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Understanding and Interrupting the Fischer Azaindolization Reaction

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Abstract

Experimental and computational studies pertaining to the Fischer azaindolization reaction are reported. These studies explain why pyridylhydrazines are poorly reactive in Fischer indolization reactions, in addition to the origin of hydrazine substituent effects. Additionally, an interrupted variant of Fischer azaindolization methodology is disclosed, which provides a synthetic entryway into fused azaindoline scaffolds.

The Fischer indolization reaction, first described in 1883,[1] remains a powerful tool in modern chemical synthesis.[2] The transformation, which typically involves the acid-mediated reaction of aryl hydrazines with ketones or aldehydes to give indoles, has many applications in medicinal chemistry.[2] The Fischer indolization has also been used extensively in natural product synthesis, including several recent examples, to generate remarkable structural complexity.[3]

One deficiency associated with the Fischer indolization involves the variant in which pyridylhydrazines are employed to furnish azaindole products (a.k.a., Fischer azaindolization).[4] This transformation was first tested over 100 years ago.[5] It is now known, particularly via the studies of Parrick[4a,b] and Robinson[4c] that the azaindolization can proceed under extreme thermal conditions. For the corresponding acid-mediated process to take place, certain substituents on the hydrazine (e.g., methoxy, halides) can be used to improve reactivity, but the origins of such beneficial effects have remained unknown.[4d–g]

The present study answers two key questions. (A) What factors govern the success or failure of the Fischer azaindolization reaction? (B) Could a general “interrupted” variant of the

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ASSOCIATED CONTENT

Supporting Information

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Experimental details and computations (PDF)

The authors declare no competing financial interest.

Fischer azaindolization[6] be developed as a method to access fused azaindoline scaffolds? Although fused azaindoline frameworks are uncommon,[7] the parent azaindole heterocycle serves as a bioisostere for indoles[8] and is present in compounds of medicinal relevance. In fact, more than 74,000 bioactive azaindoles are known,[9] including the currently marketed drugs Zelboraf (**1**, Figure 1) and Venclexta.[10] Fused indolines are present in more than 22,000 bioactive molecules, more than 870 of which are natural products (e.g., **2**).[6c,9,11] We now report mechanistic insights into the Fischer azaindolization reaction, the scope of the interrupted variant (**3** + **4** → **5**), and the use of this methodology to access azaanalogues of bioactive compounds.

With the goal of understanding the factors that lead to success or failure of the Fischer azaindolization reaction, we performed a series of SCS-MP2 calculations.[12] We first investigated if the activation barrier for [3,3]-sigmatropic rearrangement varies significantly based on the aryl hydrazine employed. Thus, as summarized in Figure 2, the $\Delta G^{\ddagger}$ was calculated for this step under four scenarios:[13] (a) the neutral phenylhydrazone, (b) protonation of the β-nitrogen of phenylhydrazone,[14] (c) protonation of the β-nitrogen of 3-pyridylhydrazone, and (d) protonation of the β-nitrogen of methoxy-substituted 3-pyridylhydrazone. In all cases, we used propionaldehyde as the Fischer indolization reaction partner. For three of the scenarios (transition states **6**, **7**, and **9**), the calculations were in good accord with experimental trends. However, for transition state **8** involving the experimentally problematic 3-pyridylhydrazine, the activation barrier was calculated to be reasonable (i.e., 13.5 kcal/mol). Thus, we sought an alternative explanation for the poor reactivity of 3-pyridylhydrazones in Fischer indolization reactions.

We next considered if the pyridine nitrogen might be protonated (Figure 3). Indeed, protonation of this nitrogen is much preferred over hydrazone protonation, and pyridinium salt **10** is the global minimum of the pathway. To convert **10** to **11** requires 21.8 kcal/mol, leading to a high total barrier of 35.3 kcal/mol for the tautomerization and [3,3]-sigmatropic rearrangement (**10** → **8**). As noted earlier, it is known that introduction of a methoxy substituent on the pyridylhydrazine (e.g., see **9**, Figure 2) leads to improved yields in experimental studies.[4d–g] This has previously been rationalized by a “push/pull” effect[4d] which, in turn, makes the [3,3]-sigmatropic rearrangement more favorable. Instead, we suggest that the methoxy group reduces the basicity of the pyridine nitrogen, thus rendering the proton transfer/tautomerization more feasible. We calculate that the tautomerization between the 2-methoxy analogues of **10** and **11** is only 14.9 kcal/mol (versus 21.8 kcal/mol for **10** to **11**).[12] Consequently, the better performance in Fischer azaindolizations of methoxy-substituted pyridylhydrazines compared to the parent pyridylhydrazines can be attributed to the diminished basicity of the pyridine nitrogen in the former case.

