JOC The Journal of Organic Chemistry

PERSPECTIVE

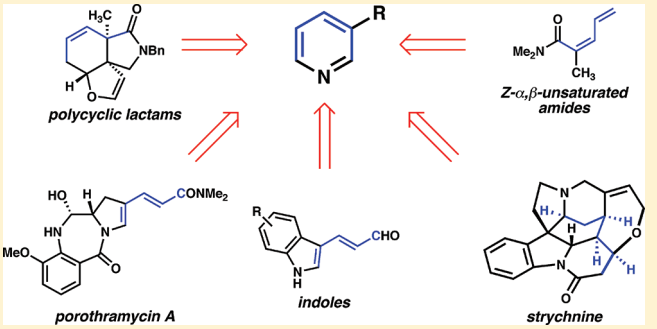
pubs.acs.org/joc

# Reactivity and Synthesis Inspired by the Zincke Ring-Opening of Pyridines

Christopher D. Vanderwal*

1102 Natural Sciences II, Department of Chemistry, University of California, Irvine, California 92697-2025, United States

**ABSTRACT:** The century-old Zincke process for ring-opening of pyridinium salts produces 5-amino-2,4-pentadienals, a type of donor−acceptor dienes known as Zincke aldehydes. Inspired by this reasonably general and often efficient process for dearomatization, my laboratory has used pyridines as a starting point for heterocycle synthesis, which resulted in unusual syntheses of indoles, pyrrolines, and a formal synthesis of the natural product porothramycin A. Furthermore, our study of the reactivity of Zincke aldehydes has led to accidental discoveries of pericyclic cascade reactions that produce *Z*-$\alpha,\beta$-unsaturated amides or polycyclic lactams, depending upon the identity of the substituents on nitrogen. Finally, a base-mediated formal cycloaddition reaction of tryptamine-derived Zincke aldehydes has served as the key step in concise syntheses of the indole alkaloids norfluorocurarine and strychnine.




## I. INTRODUCTION

For several years, my laboratory has been exploring the utility of the acyclic products derived from the ring-opening of the pyridine heterocycle. Of tremendous importance in their own right, aromatic heterocycles, including but not limited to pyridines, can serve as precursors to valuable acyclic products. Many of the heterocycle syntheses predicated on condensation reactions of acyclic precursors can also be formally reversed to generate acyclic systems, using redox neutral, oxidative, or reductive protocols for ring-opening.

The use of furan and substituted furans as precursors to valuable acyclic compounds has a rich history.[1] Because of the low resonance stabilization energy of furan, estimated to be only 16 kcal/mol, the furan/1,4-dicarbonyl equilibrium can be perturbed to generate either the aromatic or the acyclic form. Indeed, in the reverse of the venerable Paal−Knorr synthesis (**1** → **2**, Scheme 1),[2] furans can be ring-opened to afford the corresponding 1,4-dicarbonyl compounds under aqueous acidic conditions (see **3** → **4**, Scheme 1, a key step in *cis*-jasmone syntheses[3]); given the relative dearth of methods for accessing that particular oxygenation pattern, this reaction has substantial value. Furans can also be ring-opened oxidatively[1] under a variety of conditions including with epoxidizing reagents, singlet oxygen, and electrophilic halogenating reagents/water. As shown in the scheme (**5** → **6** → **7**[4]), the ultimate products of these transformations are enediones; because of the oxidative trigger for ring-opening, the acyclic reaction products are at an oxidation state that is higher than those derived from simple acidic hydrolysis. Cyclopropanation of the furan double bond can also induce ring-opening of the heterocycle, and this process has proven a valuable route to complex polyenes, as demonstrated in the Rokach synthesis of the lypoxygenase product 5-HETE (**12**).[5]

In some cases, the furan ring-opening process is coupled with a subsequent ring-closing step to afford rearranged cyclic structures. For example, the Piancatelli reaction[1,6] converts furfuryl carbinols into hydroxycyclopentenones under protic conditions (see **13** → **14**[7] as a key step en route to $PGE_2$[8] Scheme 2), and the Achmatowicz rearrangement,[9] performed under oxidative conditions, transforms the same starting materials into hydroxypyranones via ring-closure of the intermediate enedione (see **17** → **18** as a key step en route to the Prelog−Djerassi lactone **19**[10]). Both of these rearrangement processes have seen significant use in complex molecule synthesis. In a lesser known and often capricious process, furfuraldimines are converted into diaminocyclopentenones **22** and/or **23** (pyrrole **24** and pyridinium salt **25** are often also obtained) via the Stenhouse procedure.[11] The intermediacy of highly conjugated zwitterionic species named Stenhouse salts is implicated, and ring-closure likely occurs via electrocyclization, in much the same way as the cyclization in the Piancatelli reaction.[12] Clearly, the facile dearomatization of furans engenders tremendous utility to these readily available heterocycles.[13]

On going from $\pi$-rich heterocycles such as furan to the prototypical $\pi$-deficient aromatic heterocycle, pyridine, for which aromatic stabilization is much greater, ring-opening processes by simple hydrolysis, or other transformations that cause loss of aromaticity without a concomitant energetic payoff, are not readily accomplished. Nonetheless, the use of pyridines as precursors to high-value-added acyclic precursors has a long history.[14] For example, Birch reduction of pyridines provides 1,4-dihydropyridines, which are nothing more than cyclic

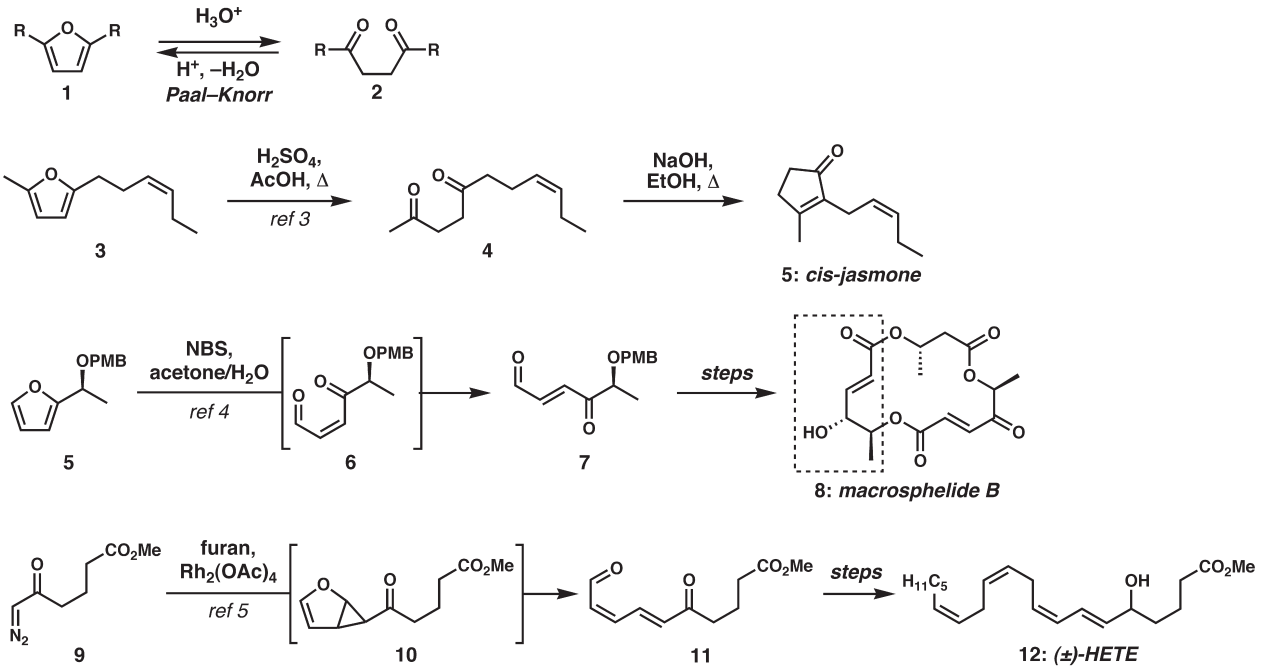
**Received:** August 3, 2011
**Published:** August 30, 2011



