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Pardon the Interruption: A Modification of Fischer's Venerable Reaction for the Synthesis of Heterocycles and Natural Products

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Abstract

This account provides an overview of our laboratory's studies of an unusual variant of the Fischer indolization reaction. We describe the discovery of the so-called 'interrupted Fischer indolization' and the development of the reaction from a methodological standpoint. In addition, our efforts to evaluate and apply this methodology in the context of akuammiline alkaloid total synthesis are discussed.

Graphical abstract

Keywords

total synthesis; alkaloids; heterocycles; natural products; akuammilines; indolines; indoles; Fischer indolization

1 Introduction

Thanks to the Thieme–IUPAC Prize Committee, and especially the one and only Victor Snieckus, it is a pleasure to write this personalized account of a research area that has been ongoing for several years.

My laboratory was launched on July 1, 2007.¹ At that time, five incoming graduate students eagerly joined my new research team with the hope of making new discoveries in the areas of catalysis, total synthesis, and heterocyclic chemistry. Most of the projects we pursued revolved around my academic job proposals. However, there were a few things we elected to

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dabble with, as any assistant professor should do, that had not been part of my job applications.

The story is one that is inspired by natural products. Between my time with Professor Brian Stoltz as a graduate student at Caltech and with Professor Larry Overman as a postdoc at UC Irvine, I had become mesmerized by naturally occurring small molecules with intricate scaffolds. Molecules such as dragmacidin D,² dragmacidin F,³ and sarain A⁴ had provided a delicate blend of pain and passion that I had grown to love. The pursuit of such molecules gave me endless intellectual stimulation in a way that was uniquely fulfilling compared to any other daunting problem-solving scenarios I had faced.

Always on the lookout for natural products, especially those containing the indole heterocycle, I had frequently encountered molecules of the type shown in Figure 1. Physovenine (**2**) and physostigmine (**3**) were widely pursued for their biological profiles and as a means to validate synthetic methodologies for the construction of quaternary stereocenters.^{5–7} Likewise, *meso*-chimonanthine (**4**) and its chiral isomer were common synthetic targets.⁸ In fact, I fondly recall seeing Professor Overman present on related studies when I was a graduate student, which, in part, inspired me to eventually pursue postdoctoral studies in his lab. Around the same time, arguably more ‘exotic’ natural products such as diazonamide A (**5**)⁹ and communesin B (**6**)¹⁰ were also ‘hot targets’. Finally, natural products like aspidodasycarpine (**7**)¹¹ and bipleiophylline (**8**)¹² appeared in isolation reports around the time I began my academic career. Although all of these natural products were not bio-synthetically related, their structures uniformly showcased a fused indoline-motif with a C3 quaternary stereocenter (e.g., **1**), albeit with varying degrees of decoration.

The common approach taken to access scaffold **1** is shown in Scheme 1. Typically, **1** would be derived from cyclization of a tethered nucleophile onto an in situ generated iminium ion as suggested by transition structure **9**. Whereas the iminium species would most often stem from an indole or oxindole precursor,⁶ an alternative approach would involve the coupling of two fragments, A and B, of reasonable complexity. This convergent (albeit vague) strategy could potentially provide a diverse range of indoline-containing products. However, what would be the identities of fragments A and B?

Although reaction design is often not straightforward and can be an intimidating task, a plausible solution presented itself. As a graduate student, I had the good fortune of working on a collaboration project with Professor Steve Quake (currently at Stanford University) aimed at achieving single-molecule DNA sequencing. My role in the project was to synthesize known and de novo fluorescently labeled deoxynucleoside triphosphates (dNTPs) that would be used as sequencing reagents.¹³ The dyes we needed were cyanines¹⁴ (**13**) (Scheme 2), which were quite costly.¹⁵ Being an indole chemist, I was happy to synthesize hundreds of milligrams of Cy3 and Cy5 that I then used to label synthetic dNTPs. The first step in the synthesis of Cy3 and Cy5 involved the Fischer indolization of aryl hydrazine **10** and ketone **11**.¹⁶ Just by heating these compounds in acetic acid, indolenine **12** was obtained in excellent yield. Of note, this uncommon variant of the classic Fischer indolization¹⁷

introduces a quaternary carbon, analogous to what we would need for our targeted methodology.