We also explored the interrupted variant of the Fischer azaindolization to access fused azaindolines since only a single example of this transformation is available in the literature[6d] and no methodology studies have been reported. To initiate our efforts in this area, we used methoxy-substituted pyridylhydrazine salt **12** (Table 1), due to its previously established favorable reactivity in Fischer azaindolization reactions. Following an initial survey of reaction conditions, mainly involving variation of solvent, acid sources, time, and temperature, we found that **12** underwent interrupted Fischer azaindolization with a variety

of aldehyde surrogates to give fused 4-azaindoline products **13**. Of note, the transformation introduces two stereocenters, one of which is quaternary. Results are depicted based on optimization of individual substrates. Upon treatment of **12** with lactol **14**, furanoazaindoline **15** was obtained in 97% yield (entry 1). Alternate substituents on the lactol were tolerated, as demonstrated by the successful interrupted Fischer azaindolization of phenyl lactol **16** and allyl lactol **18** to furnish adducts **17** and **19**, respectively (entries 2 and 3). The 6-membered lactol **20** was also deemed a suitable reaction partner, as demonstrated by the formation of 6,5,6-tricycle **21** (entry 4). In addition, we evaluated several hemiaminal substrates for the synthesis of azapyrrolidinoindolines. The use of methyl substituted *N*-Ts hemiaminal **22** led to **23** (entry 5), whereas employment of allyl derivative **24** gave azaindoline **25** (entry 6). Lastly, we evaluated carbamate-containing hemiaminal substrate **26**, which furnished **27** in 82% yield (entry 7).

Having established the tolerance of the interrupted Fischer azaindolization methodology toward variation in the aldehyde surrogate, we shifted our attention to assessing changes in the hydrazine component (Table 2). Halohydrazines **29** and **31** underwent interrupted Fischer azaindolization with lactol **14** to deliver 4-azaindoline products **30** and **32**, respectively (entries 1 and 2). Interestingly, the use of methoxyhydrazine **33** led to azaindoline product **34**, albeit in a lower yield (entry 3).[15] Efforts to further optimize this transformation were unsuccessful. Isomeric hydrazines **35**, **37**, and **39** were also evaluated with the hopes of accessing 5-, 6-, and 7-substituted azaindolines. Whereas the interrupted Fischer azaindolization reaction failed to produce 5-azaindoline **36** (entry 4), the methodology furnished 6-azaindoline **38** (entry 5) and 7-azaindoline **40** (entry 6), albeit with a modest yield in the latter case. Finally, unsubstituted 3-pyridylhydrazine **41** was tested as a point of comparison (entry 7). Consistent with expectations based on the literature[4] and our calculations (see Figure 3), the transformation proved problematic and gave **42** in a poor yield of 11%.[16]

To complement these experimental studies, calculations were performed for the reaction of each hydrazine depicted in Table 2, with propionaldehyde as a model aldehyde under acidic conditions.[12] Earlier, we hypothesized that the success or failure of the Fischer azaindolization methodology hinges on the feasibility of enehydrazine formation, rather than [3,3]-sigmatropic rearrangement. Consistent with this notion, we found the computed activation barriers for [3,3]-sigmatropic rearrangement ($\Delta G^{\ddagger}$[3,3]) were uniformly accessible and ranged from 13.4 to 16.6 kcal/mol. On the other hand, the calculated tautomerization equilibria ($\Delta G[H^+]$) varied considerably between 11.5 and 23.7 kcal/mol. In cases where the calculated $\Delta G[H^+]$ is high, the reaction is experimentally problematic (entries 4 and 7). In the cases of entries 3 and 6, the $\Delta G[H^+]$ is slightly more favorable leading to modest yields of product. However, if $\Delta G[H^+]$ is sufficiently low (i.e., less than 15 kcal/mol), the reaction proceeds more efficiently (Table 2, entries 1, 2, 5, and Table 1). Overall, hydrazines with poorly basic pyridine nitrogens had the smallest $\Delta G[H^+]$.