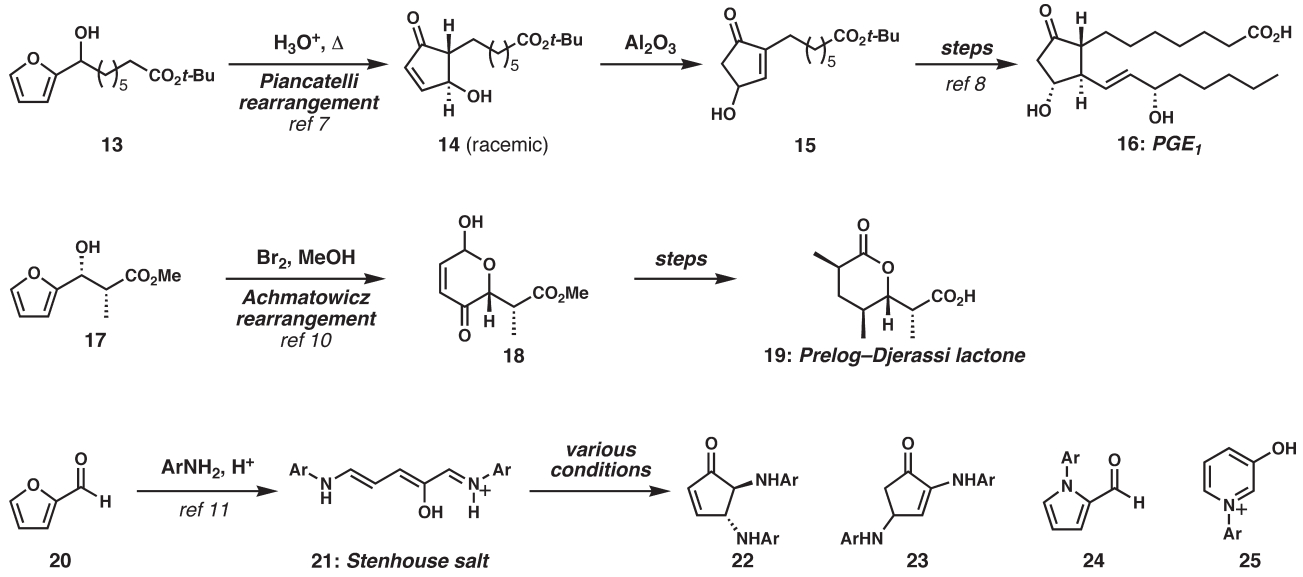


dx.doi.org/10.1021/jo201625e | *J. Org. Chem.* 2011, 76, 9555–9567

**Scheme 1. Applications of Various Furan Ring-Opening Reactions in Natural Product Synthesis**




**Scheme 2. Conversions of Furans into Diverse, Non-furanoid Cyclic Structures**

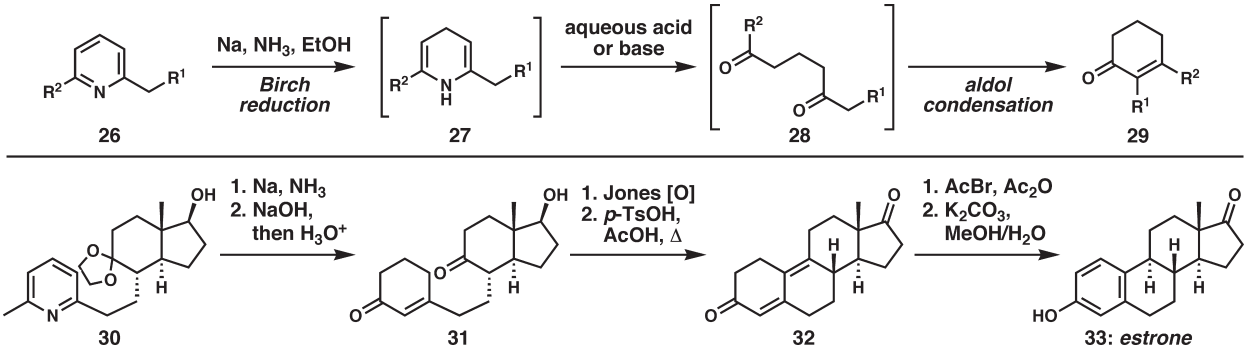



bis(enamines), poised for hydrolysis to the corresponding 1,5-dicarbonyl compound; in turn, these intermediates are readily transformed to cyclohexenones via aldol condensations (**26** → **27** → **28** → **29**, Scheme 3).[15,16] This sequence represents the reverse of a very common pyridine synthesis: the condensation of a 1,5-dicarbonyl compound with an ammonia equivalent, followed by oxidation. A striking application of this pyridine reduction/hydrolysis strategy is found in Danishefsky's pyridine route to steroids, wherein complex 2,6-disubstituted pyridines are converted to the 1,5-dicarbonyl compounds, which are promptly converted to substituted cyclohexenones by aldol condensation reactions.[17] This clever strategy was the centerpiece of an enantiocontrolled synthesis of estrone that ultimately began from 2,6-lutidine (key step: **30** → **31**).[17c−e]

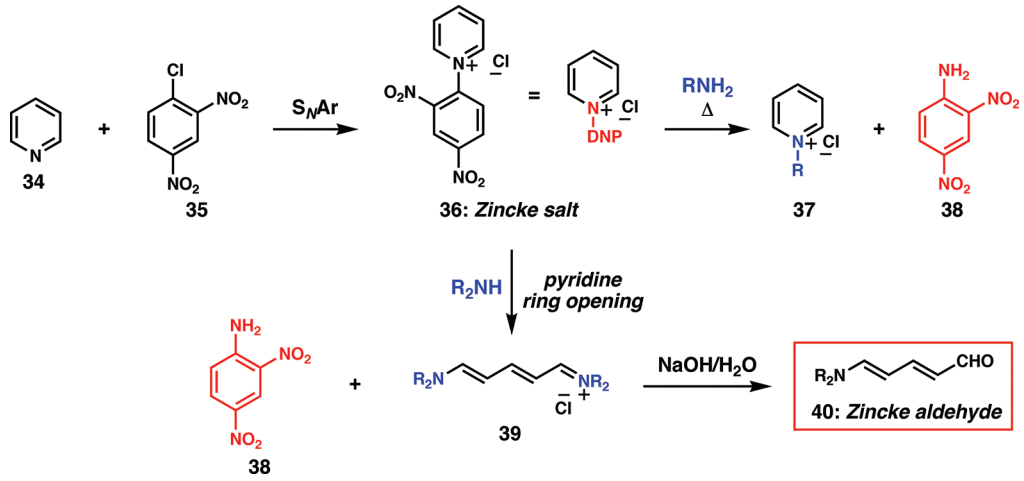
The reduction/hydrolysis of pyridines to access 1,5-dicarbonyls dates back to the work of Shaw in 1925;[15] the inspiration for this Perspective, the Zincke ring-opening of pyridines, predates that process by nearly a quarter century. Just as the reduction/hydrolysis of pyridines long preceded Danishefsky's exceptional application, the Zincke ring-opening of pyridinium salts to afford aminopentadienals and related compounds was known for a century before we initiated our studies that sought to use the Zincke ring-opening reaction and the resultant products in concise approaches to heterocycles and alkaloids.


dx.doi.org/10.1021/jo201625e |J. Org. Chem. 2011, 76, 9555–9567

**Scheme 3. Birch Reduction of Pyridines as a Means to Access 1,5-Dicarbonyl Compounds and Cyclohexenones**




**Scheme 4. Reactions of Electrophilic "Zincke" Pyridinium Salts with Amines**




## II. BACKGROUND

Zincke reported the preparation of pyridinium salts and their reactions with amines in a series of papers in 1903−1905.[18,19] The activation of pyridines by $S_NAr$ reaction with 2,4-dinitrochlorobenzene afforded the *N*-arylated pyridinium salts, which are now known as Zincke salts (**36**, Scheme 4). Treatment with primary amines led to the formation of new pyridinium salts (**37**) wherein the amine had become integrated into the heterocycle; 2,4-dinitroaniline (**38**) was released. This versatile reaction is an excellent way to make pyridinium salts that cannot be made by direct *N*-functionalization of pyridines and has seen some use in natural product synthesis, particularly by the Marazano group. This laboratory was responsible for several creative exploitations of the Zincke reaction; for example, they accessed pyridinium salts bearing chiral *N*-substituents for subsequent stereoselective transformations of the heterocycle for alkaloid synthesis,[20] and they synthesized macrocyclic dimeric pyridinium alkaloids using this reaction as a key transformation.[21]

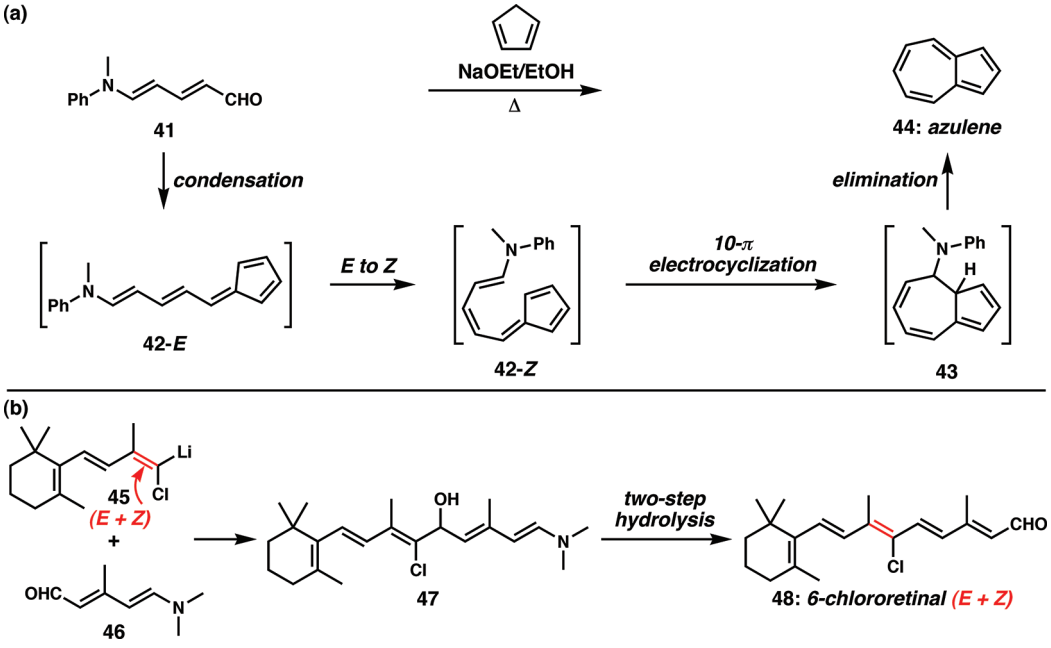
The reaction of Zincke salts with 2 equiv of a secondary amine leads to cleavage of the heterocyclic ring to form a conjugated iminium species such as **39**, again with expulsion of 2,4-dinitroaniline.[18,22] This chemistry was an important method for the synthesis of cyanine dyes,[23] which remain important in biomedical imagining applications. The iminium termini of the ring-opened products can be hydrolyzed with aqueous base to afford 5-amino-2,4-pentadienals, a versatile family of readily accessible donor−acceptor dienes known as Zincke aldehydes. These compounds display a wealth of potential reactivity, some of which we have begun to tap into in the research program that I will describe in this Perspective.

A Zincke aldehyde, like any donor−acceptor system, displays alternating nucleophilic and electrophilic atoms along the length of the molecule. The potential modes of reactivity available to donor−acceptor $\pi$-systems are many: they mimic electron-rich arenes in their ability to undergo smooth electrophilic substitution and, despite their attenuated electrophilicity relative to normal conjugate acceptors, nucleophilic addition with powerful nucleophiles is also possible. Upon first glance, the reactivity of Zincke aldehydes might also include their use as functionalized dienes in Diels−Alder cycloadditions, as well as other pericyclic processes resulting from their high degree of unsaturation.