Bearing this unusual Fischer indolization in mind, the sequence outlined in Scheme 3 was concocted. Aryl hydrazine **14** would be treated with aldehyde surrogates **15** (i.e., lactols or hemiaminals) and a suitable acid source to ultimately generate fused indoline products **16**.¹⁸ The transformation would proceed by condensation of the two fragments, followed by a charge-accelerated [3,3]-sigmatropic rearrangement (see **17**). Following rearomatization, cyclization with loss of ammonia (see **18**) would furnish an intermediate iminium species. In a typical Fischer indolization, a deprotonation event would take place to give an indole product. However, without a C3 proton, aromatization would not be possible. Instead, cyclization of the pendant nucleophile (see **19**) would generate the desired indoline product **16**.¹⁹ Much later, at the 2009 ‘Syncon’ meeting of Southern California Synthetic Chemists held at USC that year, it was recommended that we give a catchy name to this transformation. One colleague suggested ‘interrupted Fischer indolization’—although perhaps not a perfect fit, everyone seemed to like it, so we have kept that name since. Later, another colleague suggested the term ‘iFisch,’ which my research group still uses on occasion.

2 Interrupted Fischer Indolization Methodology

We were able to first try the interrupted Fischer indolization early in the summer of 2007. One of the lab’s founding members, a graduate student named Ben Boal, pursued the reaction of phenylhydrazine (**20**) and excess lactol **21** shown in Scheme 4. By simply heating the compounds in acetic acid at 60 °C, Ben obtained a mixture of products. After careful NMR and mass spectroscopic analyses, he was able to assign the compounds as diastereomers **22**. The desired transformation had occurred as we intended, although with hemiaminal formation on the indoline nitrogen. I still recall watching Ben proudly label his NMR spectrum with the product structure, for he had validated the desired interrupted Fischer indolization reaction.

Encouraged by Ben’s ‘hit’, we performed optimization studies using one equivalent of lactol **21** (Table 1). Although the use of PCl₃ (Table 1, entry 1) or ZnCl₂ (Table 1, entry 2) were unfruitful, a variety of protic acids could be used to deliver the desired indoline product **23** (Table 1, entries 3–8).¹⁹ We settled on the use of acetic acid–water (1:1) for further studies given the relatively mild nature of these reaction conditions.

At this stage, Ben teamed up with another talented graduate student named Alex Schammel. Together, they elucidated the scope of the interrupted Fischer indolization methodology. A selection of their results is summarized in Table 2.¹⁹ As suggested by entries 1 and 2, carbon-based substituents were tolerated on the internal nitrogen of the aryl hydrazine component. Additionally, rather than using lactol coupling partners to give furoindolines such as **25** and **28**, the use of hemiaminals could be employed to deliver pyrrolidinoindolines **26** and **29**. Substituents were also tolerated on the aromatic group of the hydrazine coupling partner, including halides (Table 2, entries 3 and 4). With regard to the aldehyde surrogate, allyl (Table 2, entry 5) and phenyl derivatives (not shown) could be used. Lastly, six-

membered ring substrates were well tolerated by the methodology to give homologous products (Table 2, entry 6).

Once we had developed this methodology, we were eager to pursue publication in a top journal. Obviously, we were excited about the chemistry, but this effort was also slated to be one of our group's very first papers. However, the initial reviews we obtained were heartbreaking. For example, one reviewer described our manuscript with the words "lack of urgency, novelty, and importance" – a kiss of death for publication in our targeted journal. This was also the first time I had to relay such bad news to my students. It was particularly painful given how bright and dedicated they were.

Although at least one reviewer was perhaps unreasonably harsh, I realized that some of the comments were in fact valid and would shape our future directions. For example, we had failed to cite several prior related efforts in Fischer indolization chemistry,²⁰ particularly those studies performed decades earlier by Grandberg. Not discussing literature precedent, of course, is an easy way to offend reviewers (as we learned the hard way). Reviewers also inquired about an asymmetric version, which we had not developed.²¹

With these comments in mind, we opted to revise our manuscript and publish in a respectable journal in early 2009.¹⁹ Moreover, rather than focusing on method development, we made the conscious decision to put all efforts on the project toward constructing complex molecules. We pursued the natural product psychotrimine, which led to mechanistic insight pertaining to the Fischer indolization and an exciting collaboration with my colleague Professor Ken Houk.²² We used the interrupted Fischer indolization to construct the core of the communesins.²³ Moreover, we completed a concise synthesis of phenserine,²⁴ a compound undergoing clinical trials for the treatment of Alzheimer's disease.²⁵

