Alkaloid Synthesis

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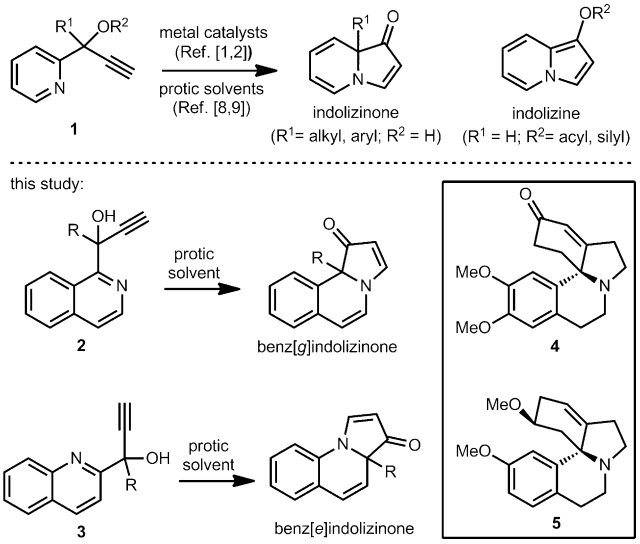
Protic-Solvent-Mediated Cycloisomerization of Quinoline and Isoquinoline Propargylic Alcohols: Syntheses of (±)-3-Demethoxyerythratidinone and (±)-Cocculidine**

*Stephen T. Heller, Toshihiro Kiho, Alison R. H. Narayan, and Richmond Sarpong**

Novel nitrogen-containing rings (azacycles) are particularly valuable in the arenas of alkaloid synthesis and medicinal chemistry. Our research group has been engaged in the development of strategies for the cycloisomerization of pyridine propargylic alcohols (e.g., **1**, Scheme 1) for the generation of indolizinones and indolizines with both Pt^{II} and



Scheme 1. Cycloisomerization approaches to indolizines, indolizinones, and benzindolizinones.

In^{III} catalysts.[1] Similarly, others have shown that a wide variety of π acids can mediate the cycloisomerization of pyridine propargylic secondary alcohols to indolizines.[2] Unfortunately, benzannulated variants of these underutilized scaffolds (especially benz[*e*]indolizinones and benz[*g*]indolizinones) that would arise from quinoline or isoquinoline tertiary alcohols, respectively (see **2** and **3**, Scheme 1), are not formed efficiently under the metal-promoted cycloisomerization conditions that were effective for the synthesis of indolizines and indolizinones. Herein, we demonstrate that benzindolizinones can be produced in high yields by the cycloisomerization of quinoline or isoquinoline alcohols in protic solvents (e.g., ethanol or *n*-propanol), which presumably form a hydrogen-bonding network that activates the substrate.

Surprisingly, the benzindolizinone framework has gone virtually unexplored: only scattered reports of benz[*e*]indolizinones[3] and only a single report of the isomeric benz[*g*]indolizinone[4] had appeared prior to the study that is described herein. To demonstrate the utility of the unique azacyclic products that can now be effectively accessed by the protic-solvent-mediated cycloisomerization, we applied the benz[*g*]indolizinone scaffold to short syntheses of the *Erythrina* alkaloids[5] (±)-3-demethoxyerythratidinone (**4**)[6] and (±)-cocculidine (**5**).[7]

The basis of our current studies rests on the concurrent discovery by Kim et al. and our group that simple protic solvents can mediate cycloisomerizations of pyridine propargylic alcohols to yield indolizines and indolizinones.[8,9] This observation suggested a potential route to benzindolizinones, given that the metal-mediated cycloisomerization (e.g., **6a**→**7a**, Scheme 2) proceeds only in low yield (36%) owing to a competing ejection of the acetylide unit to give a ketone (e.g., **8a**) and an alkyne (in this case hexyne).[10] Alternatively, as demonstrated by Kim and co-workers,[11] the subjection of quinoline propargylic alcohol **6b** to iodocycloisomerization conditions results in the formation of iodopyrrolo[1,2-*a*]-quinoline **9** and not the expected benzindolizinone **7b** or its iodinated derivative.