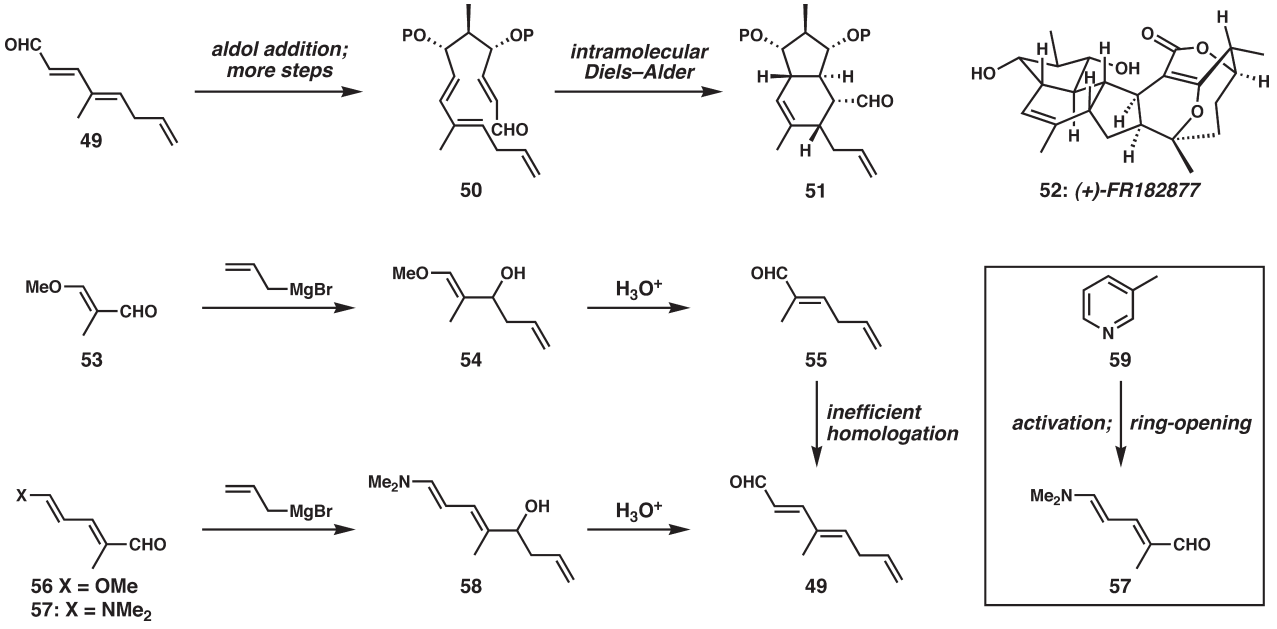
While many applications of the Zincke reactions, the resulting Zincke aldehydes, and related glutaconaldehyde derivatives have been reported over the last century, these reactions and products have been conspicuously underutilized in complex settings. Selected notable exceptions include (1) the Ziegler−Hafner two-step azulene synthesis from cyclopentadiene and the Zincke aldehyde derived from *N*-methylaniline (Scheme 5a);[24] (2) Köbrich's synthesis of polyenes, including retinoids, by organometallic additions to Zincke aldehydes and hydrolysis of the resulting doubly vinylogous hemiaminals to unveil a transposed dienal[25] (Scheme 5b; in fact, Zincke aldehydes can generally be used to transfer dienal motifs to organometallic nucleophiles in this way);


dx.doi.org/10.1021/jo201625e |J. Org. Chem. 2011, 76, 9555–9567

**Scheme 5. Selected Applications of Zincke Aldehydes in Complex Molecule Synthesis**




**Scheme 6. My Awareness and Interest in Zincke Chemistry Dates Back to the Synthesis of FR182877 during Graduate School, Sorensen Laboratory, The Scripps Research Institute**



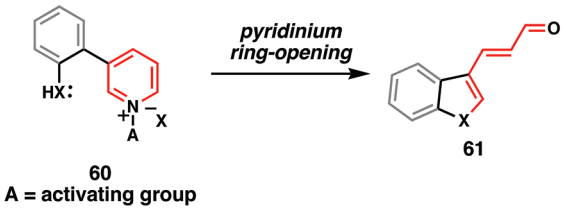

and (3) Marazano's biogenetic hypothesis and synthetic studies of the manzamine alkaloids featuring Zincke aldehydes as key intermediates (not shown).[21a,26] In fact, and as mentioned above, it is the group of Marazano that had been responsible for the majority of the interesting and creative applications of Zincke chemistry and related 5-amino-2,4-pentadienals[13,27] to complex nitrogenous molecules.

This chemistry first attracted my attention during graduate studies at the Scripps Research Institute. While engaged in the synthesis of FR182877 in the laboratory of Prof. Erik Sorensen,[28] I had cause to access the triene aldehyde **49** (Scheme 6), which was to be used in an aldol addition, and eventually in an intramolecular Diels–Alder reaction to access the A and B rings of the target (**51**). In previous work, I had made known dienal **55** by addition of allylmagnesium bromide to commercially available β-methoxymethacrolein followed by hydrolysis of resulting vinylogous hemiacetal **54**, according to the procedure of Spangler.[29] While homologation of **55** to **49** was possible, it proved difficult without conjugation of the remote alkene. I reasoned that the use of a donor–acceptor *diene* for the sequence used to make **55** from donor–acceptor *alkene* **53** would afford the desired triene aldehyde


dx.doi.org/10.1021/jo201625e |J. Org. Chem. 2011, 76, 9555–9567

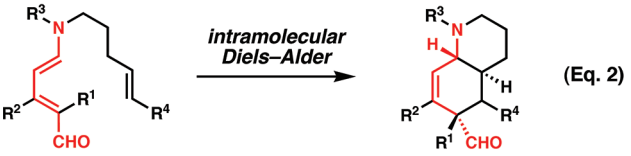
**49** (this process is closely analogous to the retinal synthesis of Köbrich shown in Scheme 5). While preparation of the desired doubly vinylogous ester **56** would have required multiple steps, I was surprised to learn that the corresponding doubly vinylogous amide **57**, a compound known as a Zincke aldehyde, was available by the ring-opening aminolysis of inexpensive 3-picoline (**59**), a two-step, simple, and apparently scalable process. Indeed, for some time, 3-picoline served as a key starting material for the Sorensen group's studies toward FR182877.[30] The ready availability of the highly functionalized Zincke aldehydes, combined with their obvious potential for interesting reactivity and the dearth of their exploitation in complex molecule synthesis led to my long-term interest in Zincke chemistry.

Two of our group's earliest ideas in this area involved the use of tethered nucleophiles to trigger the ring-opening of pyridinium salts, a process that would generate a new ring and a useful $\alpha,\beta$-unsaturated aldehyde, and the application of the diene component of Zincke aldehydes in intramolecular Diels–Alder reactions to rapidly generate polycyclic products (eqs 1 and 2). In principle, these two processes could be used in tandem to produce complex architectures in only a few steps. The successes, failures, and serendipitous discoveries that resulted from the study of these two simple ideas are described in this Perspective.




**60**
**A = activating group**

**61**

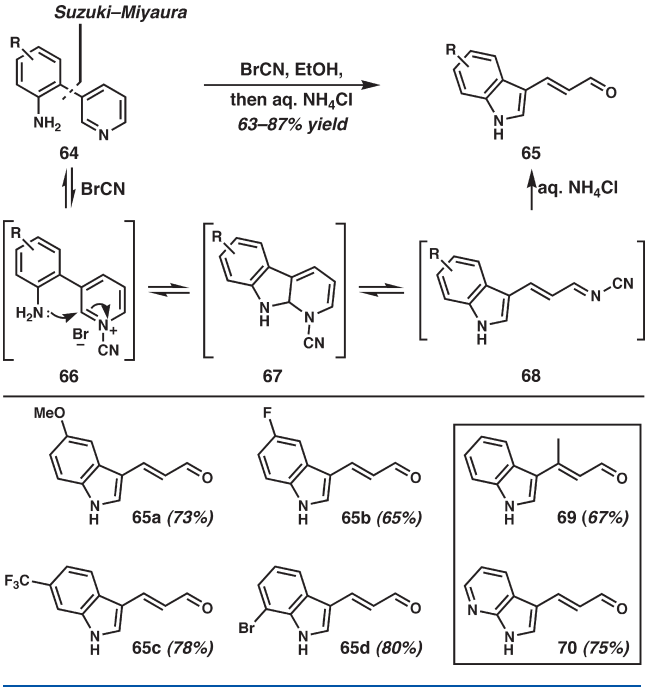



**62** **63**

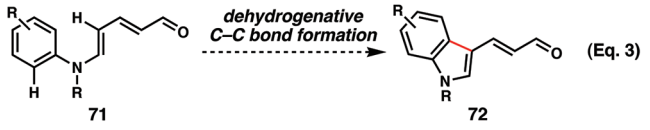
## III. THE REARRANGEMENT OF PYRIDINIUM SALTS BEARING TETHERED NUCLEOPHILES GENERATES HETEROCYCLIC PRODUCTS

Our first foray into the use of tethered nucleophiles to effect pyridinium ring-opening involved aniline-substituted pyridines. The key practical consideration for this chemistry was that the pyridine nitrogen must act as a more kinetically competent nucleophile toward the activating agent than the tethered nucleophile. On the basis of the original König procedure[22a] for pyridine ring-opening, which uses cyanogen bromide as a pyridine activating reagent in the presence of aniline, we believed that an indole-forming reaction should be possible starting from substrates such as **64** (Scheme 7). After some experimentation, we developed a general two-stage synthesis of indoles from pyridine-3-boronic acids and *o*-haloanilines; a convergent Suzuki coupling set up for the rearrangement reaction of **64** induced by cyanogen bromide leading to 3-(3-indolyl)propenal products (**65**) after hydrolysis of the presumed *N*-cyanoimine intermediate **68**.[31] This indole synthesis proved both efficient and general such that every pyridine substrate evaluated delivered the product indole in yields above 60%, including the interesting azaindole product **70**. This chemistry joins the large and growing

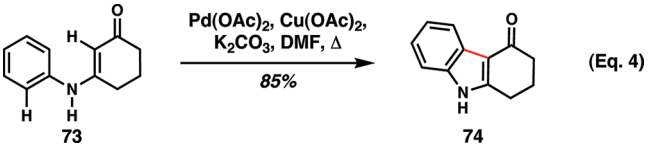
**Scheme 7. Indole Synthesis via Ring-Opening of Pyridinium Salt Using the König Procedure, Including Selected Products**




group of indole syntheses that relies on *o*-haloanilines as starting materials. We were aware that the tremendous advances in Pd-catalyzed C–H activation might be harnessed to further simplify this indole synthesis because the Zincke aldehydes derived from *N*-alkylanilines should undergo an oxidative ring closure under appropriate conditions (**71** → **72**, eq 3). Certainly, palladation of the nucleophilic C-4 of the Zincke aldehyde would be reasonable, and a number of mechanisms could be envisioned for construction of the remaining C–C bond via arene *ortho*-C–H functionalization. Before we expended any effort in this area, Glorius and co-workers beautifully demonstrated the feasibility of this type of approach in their versatile indole synthesis starting from aniline-derived vinylogous esters and carbamates (eq 4).[32]