The interrupted Fischer azaindolization methodology can be used to synthesize new aza-analogues of bioactive molecules (Figure 4). Treatment of benzyloxyhydrazine **43** with lactol **14** under acidic conditions delivered furanoazaindoline **44** in 81% yield. Using a

straightforward 3-step sequence, **44** was elaborated to carbamate **45**, a new analogue of the potent acetylcholinesterase inhibitor phensvenine.[17] Switching to a significantly more complex system, we performed the interrupted Fischer azaindolization of hydrazine **12** and known[3j] ketolactone **46**. Following the acid-mediated rearrangement and subsequent hydrolysis in the same pot, a straightforward methylation gave pentacycle **47**. In turn, azaindoline **47** was converted in two steps to **48**, an analogue of the anticancer agent aspidophylline A.[11]

We have performed an experimental and computational study of the Fischer azaindolization reaction, related to a transformation first attempted more than 100 years ago. Calculations were used to explain the difficulty in employing pyridylhydrazines in Fischer indolizations, in addition to the origin of hydrazine substituent effects. Rather than the [3,3]-sigmatropic rearrangement step being the single determining factor, we find that reactions suffer if the pyridine nitrogen is too basic, making the tautomerization step prohibitively challenging. We have also developed an interrupted Fischer azaindolization methodology, which provides a synthetic entryway into fused azaindoline scaffolds. The syntheses of new aza-analogues of phensvenine and aspidophylline A underscore the potential of this methodology to deliver new aza-derivatives of medicinally privileged fused indoline-containing compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Guillouzo C, Routier S. MedChemComm. 2011; 2:899–903.(f) Inman M, Carbone A, Moody CJ. J. Org. Chem. 2012; 77:1217–1232. [PubMed: 21977901] (g) Thomae D, Jeanty M, Coste J, Guillaumet G, Suzenet F. Eur. J. Org. Chem. 2013:3328–3336.(h) Alekseyev RS, Amirova SR, Kabanova EV, Terenin VI. Chem. Heterocycl. Compd. (N. Y., NY, U. S.). 2014; 50:1305–1315.