3 Applications in Akuammiline Alkaloid Total Synthesis

Knowing that we could access furo- and pyrrolidinoindolines, we performed structure-based searches with the hope of finding new and potentially more complex natural products with biological activity. These explorations led us to the compound aspidophylline A (**42**) (Figure 2), which was isolated in 2007.¹¹ Although we began working toward **42** immediately, we soon came to realize that **42** belonged to a larger class of natural products called the akuammiline alkaloids. Dozens of bioactive akuammilines had been isolated over many decades, primarily from plants and trees in Southeast Asia.²⁶ Extracts from the organisms that make akuammilines in Nature have long been used as traditional medicines.²⁷ Structurally, the targets provided us with no shortage of an intellectual challenge. Some possessed furoindoline cores, such as aspidophylline A (**42**) and its oxidized counterpart picrinine (**43**). On the other hand, several family members, such as strictamine (**44**), featured a methanoquinolizidine core. Finally, there were akuammilines that were 'rearranged', such as echitamine (**45**), vincorine (**46**), and scholarisine A (**47**).²⁶

My group often discusses the question: "*what makes a natural product a 'good target'?*" From our viewpoint, although heavily biased at this stage, aspidophylline A (**42**) was perfect. The target had not been synthesized previously and, more generally speaking, the

akuammilines had not yet captured the full attention of the synthetic community.^{28–30} This is especially noteworthy given that the akuammilines share a common biosynthetic precursor with the popular strychnos alkaloids.³¹ Compound **42** also possessed interesting biological activity (i.e., promising anticancer activity against resistant cell lines) and its structure was suitably complex due to its five interconnected rings and five contiguous stereocenters.¹¹ The presence of a furoindoline united to the [3.3.1]-azabicyclic would provide an ideal testing ground for our interrupted Fischer indolization methodology as suggested in Scheme 5. In fact, we recognized that many akuammilines such as **42**, **43**, and **48** could be accessible using a late-stage variant of the interrupted Fischer indolization using aryl hydrazine precursors **49** and bicyclic ketones **50** bearing tethered nucleophiles.

With these admittedly rough ideas in mind, a new postdoc named Dr. Liansuo Zu, who would later be joined by graduate student Ben Boal, began our pursuit of aspidophylline A (**42**) (Scheme 6).^{30a} We reasoned that **42** could be accessed from **51** via a straightforward functional group manipulation. Then, in the key step, the pentacyclic core of the natural product would arise from an interrupted Fischer indolization sequence involving phenylhydrazine (**20**) and ketoalcohol **52**. For the purposes of this account, we will focus on the late-stage Fischer indolization chemistry of the total syntheses. Readers should note that the early stages of our syntheses required intense intellectual and experimental efforts that should not be taken for granted.

Scheme 7 highlights some of the pain that Liansuo and Ben experienced on their quest to synthesize aspidophylline A. Although we had targeted the ketoalcohol **52** shown in Scheme 6, when we eventually arrived at this species, it was found to exist as the corresponding hemiketal **53**. Although it seemed plausible that **53** could be utilized, all efforts to employ this compound in Fischer indolization studies were met without success. Next, we sought to prepare a protected version of our initial ketoalcohol target and arrived at pivaloate ester **54**. Unfortunately, this intermediate and many others failed in our Fischer indolization studies.

Not to be deterred, we theorized about why the Fischer indolization had failed. From our experiments, we concluded that the formation of the aryl hydrazine adduct was occurring, however, the necessary charge-accelerated [3,3]-sigmatropic rearrangement was presumably the sluggish step.^{32,33} In our next hypothesis, which may be viewed as ‘hand-waving’ or an act of desperation, we wondered if this rearrangement might be more likely to occur on a rigidified system. Thus, we opted to tether back the hydroxyethyl group and designed the ketolactone substrate **56** shown in Scheme 8. Our resilience was finally rewarded, as **56** underwent reaction with phenylhydrazine (**20**) in the presence of TFA to give indolenine lactone **57**. This species could be isolated in good yield and characterized. However, we eventually found a way to process it in a manner that was more akin to our interrupted Fischer indolization methodology. Namely, once **57** was formed, we simply removed the volatiles and subjected the crude material to K₂CO₃ in methanol. This led to formation of the corresponding methyl ester with release of an alkoxide, which in turn, underwent cyclization (see **58**) to deliver pentacyclic furoindoline product **51**. By the introduction of three new rings, three new bonds, and two stereogenic centers (including the quaternary center formed in the Fischer indolization), this transformation enabled us to complete the first total synthesis of aspidophylline A (**42**).^{30a}