**71** **72**

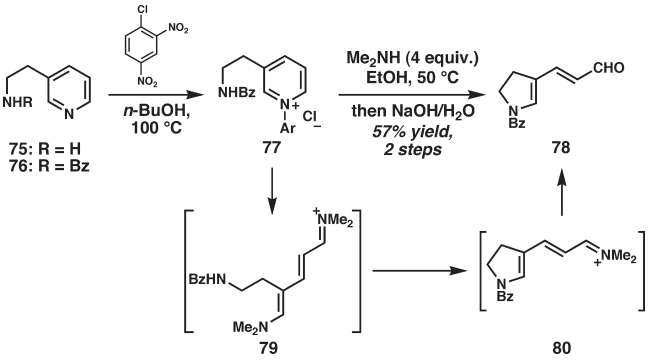



**73** **74**

The unsaturated aldehyde that results at C3 of the indole initially appeared to be highly versatile; however, preliminary experiments designed to make use of its electrophilicity were derailed by an attenuation of reactivity attributed to the donor nature of the indole ring. Attempts to perform several functionalization reactions of the $\alpha,\beta$-unsaturated aldehyde based on the organocatalysis concept of MacMillan using chiral secondary amine catalysts were unsuccessful,[33]

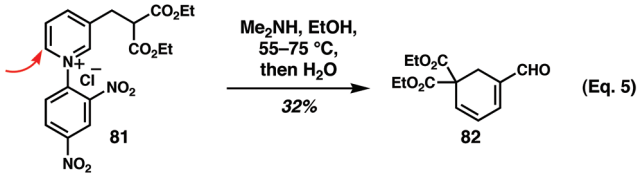

dx.doi.org/10.1021/jo201625e |J. Org. Chem. 2011, 76, 9555–9567

**Scheme 8. Synthesis of Pyrroline 78 via Presumed Zincke-Type Ring-Opening/Ring-Closing Cascade**



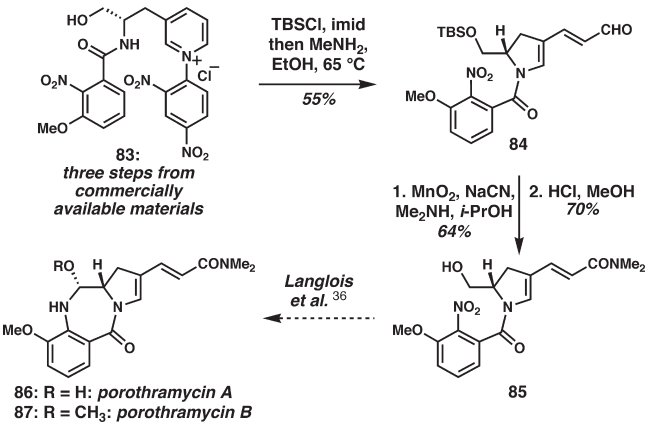

and some related work suggested that such reactivity is only workable with a strongly electron-withdrawing group on the indole nitrogen.[34]

We sought to extend the range of tethered nucleophiles away from anilines. Naturally, primary or secondary amines would react with activating reagents in preference to the pyridine nitrogen, and this supposition was rapidly borne out in simple experiments with amine **75** using both cyanogen bromide and chlorodinitrobenzene. Attenuation of nucleophilicity by amide formation appeared logical, and the benzamide of 3-(2-ethylamino)pyridine **76** was chosen because it would also serve as a model system for an eventual synthesis of the anthramycin/porothramycin family of antitumor antibiotics (Scheme 8). Treatment of the amide with cyanogen bromide under the conditions that were successful for indole formation did not cause any transformation of the starting material; presumably *N*-cyanation of the pyridine is reversible, and the amide is simply not nucleophilic enough to induce ring-opening. Activation with chlorodinitrobenzene led smoothly to pyridinium salt **77**, but the amide again proved unreactive. Reasoning that ring-opening should occur smoothly under Zincke conditions and that the corresponding doubly vinylogous amidinium ion might be more electrophilic toward the tethered amide, we treated **77** with an excess of dimethylamine. The desired *N*-benzoyldihydropyrrole **78** was obtained in 57% yield over two steps, presumably by a tandem Zincke-type ring-opening/ring-closure sequence via intermediates **79** and **80**.[31] Surprisingly, this reaction was not easily generalized to other ring sizes or to carbamate or sulfonamide nucleophiles, which was disappointing. Some success has been realized in the use of tethered soft-carbon nucleophiles. In one unoptimized reaction (eq 5), it is apparent that the ring-opening/ring-closing sequence enables access to products that would not be available if the mechanism were to be a simple ring-opening process triggered by the tethered nucleophile; the cyclohexadiene that results is formally the product of ring-opening induced by the geometrically impossible attack of the nucleophilic carbon at C6 of the pyridinium salt (see arrow).[35]




While further work to uncover the true scope of these rearrangement reactions is warranted, the success of the reaction

**Scheme 9. Formal Synthesis of the Porothramycin Using a Zincke Pyridinium Ring-Opening/Ring-Closing Cascade as a Key Step**



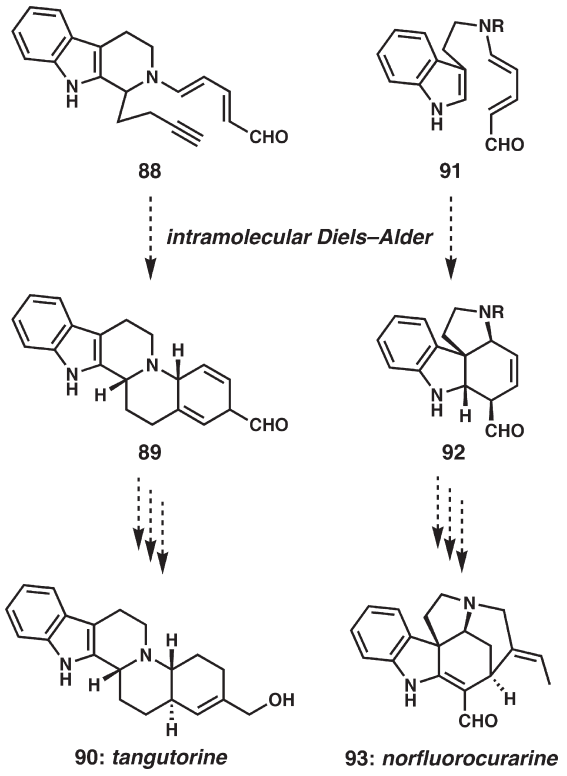

with benzamide **76** spurred on studies directed at porothramycins A and B, members of the anthramycin class of antitumor antibiotics. With some optimization, the more complex pyridinium salt **83** (Scheme 9), readily available in three steps from commercially available materials, was subjected to a one-pot hydroxyl silylation/rearrangement reaction to deliver **84**. Rearrangement reactions of the pyridinium salt bearing the free alcohol were low-yielding and capricious, which was unexpected given that the reactions generally proceed in alcoholic solvents; clearly, some intramolecular destructive pathway was interfering with the reaction. The dihydropyrrole core of the porothramycins was elaborated to amide **85**, which was a key intermediate in Langlois's synthesis of the natural products porothramycins A and B,[36] thus completing a formal synthesis. This route proved substantially shorter than the two previous syntheses,[36,37] which also began from the chiral pool, but from natural amino acid precursors. In our case, beginning from the somewhat more costly unnatural amino acid (*S*)-3-pyridylalanine enabled a nonobvious rearrangement that ultimately defined a concise route to the porothramycins.[38]

## IV. ATTEMPTED INTRAMOLECULAR DIELS–ALDER REACTION OF ZINCKE ALDEHYDES UNCOVERS AN UNUSUAL PERICYCLIC CASCADE REARRANGEMENT

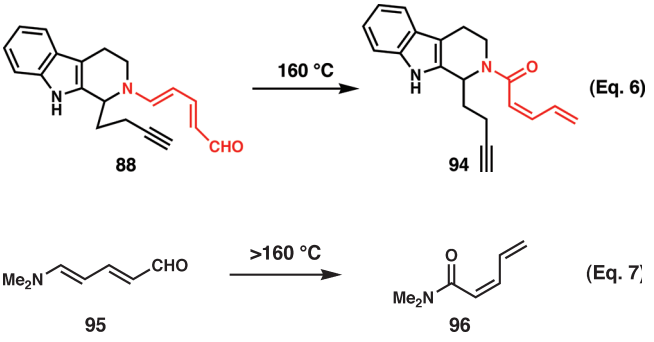
Several opportunities for the rapid assembly of complex alkaloid scaffolds presented themselves when the idea of intramolecular Diels–Alder cycloadditions of Zincke aldehydes was considered. For example, cycloaddition might rapidly convert Zincke aldehyde **88** (Scheme 10), obtained by simple Pictet–Spengler reaction and subsequent pyridine ring-opening, into the relatively complex pentacyclic architecture (**89**) of the indole alkaloid tangutorine (**90**). Second, a tryptamine-derived Zincke aldehyde could prove a direct precursor to the tetracyclic core of many indole monoterpene alkaloids (see **91** → **92**) including the *Strychnos* alkaloid norfluorocurarine (**93**), if only the donor–acceptor diene would engage the relatively unreactive C2–C3 double bond of indole. Given the well-known tendency of even poorly activated diene/dienophile pairs to participate in *intra*molecular Diels–Alder reactions as a result of the substantially decreased entropy of activation, one of the first reactions that we studied involved heating of alkyne **88**. No reactivity was observed below ~150 °C; however, at elevated temperatures, clean conversion occurred to a product displaying more alkene proton


dx.doi.org/10.1021/jo201625e |*J. Org. Chem.* 2011, 76, 9555–9567

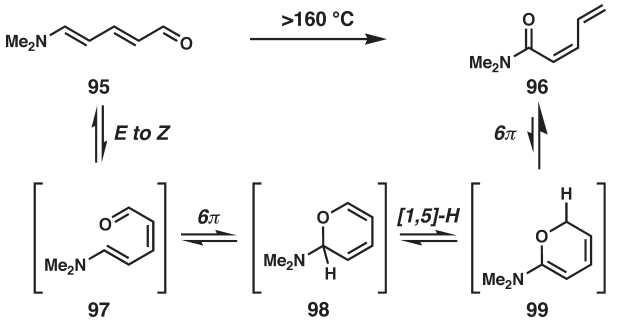
**Scheme 10. Possible Utility of the Intramolecular Diels–Alder Cycloaddition Reactions of Zincke Aldehydes for the Rapid Construction of the Polycyclic Cores of Complex Alkaloids**