We hypothesized that protic solvents would be less likely than π Lewis acids to effect the ejection of acetylides from substrates such as **6**. Thus, protic-solvent-mediated cycloisomerization could provide a possible solution to the unsolved problem of access to benzindolizinones from propargylic alcohols. Support for this assertion is evident in the effectiveness of the protic-solvent-mediated cycloisomerization conditions (*n*PrOH, 120°C, 40 h), which led to the formation of benz[*g*]indolizinone **7a** in 91% yield (for the isolated product) from the quinoline tertiary alcohol **6a**.

Aryl, alkyl, and alkenyl groups functioned as migrating groups when quinoline propargylic tertiary alcohol substrates **3** containing a terminal alkyne were employed, and the desired products were obtained in good to excellent yields (Scheme 3). Generally, these reactions were conducted at

[*] S. T. Heller, T. Kiho, A. R. H. Narayan, Prof. R. Sarpong
Department of Chemistry, University of California, Berkeley
Berkeley, CA 94720 (USA)
E-mail: rsarpong@berkeley.edu

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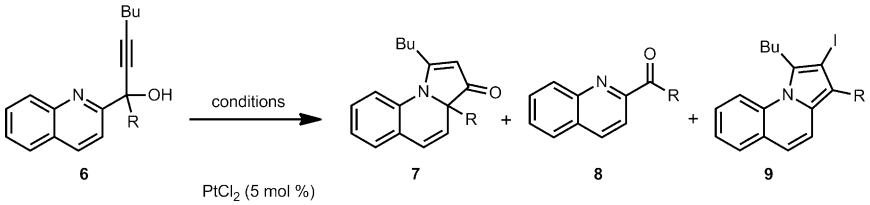
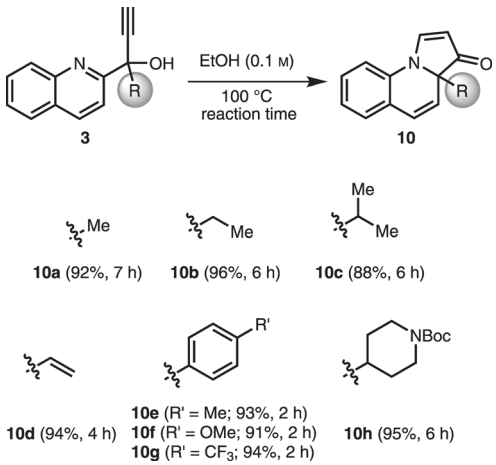


6a (R = Et)	$PtCl_2$ (5 mol %) JohnPhos (10 mol %) Cs_2CO_3 (10 mol %) PhH, 100 °C, 48 h (Ref. [1a])	36%	52%	n.a.
6b (R = Me)	I_2 (2 equiv) CH_2Cl_2, 23 °C	n.d.	n.d.	83%
6a (R = Et)	***n*PrOH (solvent) 120 °C, 40 h**	**91%**	**n.d.**	**n.a.**

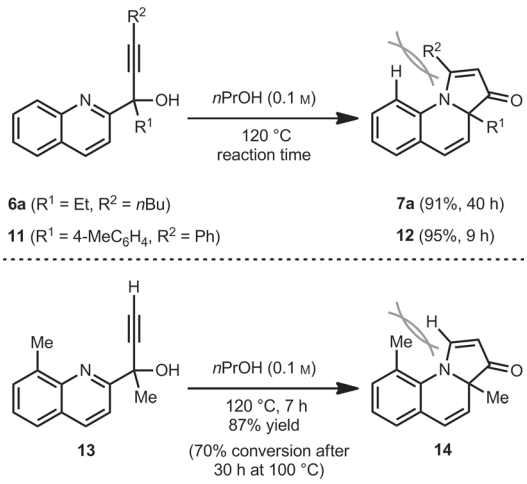
Scheme 2. Development of effective cycloisomerization conditions for benzindolizinone formation. JohnPhos = (2-biphenyl)di-*tert*-butylphosphine, n.d. = not detected, n.a. = not applicable.