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6. In the interrupted Fischer azaindolization, rather than rearomatization occurring to give an azaindole heterocycle, the transient iminium species generated is trapped by a pendant nucleophile (see mechanism for **3** + **4** → **5** in Figure 1). For reviews on the parent interrupted Fischer indolization reaction (nonaza version), see: Li S, Han J, Li A. Huaxue Xuebao. 2013; 71:295–298.Mo Y, Zhao J, Chen W, Wang Q. Res. Chem. Intermed. 2015; 41:5869–5877.Susick RB, Morrill LA, Picazo E, Garg NK. Synlett. 2017; 28:1–11.One example of the Fischer azaindolization has been reported for the synthesis of a tetracyclic pyrrolidino-4-azaindoline; see de Graaff C, Bensch L, Boersma SJ, Cioc RC, van Lint MJ, Janssen E, Turner NJ, Orru RVA, Ruijter E. Angew. Chem., Int. Ed. 2015; 54:14133–14136.
7. Only four azaindoline compounds of the type **5** are known in the literature. For two furano-4-azaindolines prepared by a Pd-catalyzed intermolecular carboamination approach; see: Bizet V, Borrajo-Calleja GM, Besnard C, Mazet C. ACS Catal. 2016; 6:7183–7187.For a pyrrolidino-7-azaindoline derived from a [3+2] alkene/isocyanate cycloaddition; see: Huang L, Cheng H, Zhang R, Wang M, Xie C. Adv. Synth. Catal. 2014; 356:2477–2484.Cheng H, Zhang R, Yang S, Wang M, Zeng X, Xie L, Xie C, Wu J, Zhong G. Adv. Synth. Catal. 2016; 358:970–976.See also reference 6d
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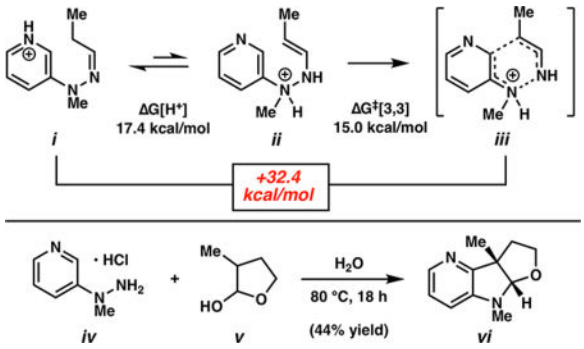
12. See the SI for details.
13. $\Delta G^{\ddagger}$[3,3] is the difference between the transition state energy of the sigmatropic rearrangement step and the energy of the enehydrazine precursor.
14. [3,3]-Sigmatropic rearrangement in the Fischer indolization is thought to proceed more favorably via protonation of the *β*-nitrogen. For prior computational studies; see: Çelebi-Olcüm N, Boal BW, Huters AD, Garg NK, Houk KN. J. Am. Chem. Soc. 2011; 133:5752–5755. [PubMed: 21443189]
15. Considering the higher basicity of 4-methoxypyridine compared to pyridine itself, this result may seem counterintuitive. However, this result underscores the need to take into account the relative basicities of the corresponding enehydrazine intermediates. We estimate that the enehydrazine derivative of 4-methoxypyridine is roughly 2 orders of magnitude more basic compared to the enehydrazine derivative of pyridine itself based on calculations. See the SI for details.
16. We also predicted that the use of *N*-methylhydrazine ***i*** would perform more favorably compared to hydrazine **41**, largely due to a more favorable tautomerization equilibrium ($\Delta G[H^+]$). Despite the high estimated overall barrier of 32.4 kcal/mol, we found that Fischer azaindolization of **iv** + **v** gave **vi** in 44% yield. Under identical conditions, the corresponding indolization of **41** gave only 12% yield of product **42**.