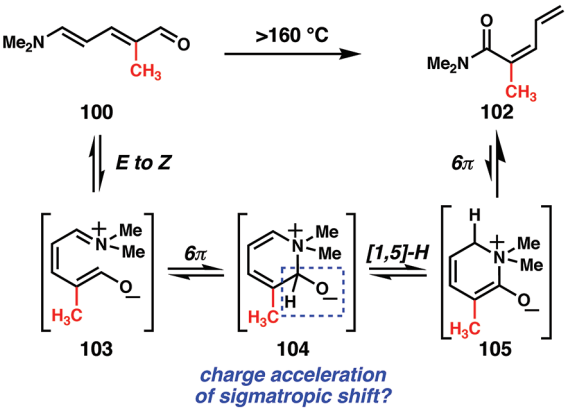

NMR signals than the starting material, clearly not the hallmark of a successful cycloaddition. Deduction of the structure of the product as *Z*-α,β,γ,δ-unsaturated amide **94** (eq 6) led us to heat simple dimethylamine-derived Zincke aldehyde **95**, which provided the same outcome (eq 7).[39] Shortly thereafter, the same reaction was seen with tryptamine-derived Zincke aldehyde **91** (Scheme 10), in spite of the fact that, in that case, the polarity of prospective diene and dienophile appeared well-suited to an asynchronous cycloaddition reaction. This result served to remind us that the C2–C3 double bonds of indoles are notoriously poor dienophiles; similarly, we learned that the donor–acceptor properties of the Zincke aldehydes apparently did not favor cycloaddition reactions.[40] In fact, this type of thermal rearrangement behavior was found to be general among Zincke aldehydes regardless of the substitution on nitrogen or on C2/C3, the only substitution patterns that are readily available from the Zincke ring-opening procedure (for the scope of the rearrangement, see ref 39).




**Scheme 11. Possible Mechanism To Account for Thermal Rearrangement of Zincke Aldehyde 95 to Unsaturated Amide 96**




**Scheme 12. Possible Mechanism That Accounts for Observed Regioselectivity in the Thermal Behavior of Zincke Aldehydes**

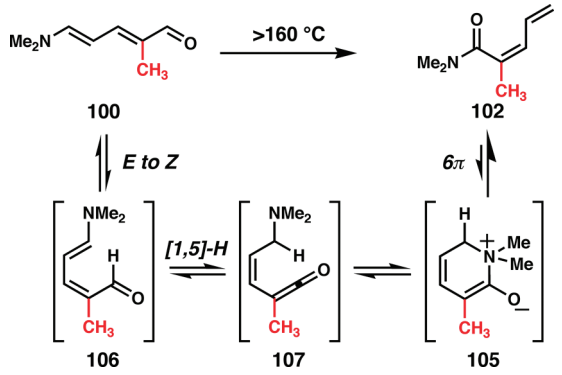



The outcome of these internal redox processes could be accounted for by invoking a thermal *E* to *Z* double bond isomerization (a reaction that should be relatively facile, given the relatively weak nature of the Zincke aldehyde π-bonds), a 6-π electrocyclization to generate a pyran (**98**, Scheme 11), a [1,5]-sigmatropic shift of hydrogen to afford isomeric pyran **99**, and a final 6-π electrocyclic ring-opening to afford product. This mechanism neatly accomplishes the transposition of the carbonyl oxygen from one terminus of the molecule to the other, and the postulated cyclic intermediates accounted for the formation of the *Z*-configured diene product.

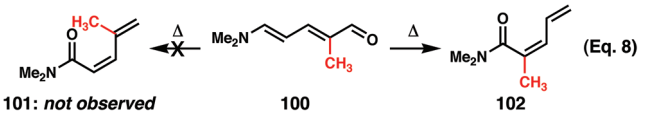
Investigation of the scope of the rearrangement rapidly precluded our original mechanistic postulate: 2-methyl-substituted Zincke aldehyde **100** (generated from 3-picoline) did not provide **101** but rather yielded only **102** with the methyl group still positioned adjacent to the carbonyl carbon (eq 8). This result suggested the possibility of an analogous mechanism involving transposition of the amino group, rather than the oxygen, as shown in Scheme 12. In this case, alkene isomerization would enable formation of dihydropyridinium zwitterion **104** by attack of the amine nitrogen onto the carbonyl carbon (also can be formulated by an electrocyclic ring closure of zwitterionic resonance structure **103**, as shown). Sigmatropic shift of hydrogen would afford isomeric heterocycle **105** that could ring open to the product via an electrocyclic process. Later experiments described below would lend strong support for the intermediacy of zwitterionic dienolate intermediate **105** (see below). If this mechanism were to be operative, the


dx.doi.org/10.1021/jo201625e |*J. Org. Chem.* 2011, 76, 9555–9567

**Scheme 13. Mechanism for Zincke Aldehyde Rearrangement That Is Preferred on the Basis of Calculation and Experiment**




preference for this mode of rearrangement over that shown in Scheme 11 could be explained by the possible lowering of the activation barrier for sigmatropic shift owing to weakening of the C−H bond by the adjacent alkoxide (similar to the dramatic effect in the anionic oxy-Cope rearrangement, for example).[41]




While this nitrogen transposition mechanism accounted for all of our observations, there remained the very reasonable possibility that the [1,5]-sigmatropic shift of hydrogen might precede ring closure (Scheme 13); indeed, the insight and computational experiments that arose from fruitful collaboration with the Houk group at UCLA strongly militate for this mechanism over any mechanism involving the sigmatropic shift occurring in cyclic contexts.[42] Computed barriers for the 1,5-sigmatropic H-shift in the transformation of **95** to **96** in our original oxygen transposition mechanism (Scheme 11) were over 45 kcal/mol, likely reflecting the strain associated with the requisite bicyclic transition state, clearly disfavoring this pathway. For the nitrogen transposition mechanism shown in Scheme 12, no minimum could be found for the initial ring-closed zwitterionic product (**104**); optimization always led to the ring-opened product. Finally, the barrier to sigmatropic shift in 2-*Z* Zincke aldehyde **106** (Scheme 13) was computed to be on the order of 31 kcal/mol, a reasonable barrier for a reaction that required ≥150 °C to proceed. The resulting amine-bearing vinylketene **107** appears to ring close to the zwitterionic dienolate **105** with essentially no barrier, and ring-opening by an electrocyclic process also appears feasible. Other features of the reaction, including the effects of substituents on the rates of rearrangement, were very well predicted by computation.[42,43] Prior to this revelation, we had noticed the possible equilibrium between the cyclic zwitterionic dienolate and a ring-opened aminoketene and had been considering adapting other well-known methods for vinylketene synthesis to offer another entry into this cascade to generate stereodefined dienes.

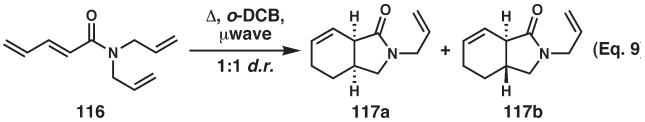
The improved understanding of the energetics of the rearrangement reaction has spurred on our deliberate development of new pericyclic cascades of appropriately substituted Zincke aldehydes. The accidental discovery of this thermal pericyclic cascade has led to a long-term interest in developing new reaction cascades for the stereoselective synthesis of substituted alkenes, and we are eager to apply these methods to the synthesis of bioactive polyene natural products.

## V. A SIMPLE MECHANISTIC PROBE OF THE REARRANGEMENT LEADS TO A GENERAL SYNTHESIS OF POLYCYCLIC LACTAMS

Even prior to our realization that a ketene-based mechanism was most likely responsible for the rearrangement, we devised a simple experiment to validate the proposed intermediacy of penultimate zwitterionic dienolates of type **105** (Schemes 12 and 13). Zincke aldehyde **108** (Scheme 14) was synthesized from diallylamine and 3-picoline. The *N*-allyl groups were expected to set up a competition between the terminal electrocyclic ring-opening reaction of the rearrangement and a potential [3,3]-sigmatropic rearrangement that would proceed with charge neutralization to afford dihydropyridones of types **110** or **111**, depending on whether a further Cope rearrangement took place to generate the conjugated lactam. Sure enough, heating of **108** to 200 °C resulted in the formation of conjugated lactam **111** in 15% yield, providing strong support for the intermediacy of zwitterionic dienolates of type **105**/**109**. We were more excited to see that much of the mass balance in these reactions was found in the form of bicyclic lactam **113**, which appeared to arise from the usual rearrangement reaction to afford the α,β,γ,δ-unsaturated amide **112** followed by an unexpected intramolecular Diels−Alder reaction wherein the newly formed diene engaged the pendant unactivated alkene.

We were pleased that this reaction was general. Polycyclic lactam products were isolated in all cases when Zincke aldehydes derived from allylic or homoallylic amines were heated, and substituents at the six positions that were easily manipulated were tolerated (Figure 1). Good to complete selectivity for the rearrangement/Diels−Alder product was observed in most cases, and the cycloaddition reaction was highly diastereoselective for the cis ring junction in nearly every case. A fascinating array of different scaffolds of potential utility for medicinal chemistry are generated in only two steps from pyridinium salts and unsaturated secondary amines via this cascade reaction involving *E* to *Z* alkene isomerization, [1,5]-sigmatropic shift of hydrogen, intramolecular ketene capture, 6-π electrocyclic ring-opening, and intramolecular Diels−Alder cycloaddition.[44]