over the same time period. Similarly, the aryl-substituted alkynol **11** underwent complete conversion over 9 h at 120 °C to afford **12** in 95 % yield. Importantly, our observation that the reaction of the methyl-substituted quinoline propargyl alcohol substrate **13**, which possesses a terminal alkyne group, is slow at 100 °C and only proceeds to full conversion at a higher reaction temperature of 120 °C indicates that the lower reactivity of **6a** and **11** is probably because of peri strain and not because these substrates are internal alkynes.

In analogy to the developments with quinoline propargylic alcohols for access to benz[*e*]indolizinones (Scheme 3), iso-



Scheme 3. Scope of the reaction for benz[*e*]indolizinone formation with respect to the migrating group. Boc = *tert*-butoxycarbonyl.



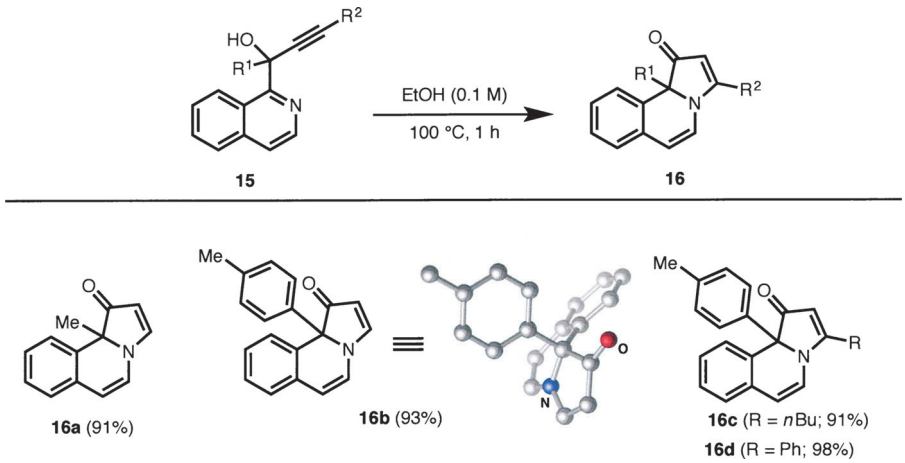
Scheme 4. The influence of peri strain on reactivity.

100 °C in sealed vessels with ethanol as the solvent. The observed reaction rates approximately correlate with the nature of the migrating group (aryl > alkenyl > alkyl). However, the rate of benzindolizinone formation does not appear to correlate with the electronic nature of the aryl migrating groups. Notably, saturated azacycles, such as a protected piperidine (see **10h**), also serve competently as migrating groups. Additionally, in the case of propargylic–allylic alcohol substrates (i.e., R = alkenyl in **3**), complete chemoselectivity for cycloisomerization involving the alkyne group was observed (see **10d**).