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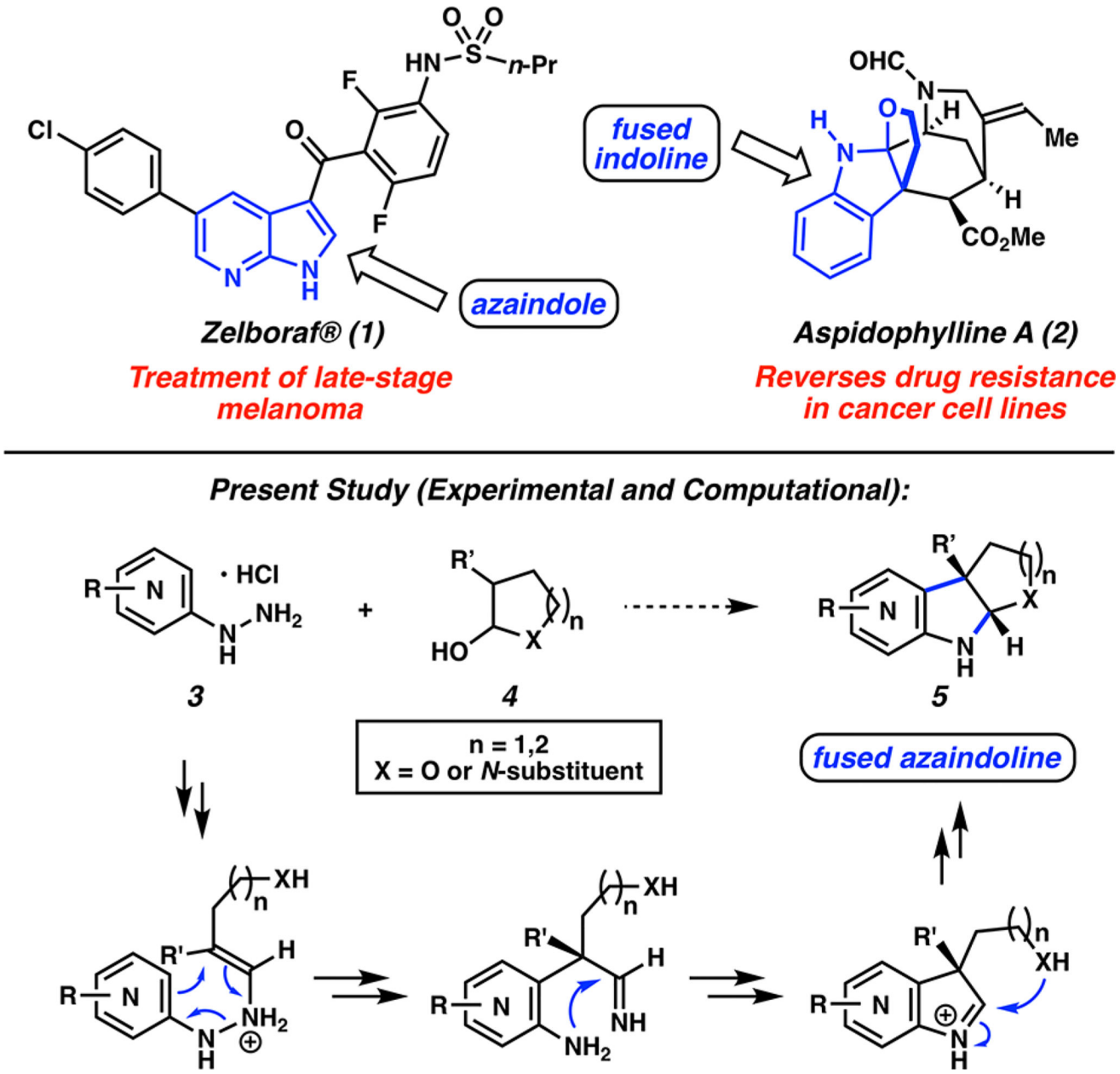


Figure 1.

Azaindole drug Zelboraf (**1**), indoline-containing natural product aspidophylline A (**2**), and interrupted Fischer azaindolization methodology.