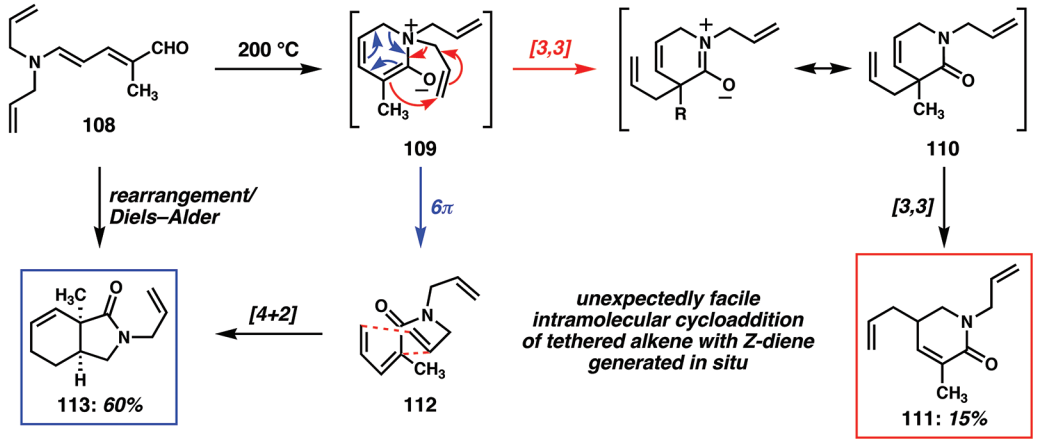
Control cycloaddition experiments using *E*-diene **116** (eq 9), made by simple amine acylation, yielded an equimolar mixture of diastereomeric products **117a** and **117b**; therefore, there is a clear advantage in terms of stereocontrol gained by the in situ formation of the *Z*-dienes by the thermal rearrangement cascade (although not shown, cis-diastereomer **117a** is formed exclusively from the Zincke aldehyde precursor, in analogy to the formation of **113** in Scheme 14). Moreover, the ability to take Zincke aldehydes derived from readily available substituted pyridines and convert them in situ to more complex dienes with control of alkene geometry is of great value. Both of these characteristics of this cascade reaction afford it significant potential utility for applications in alkaloid synthesis. For example, thermal pericyclic rearrangement of a suitably functionalized Zincke aldehyde such as **118** (eq 10) should provide bicyclic





dx.doi.org/10.1021/jo201625e |J. Org. Chem. 2011, 76, 9555–9567

**Scheme 14. Unexpected Formation of Bicyclic Lactams in the Course of a Simple Mechanistic Probe of the Zincke Aldehyde Rearrangement Reaction**



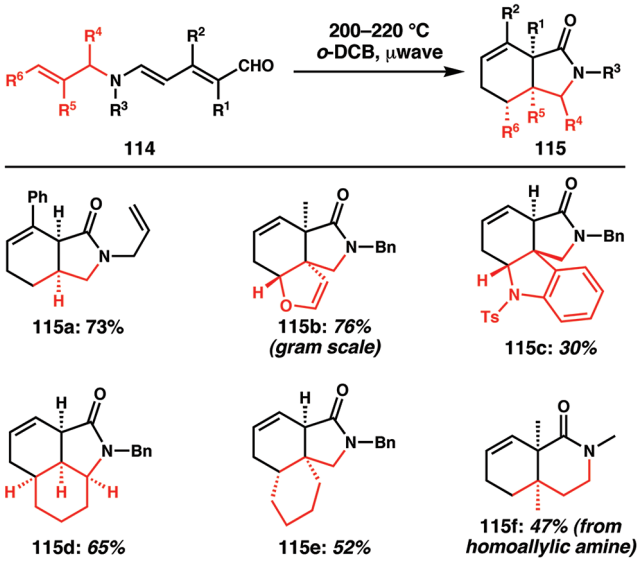
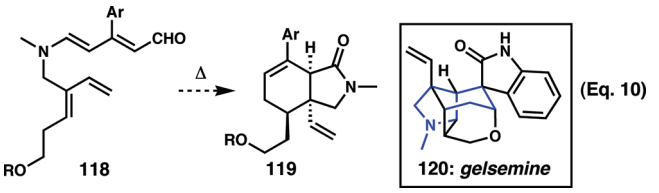




**Figure 1.** Examples of polycyclic lactams generated by the pericyclic cascade reactions of Zincke aldehydes derived from unsaturated amines.

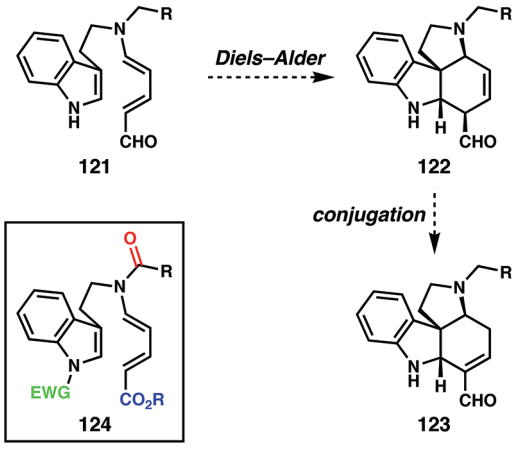
product **119** that is well functionalized for elaboration toward the complex, polycyclic spirooxindole alkaloid gelsemine[45] (**120**, the cis-fused azabicyclo[4.3.0]nonane is highlighted). Efforts to reduce such a general plan to practice are ongoing in our group.




## VI. A SUCCESSFUL INTRAMOLECULAR CYCLOADDITION REACTION OF ZINCKE ALDEHYDES ENABLES CONCISE SYNTHESES OF INDOLE ALKALOIDS

The initial frustration of the failed thermal intramolecular Diels–Alder reaction of Zincke aldehydes inadvertently led to some very interesting, and perhaps broadly useful, reactivity of these donor–acceptor dienes. Nonetheless, the potential power of the Zincke aldehyde cycloadditions (**121** → **122** → **123**, Scheme 15) for the synthesis of complex indole alkaloids required that we find a solution to the problem of kinetically low reactivity of the donor–acceptor diene with the indole double bond. There was good reason to suspect that changes to the substrate would provide a favorable outcome (see **124**), for example: (1) changing the aldehyde to the corresponding ester precluded thermal rearrangement of the donor–acceptor diene in simple cases and might enable cycloaddition to be successful; (2) placement of an electron-withdrawing group on the indole nitrogen would engender greater stability of this heterocycle toward Lewis acid or protic acid initiation of cycloaddition; (3) incorporation of an electron-withdrawing group on the Zincke aldehyde nitrogen would attenuate the donor–acceptor stabilization of the diene, favoring cycloaddition. None of these options or other related substrate modifications were deemed attractive, because the aldehyde oxidation state was the most versatile for accessing a variety of different indole monoterpene alkaloids, and we wished to avoid protecting groups on either nitrogen of the

**Scheme 15. Proposed Cycloaddition Reaction of Tryptamine-Derived Zincke Aldehydes, and Potential Electronic Perturbations to the Substrate**

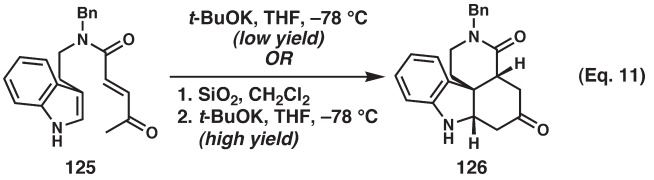




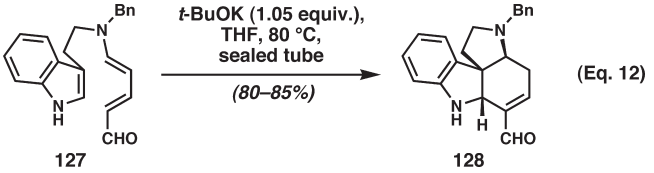
dx.doi.org/10.1021/jo201625e |J. Org. Chem. 2011, 76, 9555–9567

substrate, if at all possible. In some instances, concession to use a single protecting group on the aliphatic nitrogen atom proved necessary for success (see below).

We resigned ourselves to inducing substrates of type **121** to engage in a formal [4 + 2] cycloaddition reaction by any means available. An extensive survey of protic and Lewis acids was conducted in the hope of effecting the desired transformation in a stepwise fashion. Under the milder conditions examined, no reactivity was observed, and not surprisingly, under more forcing conditions, the acid-sensitive indole ring was degraded; however, we did see some tentative evidence for Pictet–Spengler-type reactivity with some acids,[46] which has since led us in other directions toward different classes of indole monoterpene alkaloids. Attempted catalysis by aminium radicals, which might have effected bicyclization via radical cation intermediates,[47] was not productive. Finally, we recognized that deprotonation of the indole nitrogen could lead to the desired tetracycle via a sequence of intramolecular 1,6-addition of C3 of the metalated indole to the Zincke aldehyde, followed by a terminal Mannich-type ring closure. Related bicyclization reactions were known in the work of Markó (see **125** → **126**, eq 11).[48] After a few experiments, we found that very similar conditions to this previous work, albeit with substantial thermal assistance, provided the desired formal Diels–Alder product in reasonable yield, with the $\alpha,\beta$-unsaturated aldehyde arising under the basic conditions (see **127** → **128**, eq 12). After a great deal of experimentation, we concluded that (1) only potassium bases were competent (KO-*t*-Bu was the best); (2) THF was the preferred solvent; and (3) a reaction temperature of 80 °C, necessitating a sealed tube for THF, was ideal for promoting clean reactivity. For the model system derived from $N_b$-benzyltryptamine, the cycloaddition could be routinely achieved in yields from 80 to 85%.



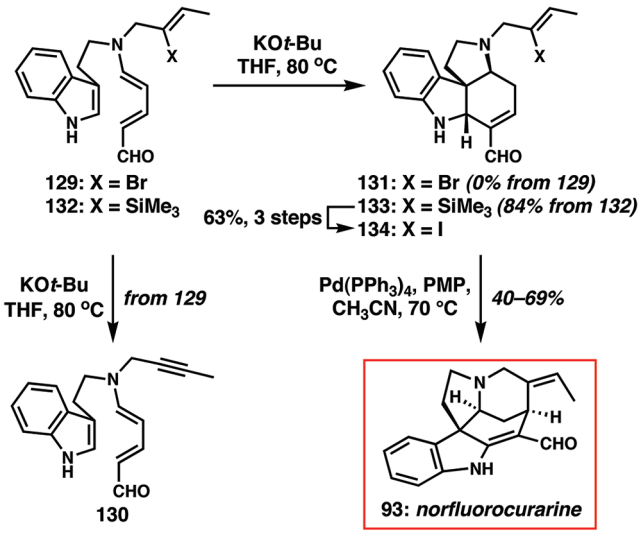

(Eq. 11)




(Eq. 12)

