyzed reaction betwee benzaldehyde and pyrrolidine [in kcal mol^{-1} and Å; M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].

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 (ΔG = –22.7 kcal mol^{-1}) is the thermodynamic driving force and partially compensates the high activation barrier under these conditions.

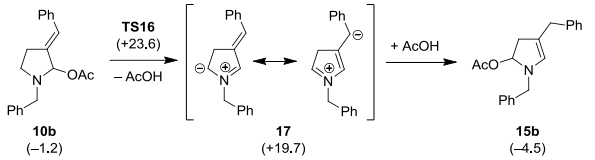
Carboxylic-acid-catalyzed reaction. After establishing the reaction mechanism for the uncatalyzed reaction, we investigated the role of acetic acid as a model carboxylic acid in these transformations. In previous investigations, the catalytic efficiency of AcOH was traced back to either proton-shuttle 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*-aceta (**2b**) in a slightly endergonic step. However, we were unable t calculate any transition states for the formation of **2b**, as th addition of acetate to the corresponding iminium ion occur barrierless. A reaction involving a concerted proton transfer an substitution between the hemiaminal **2a** (Scheme 13) and aceti acid did not result in any transition states either, probably due t the unfavorable alignment of the acetate as a hydrogen-bon acceptor and the attacking nucleophile. In contrast to the reactio in the absence of AcOH, no iminium acetates are formed in thi process. These species are either unstable and collapse to th corresponding *N*,*O*-acetals or are significantly higher in energy Instead, a concerted elimination of acetic acid through **TS0** (Scheme 14) takes place forming the azomethine ylide **4** from th *N*,*O*-acetal **2b**. Similar transition states have been described fo 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 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.

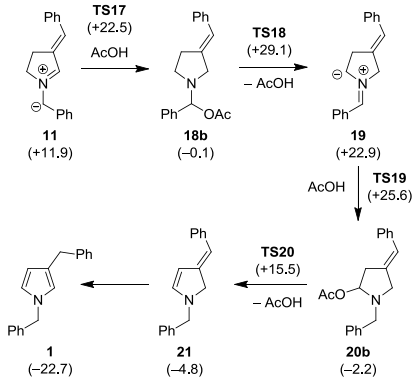
After another elimination of AcOH through **TS12**, the same azomethine ylide (**11**) is obtained that has been discussed above for the uncatalyzed reaction. Next, acetic acid is added (→ **12b**) and no transition states could be located for this process. It is likely that this process occurs in a 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.



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

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.



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

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 complet mechanistic analysis is presented in the supporting informatio and Scheme 17 summarizes the lowest-energy pathwa According to our calculations, the reactions of both aldehyde proceed through the same reaction mechanism and the free energy profile for benzaldehyde (Scheme 14) and 2,6 dichlorobenzaldehyde (Scheme 17) are qualitatively similar. I general, the additional chlorine substituents stabilize mos species involved in the transition state and the largest effect were calculated for the zwitterionic azomethine ylides (e.g., **43 50**, **52**). However, this stabilization effect is not paralleled in th transition states to the same extent. As a consequence, th transition-state energies for the crucial steps increase for chlorin 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, th activation free energy for the rate-limiting step (**TS24**) in th dichlorobenzaldehyde series was found to be 3.6 kcal mol higher in energy than in the corresponding benzaldehyde serie (Scheme 14). These higher transition state energies calculate for the reaction involving 2,6-dichlorobenzaldehyde also provide rationalization for why it is easier to trap reactive intermediate compared to the unsubstituted benzaldehyde.

Alternate Products. The computational studies have so fa shown why carboxylic acids are required for an efficier transformation and that the redox-neutral aromatization is les favorable for dichlorobenzaldehyde. The experimenta investigations additionally provided strong evidence for th presence of azomethine ylides (e.g., **4** or **11**) in the reactio mixture, and these species could be trapped in different (3+2 cycloaddition reactions with either benzaldehyde (→ **22**, Schem 3) or N-methylmaleimide (→ **27** and **28**, Scheme 4). In additior intermediately formed enamines (e.g., **7**) could be detected an higher enamine aggregates could be isolated. Accordingly, w have included these pathways in our DFT analysis and compar them with the energy profiles of Schemes 13 and 14.