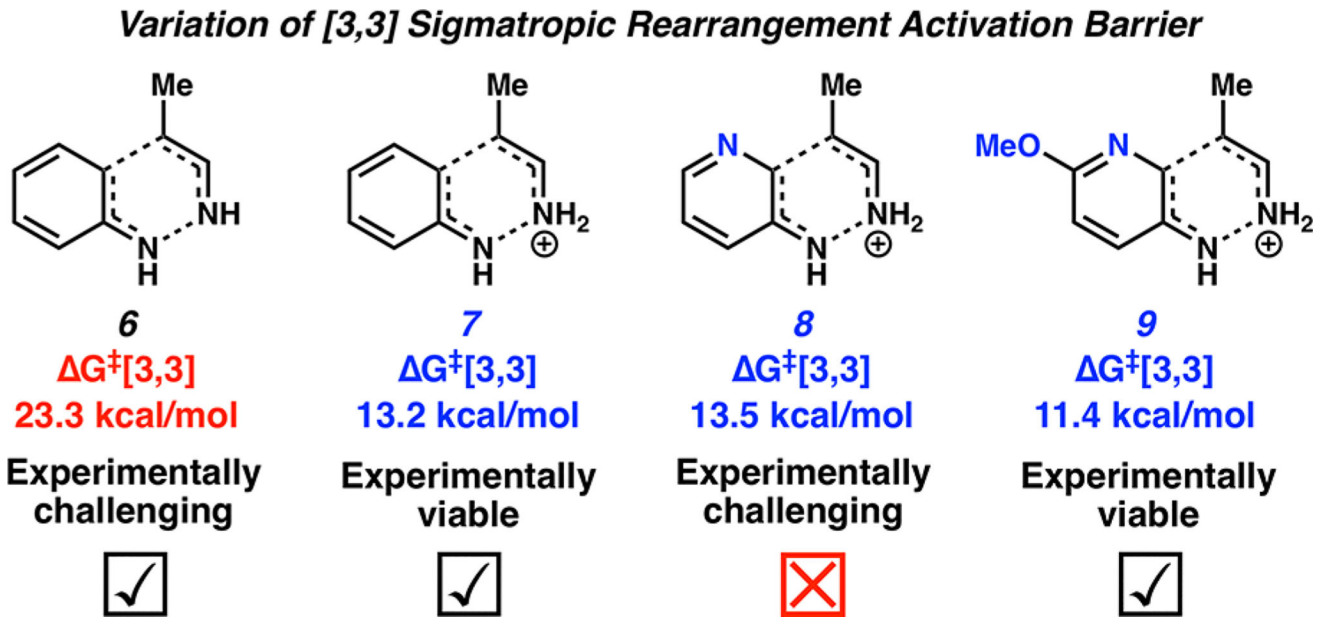


Figure 2.

Comparative calculations of the [3,3]-sigmatropic rearrangement transition states as a function of the arylhydrazine component.

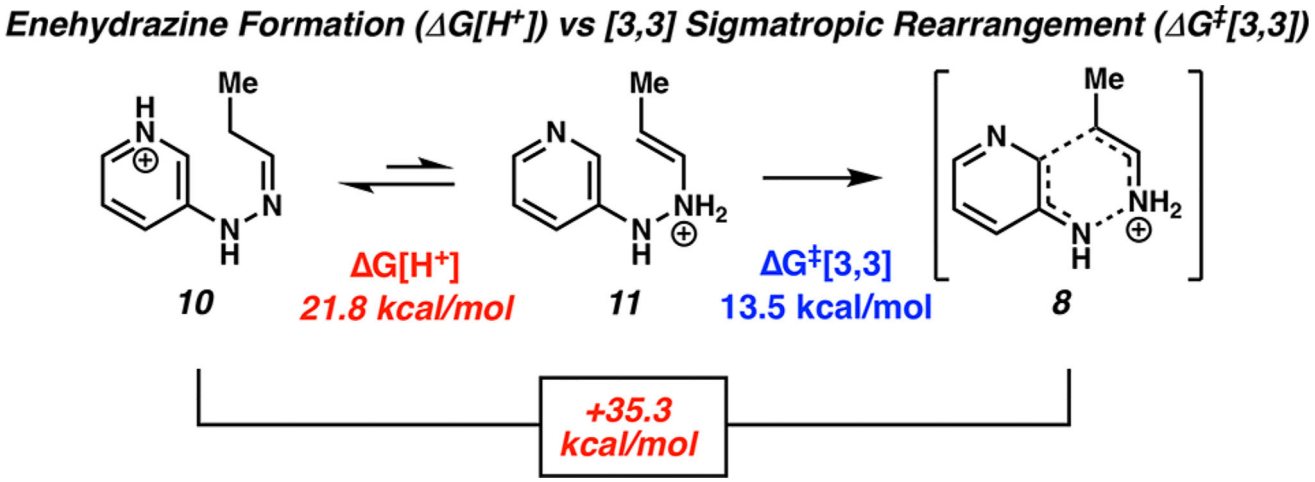


Figure 3.

Calculations suggest that an unfavorable equilibrium between **10** and **11** leads to challenging Fischer azaindolization of 3-pyridylhydrazones.