We quickly recognized that some of the simpler members of the *Strychnos* family of alkaloids should be readily within our grasp; formal cycloaddition of a Zincke aldehyde bearing a vinyl halide appendage would enable a terminal Heck cyclization that would directly afford norfluorocurarine (Scheme 16). Of course, the conditions that we had identified for the cycloaddition were likely also suitable for effecting E2 dehydrohalogenation; indeed, exposure of substrate **129** to a variety of potassium bases provided the corresponding alkyne-bearing Zincke aldehyde (**130**) as the only identifiable product; no cycloadduct **131** was ever observed. We presume that much of the mass balance of the reaction consisted of products from elimination to an intermediate allenamine that would have several pathways for decomposition. In view of the seemingly narrow window of conditions for successful bicyclization, it was clear that substrate modification was required. A logical surrogate for the sensitive vinyl halide was vinylsilane **132**, which was easily prepared in four steps from

**Scheme 16. Synthesis of Norfluorocurarine via Zincke Aldehyde Formal Cycloaddition and Intramolecular Heck Reaction**

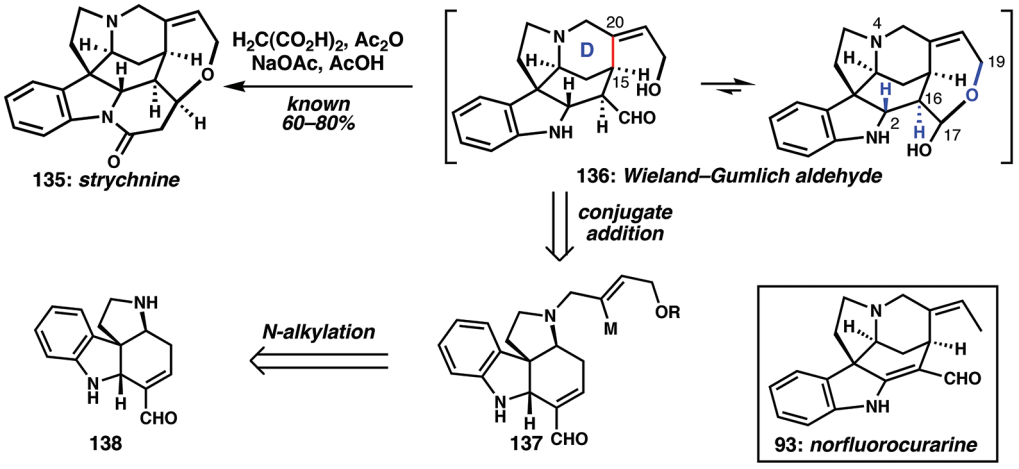



1-(trimethylsilyl)propyne. As expected, the vinylsilane survived the relatively harsh conditions, and product **133** was isolated in 84% yield. To set up for the planned Heck cyclization, only a halodesilylation reaction was required; however, the electron-rich aromatic ring of the indoline provided substantial complications. Although conditions to effect a low-yielding (<20%) single-step iododesilylation reaction were uncovered, a three-step sequence involving temporary *N*-trifluoroacetylation of the indoline enabled access to vinyl iodide **134** in a more reasonable overall yield. Finally, Heck cyclization provided (±)-norfluorocurarine (**93**), completing the first demonstration of the utility of our formal intramolecular cycloaddition reaction of Zincke aldehydes in alkaloid synthesis.[49] This synthesis was accomplished in only seven steps from tryptamine and nine steps from 1-trimethylsilylpropyne. Optimization of this synthesis is ongoing, with the groundwork now in place for a high-yielding synthesis that is only five steps from commercially available materials.

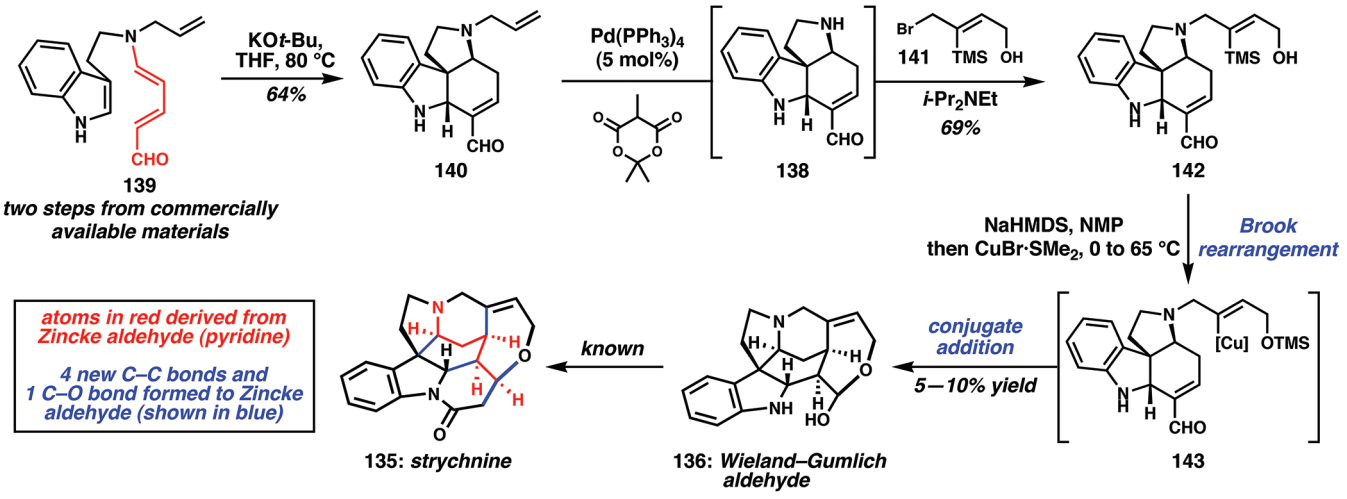
The formal cycloaddition reaction of Zincke aldehydes appeared ideally suited to a synthesis of strychnine (**135**, Scheme 17), the flagship member of the *Strychnos* alkaloids. Indeed, the difference between norfluorocurarine and the Wieland–Gumlich aldehyde (**136**), a well-known direct synthetic progenitor to strychnine, is only a C19 hydroxyl group and a saturated C2–C16 bond. We therefore anticipated a relatively rapid extension of our strategy to a short synthesis of this target, which has become a benchmark for the state-of-the-art in alkaloid synthesis. Certainly, the availability of C17 at the aldehyde oxidation state, a virtue that contributed to the brevity of our norfluorocurarine synthesis, would avoid undesired redox manipulations en route to the Wieland–Gumlich aldehyde. We simply needed to elaborate a tetracycle with an appropriate hydroxyl group-bearing N4 side chain that would permit a conjugate addition between C20 and C15 to forge the D ring (see **137** → **136**, and contrast with the Heck reaction for norfluorocurarine that generates a C2–C16 alkene). Because of the previously described intolerance of the harshly basic conditions for bicyclization toward reactive functional groups (which, after further investigations, included vinyl halides, alkynes, and free hydroxyl groups), we focused on accessing tetracyclic core **138** that bears a free secondary amine at N4 for subsequent functionalization via N-alkylation.


dx.doi.org/10.1021/jo201625e |*J. Org. Chem.* 2011, 76, 9555–9567

**Scheme 17. Wieland−Gumlich Aldehyde Is the Penultimate Target en Route to Strychnine and Shares Many Structural Features with Norfluorocurarine**




**Scheme 18. Six-Step (Linear) Synthesis of Strychnine**




These plans were eventually reduced to practice as shown in Scheme 18. After much experimentation, we found that the allyl group served optimally to protect N4 because it survived the harsh cycloaddition conditions that converted Zincke aldehyde **139** to tetracycle **140** and could be removed using a modification of the Pd(0)-catalyzed conditions developed by Guibé and co-workers.[50] The key variation was the use of methyl Meldrum's acid as the pronucleophile/allyl scavenger; use of the usual active methylene compounds, such as *N*,*N*′-dimethylbarbituric acid or Meldrum's acid, led to undesired Knoevenagel condensation on the C17 aldehyde followed by Michael addition. Using this protocol, the deallylation reaction proceeded without complications to afford key intermediate **138**, which demonstrated some stability issues upon isolation and storage. The presence of two nucleophilic nitrogens and two electrophilic carbons within this compound appear to conspire against handling of this compound without decomposition. Fortunately, it did not prove necessary to isolate this intermediate; rather, allylic bromide electrophile **141** (available in gram scale in three steps from commercially available materials) could be introduced to the deallylation reaction mixture, enabling a one-pot deallylation/alkylation sequence that proceeded in good yield. In the key D-ring-forming step, treatment of **142** with strong base presumably generated a sodium alkoxide that should participate in a Brook equilibrium with the proximal vinylsilane. Transmetalation to copper (see **143**) appears to precede conjugate addition to the $\alpha,\beta$-unsaturated aldehyde, delivering the Wieland−Gumlich aldehyde (**136**). The yield of this transformation was never improved above ca. 10%; nonetheless, this successful route serves as a strategic advance, cutting in half the length of previous syntheses of this classic target (a six step longest linear sequence).[51] In only four reaction vessels, four new C−C bonds and one new C−O bond were formed to the Zincke aldehyde, resulting in complete saturation of the all $sp^2$-hybridized system. Moreover, five of strychnine's seven rings and all six of its stereogenic centers were formed in these four steps. This work clearly demonstrates the enormous potential utility of Zincke aldehydes specifically, and donor−acceptor dienes more generally, for the rapid buildup of structural complexity.


dx.doi.org/10.1021/jo201625e |*J. Org. Chem.* 2011, 76, 9555–9567

## VI. CONCLUSIONS AND OUTLOOK

This stimulating research program arose serendipitously out of the need for a simple starting material in the course of an unrelated endeavor in complex natural product synthesis. In that regard, the lessons learned from our forays into Zincke chemistry demonstrate the importance of natural product synthesis as a stimulant for discovery of new and broadly useful reactivity; sometimes this reactivity is designed, and sometimes it is found by chance. Furthermore, the adoption of a research project that focused on small molecules with the potential for myriad modes of reactivity provided a wealth of unexpected, potentially valuable chemistry. In this case, the interesting science that was found serendipitously roughly equaled the output of the chemistry that had been rationally planned. Finally, this research program highlights the benefits of manipulating simple, readily available starting materials to quickly access high-value-added compounds and suggests that there might be many as yet undiscovered ways of manipulating heteroaromatic and aromatic compounds other than those discussed herein.

## AUTHOR INFORMATION

**Corresponding Author**
*E-mail: cdv@uci.edu.

## BIOGRAPHY

Chris Vanderwal received B.Sc. (Biochemistry) and M.Sc. (Chemistry) degrees from the University of Ottawa. He earned his Ph.D. from the Scripps Research Institute in 2003 based on his work on FR182877, a covalent binder of tubulin, with Prof. Erik Sorensen. After postdoctoral work with Prof. Eric Jacobsen at Harvard, Chris joined UC Irvine in 2005, where he is currently an Associate Professor of Chemistry. His group focuses on complex molecule synthesis, targeting polychlorinated natural products, alkaloids, and terpenes.