At this juncture, Liansuo was able to wrap-up his postdoctoral stay and Ben began the pursuit of our next target, picrinine (**43**)³⁴ (Scheme 9). Structurally, picrinine (**43**) is very similar to aspidophylline A (**42**) and one might think about assembling the C5–N bond at a late stage in the synthesis. Indeed, Ben's initial efforts to convert aspidophylline-type compounds into picrinine (**43**) were not successful. We next considered an alternate plan, wherein the *N,O*-acetal motifs would be introduced in the final step of the synthesis by in situ cyclization of aminoaldehyde **59**. Compound **59** would arise from oxidative cleavage of olefin **60**, which in turn would derive from a Fischer indolization of **61**. Ideally, the R group of **61** would be an ester, but the failed Fischer indolization of this substrate eventually led us to pursue the other variations described herein. Although Ben Boal initiated our efforts toward picrinine (**43**), he would eventually pass the torch to graduate students Joel Smith and Jesus Moreno who took the reins and completed the total synthesis.^{30b,c}

Scheme 10 shows one of the exciting scenarios we pursued, which was ultimately met with despair. After much experimentation, we had arrived at ketone **62** and pursued its use in the Fischer indolization with phenylhydrazine (**20**). Upon treatment with TFA at 40 °C, we obtained the desired indolenine product **63** in 65% yield. Completing the synthesis appeared to be within our reach, so we proceeded to elaborate pivalate **63** into methyl ester **60**. With **60** in hand, we attempted the critical oxidative cleavage of the olefin. However, rather than obtaining the desired product **66**, we only observed formation of undesired product **65**. Presumably, dihydroxylation had proceeded to give **64**, but this compound underwent cyclization more readily than C–C bond cleavage. Attempts to sidestep this problem by using alternate reaction conditions or more direct oxidative cleavage protocols were not successful.³⁵ Similarly, attempts to further manipulate the undesired product **65** were not fruitful.

Given that cyclization was occurring pre-emptively, prior to C–C bond cleavage, we wondered if the diol motif could be tethered back to prevent the cyclization we had observed, thus enabling necessary rupture of the C–C bond. We pursued several substrates toward this notion and the path that ultimately panned out is depicted in Scheme 11. Tricycle **67**, which contains the key alkene embedded in the cyclopentene ring, was subjected to a dihydroxylation³⁶/protection³⁷ sequence to afford carbonate **68**. In the key Fischer indolization, treatment of substrate **68** with phenylhydrazine (**20**) and TFA furnished two major products in good yield. To complicate matters, the two compounds interconverted on silica gel and in the NMR tube when CDCl₃ was used as the solvent. Eventually, careful chromatography using a pipette column and NMR analysis in C₆D₆ led us to assign the compounds as hemiaminal **69** and indolenine **70**. Interestingly, hemiaminal **69** displayed a higher *R_F* value by normal phase TLC compared to **70**, so we had not initially considered this structure. The finding has served as a useful reminder for my laboratory to always be cautious when interpreting *R_F* values and TLC data. Nonetheless, it should be emphasized that the key Fischer indolization allowed for the efficient assembly of two new rings, three new bonds, and the critical quaternary stereocenter needed for our total synthesis.

From **69** and **70**, hydrolysis and oxidative cleavage proceeded without event, en route to lactol ester **64**. To remove the nosyl group, **64** was treated under basic conditions in the

presence of thiol nucleophiles. Although it appeared the nosyl was being removed, purification of the resulting polar product(s) proved exceptionally difficult. In part inspired by my experience using solid-supported reagents as a graduate student to facilitate purifications,^{13a} we attempted the denosylation using a solid-supported thiol resin³⁸ under basic conditions. Gratifyingly, in addition to nosyl cleavage, the desired cyclization between N4 and C5 took place to deliver the natural product picrinine (**43**). This effort marked the first total synthesis of this natural product and remains the only total synthesis of **43** to date.^{30b,c}