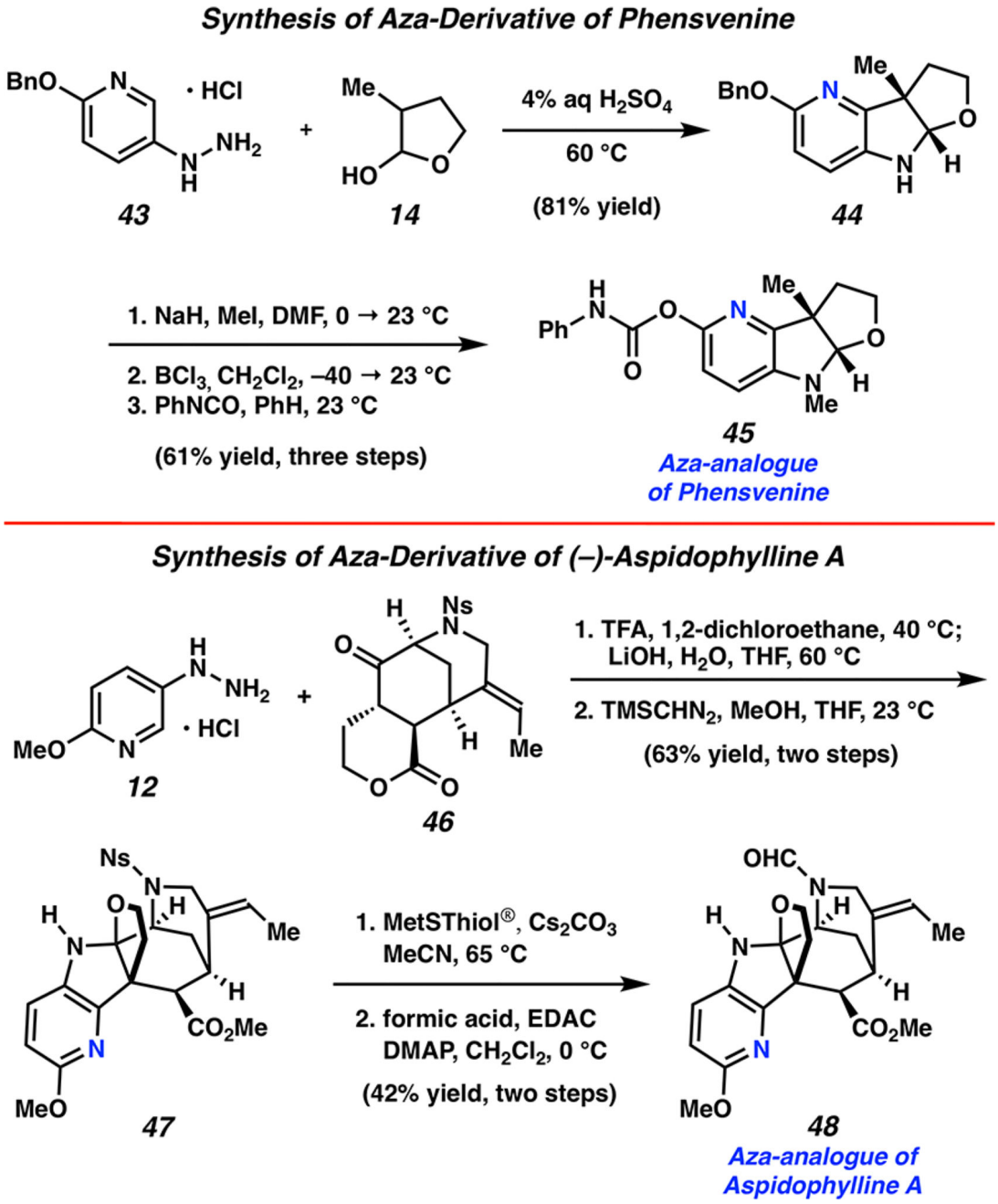
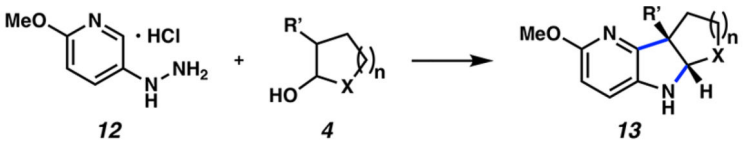
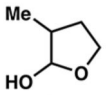
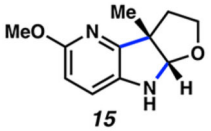
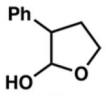
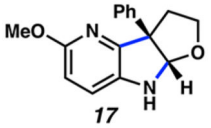
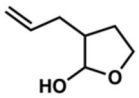
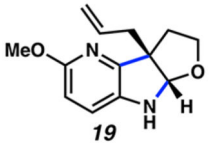
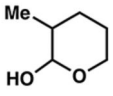
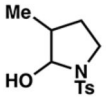
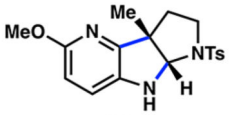
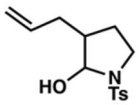
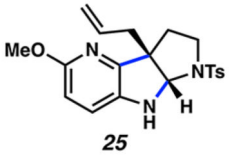
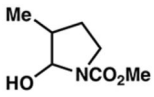
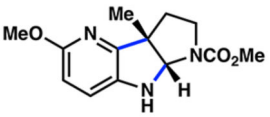


Figure 4.
Synthesis of aza-analogues.