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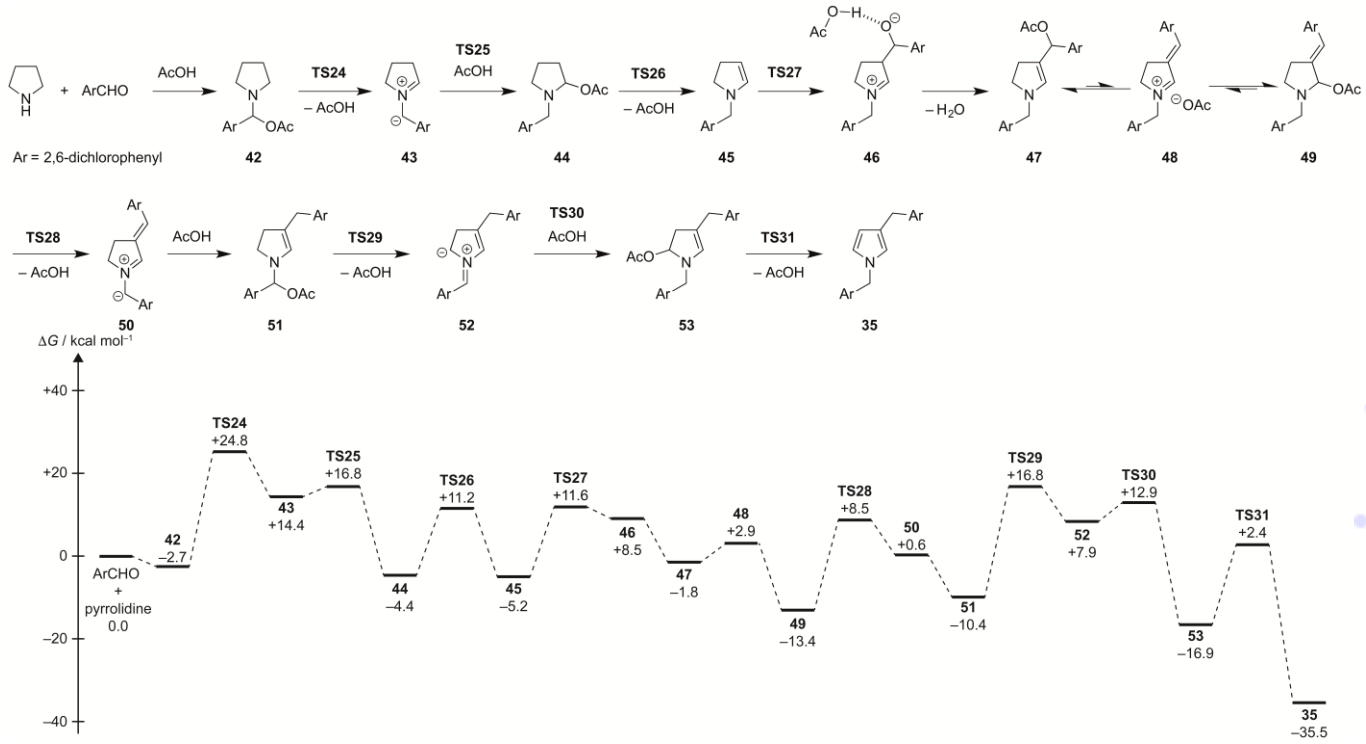


Scheme 17. Calculated free energy profile for the lowest-energy pathway for the acetic-acid-catalyzed reaction between 2,6-dichlorobenzaldehyde and pyrrolidin [in kcal mol^{-1}; M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].

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 (Δ*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-dichlorobenzadehyde. 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.

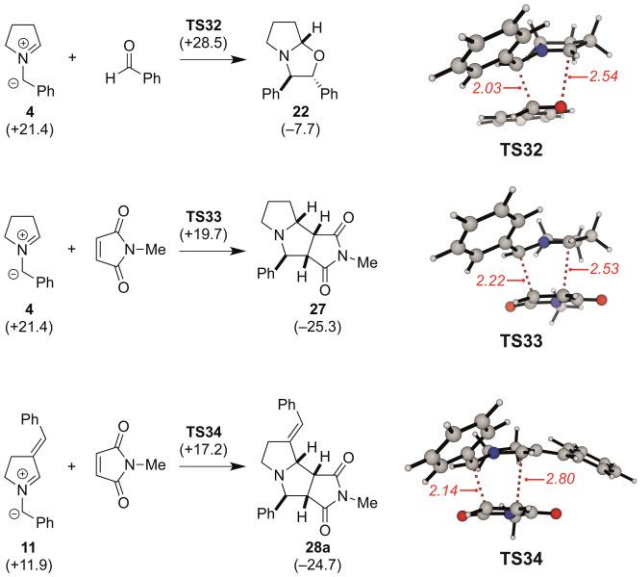
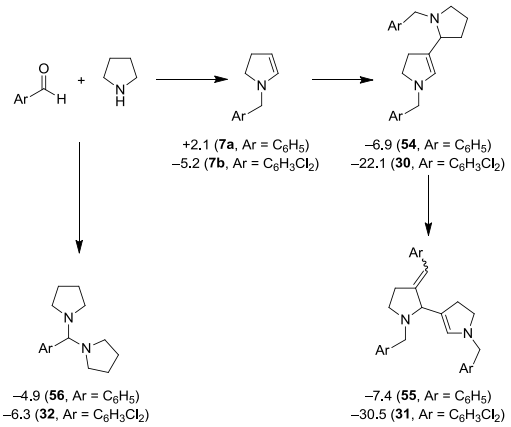


Figure 1. Calculated activation and reaction free energies and transition states for the trapping of the azomethine ylides **4** and **11** [in kcal mol^{-1} and Å, M06-2X-D3/def2-QZVP/IEFPCM(toluene)//M06-L-D3/6-31+G(d,p)/IEFPCM].



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)/IEFPCM].

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 heavy-atom root-mean-square 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 dispersion-correction 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.

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Keywords: C–H functionalization • redox-neutral • azomethine ylides • heterocycles

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[19] In addition, approximately 13% of what appears to be the enamine trimer was isolated in impure form (apparently contaminated with the

corresponding tetramer). However, this material was not fully characterized. An enamine trimer based on *N*-methyl pyrrolidine has previously been reported. See reference [20c].

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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.

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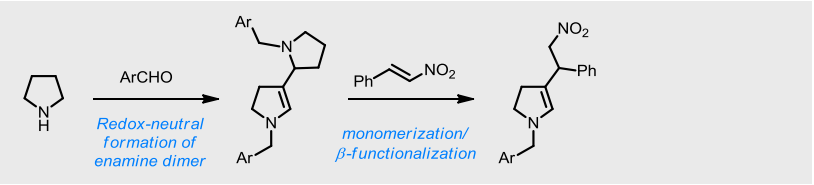

A combined experimental and computational study provides detailed insights into the mechanism of pyrrole formation from pyrrolidine and aromatic aldehydes. A number of reactive intermediates (e.g., azomethine ylides, conjugated azomethine ylides, enamines) were intercepted; outlining strategies for circumventing aromatization as a valuable pathway for amine C–H functionalization.

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