Our most recent efforts in the area of akuammiline alkaloid total synthesis involved the natural product strict-amine (**44**) (Scheme 12),^{30d} a natural product that was first isolated in 1966³⁹ and was the subject of several previous⁴⁰ and ongoing investigations.^{29h,30d} Of note, **44** possesses a methanoquinolizidine core and all akuammilines with this framework had evaded total synthesis. In our retrosynthetic thinking, we hoped to assemble the methanoquinolizidine at a late stage, and would therefore access the natural product from alkyl halide **72**. In the forward sense, deprotection and halide displacement would allow us to forge the key C–N bond, whereas oxidation would install the indolenine. It was thought that **72** could arise from lactone **73**, a product of a reductive Fischer indolization between phenylhydrazine (**20**) and ketolactone **74**.⁴¹ We reasoned that the use of a reductive Fischer indolization could also allow access to 2(*S*)-cathafoline (**75**), a more recently isolated natural product.⁴²

By design, ketolactone **74** is reminiscent of the key substrate used in our total synthesis of aspidophylline A (**42**), albeit with a nosyl protecting group in place of a tosyl protecting group.⁴³ Although we had a conceivable route to **74** based on our prior studies, we elected to re-evaluate the sequence and develop an asymmetric approach to **74**. While not described here, exhaustive design and experimentation was carried out by ‘Team Akuammiline’, which ultimately allowed us to access **74** in gram quantities and in high enantiopurity.^{30d} Without having access to so much material, undoubtedly our efforts toward the total synthesis would have been severely hampered.

The total synthesis of strictamine (**44**) and 2(*S*)-cathafoline (**75**) was first taken on by graduate students Jesus Moreno, Elias Picazo, and Joel Smith. Joel would go on to graduate, at which point another graduate student, Lucas Morrill, joined the efforts. Together, the team was able to access **74** and pursue the key interrupted Fischer indolization (Scheme 13). In the event, treatment of phenylhydrazine (**20**) with ketolactone **74** in the presence of TFA led, as expected, to Fischer indolization to furnish indolenine product **76**. Although not the focus of this story, it should be noted that **76** could be carried forward to (–)-aspidophylline A (by ‘interruption’ upon exposure to methoxide), thus completing an enantioselective synthesis of **7**. Alternatively, **76** could undergo reduction upon the addition of TFA and triethylsilane. The one-pot sequence gave the desired product **73** in 83% yield. Like the other Fischer indolizations described herein, this transformation generates great complexity. Specifically, two new rings are introduced by the formation of four new bonds and two stereogenic centers. Only a single diastereomer of the product is detectable. From **73**, we were able to access alkyl chloride **72**, albeit with much more experimentation than we would have

anticipated due to unforeseen epimerization challenges encountered during lactone opening. In turn, **72** was found to be a suitable precursor to both natural products, strict-amine (**44**) and 2(*S*)-cathafoline (**75**).

As we performed optimization and characterization, I had the good fortune to visit Professor Jieping Zhu at École Polytechnique Fédérale de Lausanne (EPFL). We had met previously at a conference in Nara, Japan, and we were well aware that both of our labs were actively pursuing the total synthesis of strictamine. Rather than competing, we decided to openly share all of our latest results and provide suggestions to one another. We also made the decision to time our manuscript submissions to allow for nearly simultaneous publication, rather than having one of us be ‘scooped’. This strategy panned out, both scientifically and in terms of the timing for when our publications appeared in the literature.^{29h,30d} It is hoped that this anecdote only helps to encourage a greater spirit of collaboration in the field of total synthesis.

4 Concluding Thoughts

In summary, over the past 9+ years, we developed an efficient method to assemble fused indoline scaffolds, which has been termed the ‘interrupted Fischer indolization’. The methodology is modeled after Emil Fischer’s classic indolization reaction and allows for the union of two fragments, an aryl hydrazine, and a carbonyl unit (often bearing a tethered nucleophile), to rapidly assemble complex heterocyclic frameworks. The heterocyclic products obtained bear quaternary stereocenters and are commonly seen in natural products. We have validated that this methodology can be used strategically in total synthesis, as seen in the syntheses of aspidophylline A (**42**), picrinine (**43**), strictamine (**44**), and 2(*S*)-cathafoline (**75**). The examples we have described in this account showcase a modern spin on a classic reaction, which has led to some of the most complex Fischer indolizations reported to date.⁴⁴