Table 1

Scope of the Aldehyde Surrogate in the Interrupted Fischer Azaindolization[a]

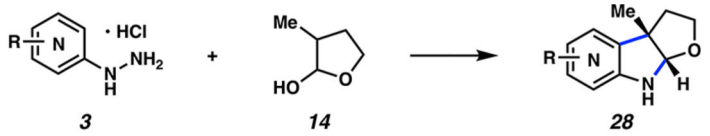


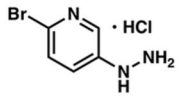
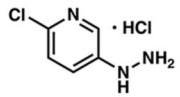
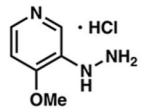
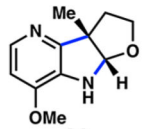
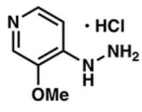
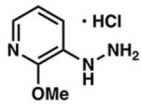
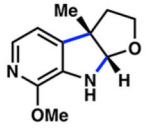
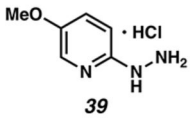
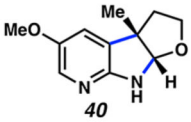
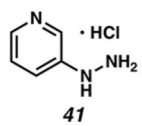
Entry	Aldehyde Surrogate	Product	Conditions Yield (%)
1	 14	 15	H_2O, 100 °C, 1 h *97% yield*
2	 16	 17	4% aq H_2SO_4 60 °C, 5 h *80% yield*
3	 18	 19	4% aq H_2SO_4 60 °C, 5 h *74% yield*
4	 20	 21	4% aq H_2SO_4 23 °C, 24 h *62% yield*
5	 22	 23	H_2O, 100 °C, 1 h *94% yield*
6	 24	 25	AcOH, 90 °C, 1 h *58% yield*
7	 26	 27	4% aq H_2SO_4 120 °C, 1 h *82% yield*

[a]Conditions unless otherwise stated: hydrazine **12** (1.5 equiv), aldehyde surrogate (1.0 equiv), solvent (0.05 M). Yields shown reflect the average of two isolation experiments.

Table 2

Scope of Hydrazine Component and Correlation to Calculated Free Energies[a]



Entry	Hydrazine	Product	Conditions Yield (%)	ΔG[H+]b ΔG‡[3,3]
1	 29	 30	4% aq H_2SO_4 120 °C, 1 h 62% yield	+12.1 +14.7
2	 31	 32	4% aq H_2SO_4 120 °C, 1 h 72% yield	+12.5 +15.1
3	 33	 34	4% aq H_2SO_4 120 °C, 3 h 48% yield	+20.1 +14.4
4	 35	 36	4% aq H_2SO_4 120 °C, 3 h No Reaction	+23.7 +16.6
5	 37	 38	4% aq H_2SO_4 120 °C, 1 h 70% yield	+11.5 +14.1
6	 39	 40	4% aq H_2SO_4 120 °C, 3 h 53% yield	+18.8 +13.4
7	 41	 42	4% aq H_2SO_4 120 °C, 3 h 11% yield	+21.8 +13.5

[a] Conditions unless otherwise stated: hydrazine (1.5 equiv), aldehyde surrogate **14** (1.0 equiv), solvent (0.05 M). Yields shown reflect the average of two isolation experiments.

[b] Free energies (kcal/mol) for [3,3]-sigmatropic rearrangement ($\Delta G^{\ddagger}$[3,3]) and enehydrazine formation ($\Delta G[H^+]$) were obtained using SCS-MP2 calculations with propionaldehyde as a surrogate aldehyde model under acidic reaction conditions.