## ACKNOWLEDGMENT

I thank the University of California, Irvine, the American Chemical Society's Petroleum Research Fund, the American Cancer Society (Institutional Research Grant—Seed Grant to C.D.V.), and the NSF (CAREER award CHE-0847061 to C.D.V.) for funding the research described in this Perspective. Graduate fellowships from the NSERC of Canada, Bristol-Myers Squibb, Eli Lilly, Eastman Chemical, the California TRDRP, and UC Irvine are gratefully acknowledged. C.D.V. is a fellow of the A. P. Sloan Foundation, the recipient of an Amgen Young Investigator Award and an AstraZeneca Excellence in Chemistry Award, and a Lilly Grantee. I gratefully acknowledge Professor Ken Houk and his group for a wonderful continuing collaboration on this project. I thank Professors Erik Sorensen and Larry Overman for their valued mentoring and encouragement. Finally, and most importantly, the efforts of all of the Vanderwal group members who tirelessly performed all of the work described in this Perspective are tremendously appreciated.

## REFERENCES

(1) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867–889.

(2) (a) Shea, K. M. Furans. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, 2005; pp 168−181. (b) Joule, J. A.; Mills, K. Furans: Reactions and Synthesis. *Heterocyclic Chemistry*, 4th ed.; Blackwell Publishing: Oxford, 2000; pp 308−309. (c) For a comprehensive review of furan synthesis methods, including the Paal−Knorr method, see: König, B. *Sci. Synth.* **2002**, *9*, 183–285.

(3) (a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1966**, *31*, 977–978. (b) Crombie, L.; Hemesley, P.; Pattenden, G. *J. Chem. Soc. C* **1969**, 1024–1027.

(4) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011–2018.

(5) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185–5188.

(6) For excellent recent extensions of Piancatelli reactivity to inter- and intramolecular amination reactions, see: (a) Veits, G. K.; Wenz, D. R.; Read de Alaniz, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9484–9487. (b) Palmer, L. I.; Read de Alaniz, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7167–7170.

(7) Piancatelli, G.; Scettri, A. *Tetrahedron Lett.* **1977**, *18*, 1131–1134.

(8) Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857–865.

(9) Achmatowicz, O., Jr.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973–1996.

(10) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588–5593.

(11) Lewis, K. G.; Mulquiney, C. E. *Tetrahedron* **1977**, *33*, 463–475.

(12) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2007**, 3759–3761.

(13) For another interesting connection between furans and 5-amino-2,4-pentadienals, which are the subject of this Perspective, see: Ouairy, C.; Michel, P.; Delpech, B.; Crich, D.; Marazano, C. *J. Org. Chem.* **2010**, *75*, 4311–4314.

(14) Although not directly relevant to this Perspective, the pyridinium salt photochemistry first discovered by Kaplan and developed extensively by Mariano and co-workers is a remarkable example of the conversion of readily available pyridines into complex, nonaromatic products. See: (a) Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283–3284. (b) Zou, J.; Mariano, P. S. *Photochem. Photobiol. Sci.* **2008**, *7*, 393–404.

(15) Shaw originally disclosed this reductive strategy to obtain 1,5-dicarbonyl compounds (as their bis-oximes) from pyridines: (a) Shaw, B. D. *J. Chem. Soc.* **1925**, 215–216. (b) Shaw, B. D. *J. Chem. Soc.* **1937**, 300–302.

(16) Birch pioneered the combined alkali metal reduction/hydrolysis/aldol cyclization approach to cyclohexenones: Birch, A. J. *J. Chem. Soc.* **1947**, 1270.

(17) (a) Danishefsky, S.; Cavanaugh, R. *J. Am. Chem. Soc.* **1968**, *90*, 520–521. (b) Danishefsky, S.; Cain, P. *J. Org. Chem.* **1975**, *40*, 3606–3608. (c) Danishefsky, S.; Cain, P. *J. Steroid Biochem.* **1975**, *6*, 177–181. (d) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1975**, *97*, 5282–5284. (e) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975–4983.

(18) (a) Zincke, T. *Liebigs Ann. Chem.* **1904**, *330*, 361–374. (b) Zincke, T.; Heuser, G.; Möller, W. *Liebigs Ann. Chem.* **1904**,

333, 296–345. (c) Zincke, T.; Wurker, W. *Liebigs Ann. Chem.* **1905**, *338*, 107–141.

(19) For reviews, see: (a) Becher, J. *Synthesis* **1980**, 589–612. (b) Becher, J.; Finsen, L.; Winckelmann, I. *Tetrahedron* **1981**, *37*, 2375–2378. (c) Cheng, W.-C.; Kurth, M. J. *Org. Prep. Proced. Int.* **2002**, *34*, 587–608.

(20) For select examples, see: (a) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596–9598. (b) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729–733. (c) Barbier, D.; Marazano, C.; Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1998**, *63*, 1767–1772. (d) Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528–4532. (e) Youte, J.-J.; Barbier, D.; Al-Mourabit, A.; Gnecco, D.; Marazano, C. *J. Org. Chem.* **2004**, *69*, 2737–2740.

(21) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026–8034. (b) Michelliza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 6474–6478.

(22) Other methods are known to effect ring opening of pyridines. The König method features activation of the pyridine with cyanogen bromide and aminolysis of the in situ formed pyridinium salt with anilines: (a) König, W. *J. Prakt. Chem.* **1904**, *69*, 105–137. The Baumgarten method begins with sulfur trioxide complexes of pyridines, which are ring opened by hydroxide to give the corresponding glutaconaldehyde anion, a molecule that can be functionalized and engaged in rich chemistry: (b) Baumgarten, P. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1622–1627. (c) Baumgarten, P. *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 1166–1171. (d) Becher, J. *Org. Synth.* **1980**, *59*, 79–84. For a brief discussion of other methods, including with pyridine *N*-oxide derivatives, see ref 19a.

(23) For a review, see: Mishra, A.; Behera, R. K.; Behera, P. K.; Mishra, B. K.; Behera, G. B. *Chem. Rev.* **2000**, *100*, 1973–2011.

(24) Ziegler, K.; Hafner, K. *Angew. Chem.* **1955**, *67*, 301.

(25) Köbrich, G.; Breckoff, W. E.; Drischel, W. *Liebigs Ann. Chem.* **1967**, *704*, 51–69.

(26) (a) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Al-Mourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381–7387. (b) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890–1897. (c) Wypych, J.-C.; Nguyen, T. M.; Nuhant, P.; Benechie, M.; Marazano, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 5418–5421. (d) Sinigaglia, I.; Nguyen, T. M.; Wypych, J.-C.; Delpech, B.; Marazano, C. *Chem.—Eur. J.* **2010**, *16*, 3594–3597.

(27) For other work by the group of Marazano involving aminopentadienals related to Zincke aldehydes, see: (a) Sanchez-Salvatori, M.; Lopez-Giral, A.; Ben Abdeljelil, K.; Marazano, C. *Tetrahedron Lett.* **2006**, *47*, 5503–5506. (b) Nguyen, T. M.; Sanchez-Salvatori, M.; Wypych, J.-C.; Marazano, C. *J. Org. Chem.* **2007**, *72*, 5916–5919. (c) Wypych, J.-C.; Nguyen, T. M.; Benechie, M.; Marazano, C. *J. Org. Chem.* **2008**, *73*, 1168–1172. (d) Nuhant, P.; Raikar, S. B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, *74*, 9413–9421. (e) Nguyen, T. M.; Peixoto, S.; Ouairy, C.; Nguyen, T. D.; Benechie, M.; Marazano, C.; Michel, P. *Synthesis* **2010**, 103–109. (f) Peixoto, S.; Nguyen, T. M.; Crich, D.; Delpech, B.; Marazano, C. *Org. Lett.* **2010**, *12*, 4760–4763.

(28) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393–5407.

(29) Spangler, C. W.; McCoy, R. K.; Karavakis, A. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1203–1207.

(30) See the Supporting Information of ref 28 for details.

(31) Kearney, A. M.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7803–7806.

(32) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230–7233.

(33) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79–87.

(34) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120–14125.

(35) Michels, T. D.; Vanderwal, C. D. Unpublished results.

(36) Langlois, N.; Favre, F.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 4635–4638.

(37) Fukuyama, T.; Liu, G.; Linton, S. D.; Lin, S. C.; Nishino, H. *Tetrahedron Lett.* **1993**, *34*, 2577–2580.

(38) Michels, T. D.; Kier, M. J.; Kearney, A. M.; Vanderwal, C. D. *Org. Lett.* **2010**, *12*, 3093–3095.

(39) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561.

(40) Zincke aldehydes are known to be recalcitrant dienes in *intermolecular* cycloadditions: Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem.—Eur. J.* **1999**, *5*, 3154–3161 and references therein.

(41) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.

(42) Paton, R. S.; Steinhardt, S. E.; Vanderwal, C. D.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 3895–3905.

(43) For the most closely related rearrangement that we have found in the literature, see: Roedig, A.; Göpfert, H. *Chem. Ber.* **1981**, *114*, 3625–3633. This thermal rearrangement of an unusual tetrachlorinated doubly vinylogous thioester to the corresponding $\alpha,\beta,\gamma,\delta$-unsaturated thioester was proposed to proceed via pyran intermediates and a [1,5]-Cl shift, which was also supported by our collaboration with the Houk group. See ref 42 for details.

(44) Steinhardt, S. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7546–7547.

(45) For a review, see: Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36–51.

(46) This type of reactivity of related 5-amino-2,4-pentadienals has been nicely capitalized upon by Nuhant, Delpech, and co-workers (Marazano research group). See ref 27d for details.

(47) Bauld, N. L. *Tetrahedron* **1989**, *45*, 5307–5363.

(48) (a) Markó, I. E.; Southern, J. M.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657–4660. (b) Turet, L.; Markó, I. E.; Tinant, B.; Declercq, J.-P.; Touillaux, R. *Tetrahedron Lett.* **2002**, *43*, 6591–6595. (c) Heureux, N.; Wouters, J.; Markó, I. E. *Org. Lett.* **2005**, *7*, 5245–5248.

(49) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.

(50) Garro-Helion, F.; Merzouk., A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109–6113.

(51) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649–651.