Importantly, our efforts in the area of interrupted Fischer indolization chemistry have provided a stellar training ground for several tremendous scientists. Graduate students Ben Boal and Alex Schammel earned their Ph.D. degrees in 2012, after laying the foundation for their projects and the lab in general. They performed postdoctoral studies with Professors Mark Davis (Caltech) and Dale Boger (Scripps), respectively, before entering the work force. Ben is currently employed at Thermo Fisher (no pun intended), whereas Alex is happily working at Abbvie Stemcentrx. Dr. Liansuo Zu conducted a short postdoctoral stint with Professor Dean Tantillo (UC Davis), before accepting an academic position at Tsinghua University. Joel Smith earned his doctorate in 2015 and is now a Beckman postdoctoral scholar in Professor Phil Baran’s lab (Scripps). Jesus Moreno is wrapping up his Ph.D. studies and will soon join the medicinal chemistry team at Merck. Finally, the co-authors of this account, graduate students Elias Picazo, Lucas Morrill, and Robert Susick, continue to innovate in their pursuits of daunting natural products.

Overall, our laboratory was extremely fortunate to come upon the ‘interrupted Fischer indolization’ methodology in 2007. Since then, the exploration of this chemistry, especially in the pursuit of natural products, has provided us with endless intellectual stimulation. We

view these endeavors as being critical training grounds for students and postdocs interested in academia or industrial positions. Moreover, it should never be forgotten that such pursuits remain the backbone of modern synthetic chemistry, which in turn, is essential for the discovery and manufacturing of countless medicines used to benefit society.

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Neil Garg is a professor of chemistry at the University of California, Los Angeles. Professor Garg received a B.S. in chemistry from New York University where he did undergraduate research with Professor Marc Walters. During his undergraduate years, he spent several months in Strasbourg, France while conducting research with Professor Mir Wais Hosseini at Université Louis Pasteur as an NSF REU Fellow. He obtained his Ph.D. in 2005 from the California Institute of Technology under the direction of Professor Brian Stoltz. He then joined Professor Larry Overman's research laboratory at the University of California, Irvine as an NIH Postdoctoral Scholar. Garg joined the faculty at UCLA in 2007. His laboratory develops synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.

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Scheme 1.

A common approach to fused indoline scaffolds and our general strategy

Scheme 2.

Fischer indolization for the introduction of quaternary centers used in the preparation of cyanine dyes

Scheme 3.

Proposed mechanism of the 'interrupted Fischer indolization'

Scheme 4.

Initial validation of the interrupted Fischer indolization, albeit with gratuitous functionalization of the indoline nitrogen

Scheme 5.

The Fischer indolization approach to akuammiline alkaloids

Scheme 6.

Abbreviated retrosynthetic analysis of aspidophylline A (42)

Scheme 7.
Examples of failed Fischer indolizations

Scheme 8.

Successful Fischer indolization and total synthesis of aspidophylline A (42)

Scheme 9.
Abbreviated retrosynthetic analysis of picrinine (43)

Scheme 10.

One failed approach toward picrinine (43)

Scheme 11.

Revised Fischer indolization sequence and total synthesis of picrinine (43)

Scheme 12. Abbreviated retrosynthetic analysis of strictamine (44) and 2(*S*)-cathafoline (75)

Scheme 13.

Reductive Fischer indolization sequence and total synthesis of strictamine (**44**) and 2(*S*)-cathafoline (**75**)

Figure 1.
Representative indoline-containing natural products

Figure 2.
Representative akuammiline alkaloids

Table 1

Optimization of the Interrupted Fischer Indolization

Entry	Acid source	Conditions	Yield (%)
1	PCl ₃	benzene, 60 °C	<5
2	ZnCl ₂	EtOH, 100 °C	<5
3	TsOH	EtOH, H ₂ O, 60 °C	51
4	TFA	MeCN, 60 °C	64
5	5% HCl	MeCN, 60 °C	70
6	4% H ₂ SO ₄	MeCN, 60 °C	87
7	AcOH	AcOH, 60 °C	52
8	AcOH	AcOH–H ₂ O (1:1), 60 °C	89

Table 2

Scope of the Interrupted Fischer Indolization

Entry	Coupling Partners	Product, yield
1	 24 21	 X = O, 70% (25) X = NTs, 81% (26)
2	 27 21	 X = O, 60% (28) X = NTs, 70% (29)
3	 30 21	 X = O, 67% (31) X = NTs, 77% (32)
4	 33 21	 X = O, 60% (34) X = NTs, 84% (35)
5	 20 36	 X = O, 89% (37) X = NTs, 68% (38)
6	 20 39	 X = O, 65% (40) X = NTs, 81% (41)