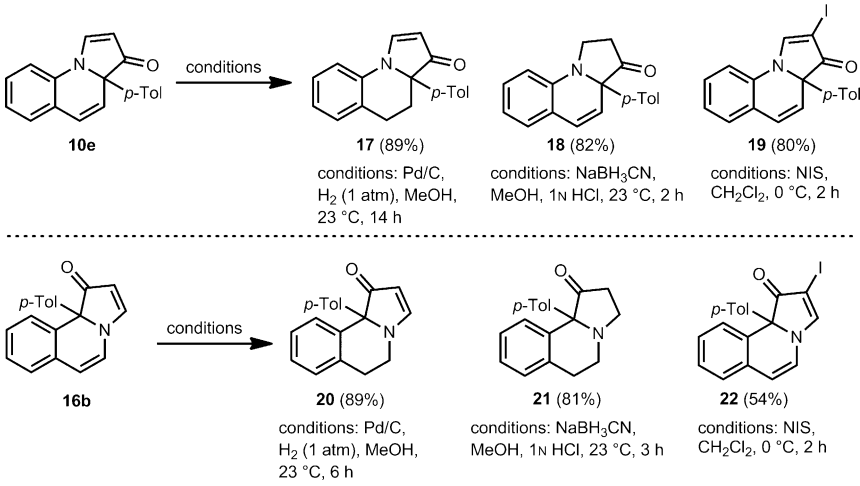
The most significant impact on the facility of the cycloisomerization of quinoline alcohols to form benz[*e*]indolizinones appears to arise in situations in which significant peri strain develops en route to the product, as demonstrated in Scheme 4. Thus, for substrates containing an internal alkyne (e.g., **6a** and **11**), cycloisomerization proceeds only slowly at 100 °C (e.g., 50 % conversion of **6a** into **7a** after heating in ethanol for 40 h). Gratifyingly, an increase in the reaction temperature to 120 °C (which necessitated a switch to the higher-boiling solvent *n*PrOH) led to complete conversion quinoline propargylic alcohols served as effective substrates for the synthesis of benz[*g*]indolizinones. With both aryl and alkyl migrating groups, the desired benz[*g*]indolizinones were obtained in excellent yield (Scheme 5). Qualitatively, the cycloisomerization reactions to afford benz[*g*]indolizinones proceeded more quickly than the corresponding formation of benz[*e*]indolizinones.

The benzindolizinone frameworks that can now be effectively accessed may be manipulated selectively (Scheme 6). For example, oxidation-level adjustments can be performed chemoselectively by exploiting differences in electronic bias between the vinylogous amide, enamine, and alkene groups (see **17, 18**, **20**, and **21**).[12] Alternatively, iodination can be effected with *N*-iodosuccimide; thus, **19** and **22** were obtained as the major products from **10e** and **16b**, respectively.[13]

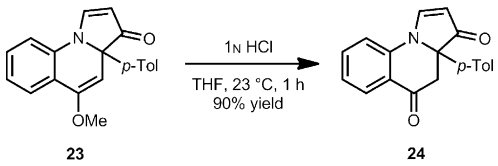
Finally, substituted benzindolizinones (e.g., the methoxybenz[*g*]indolizinone **23**, prepared in 93 % yield from the appropriate propargylic alcohol) can also undergo selective hydrolysis to provide, for example, **24** [Eq. (1)], which possesses a carbonyl group that may be further manipulated.



Scheme 5. Cycloisomerization of isoquinoline propargylic alcohols. (An ORTEP drawing of **16b** is shown with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms have been removed for clarity.)



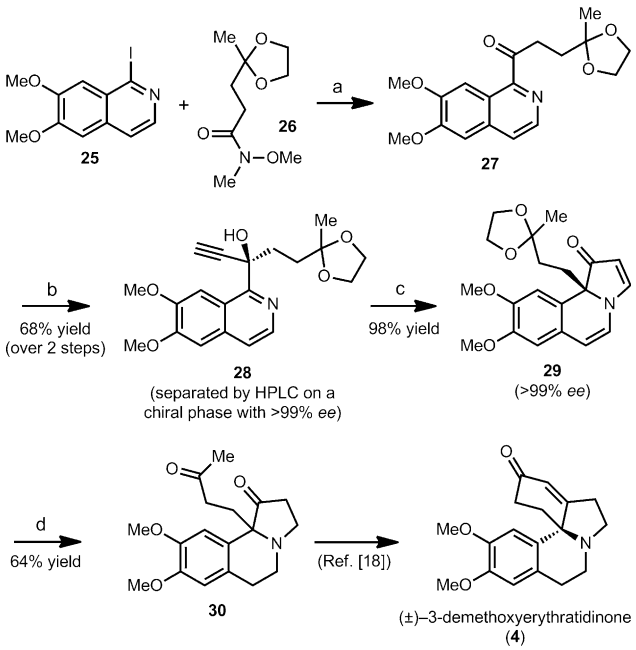
Scheme 6. Selective manipulation of benzindolizinones.



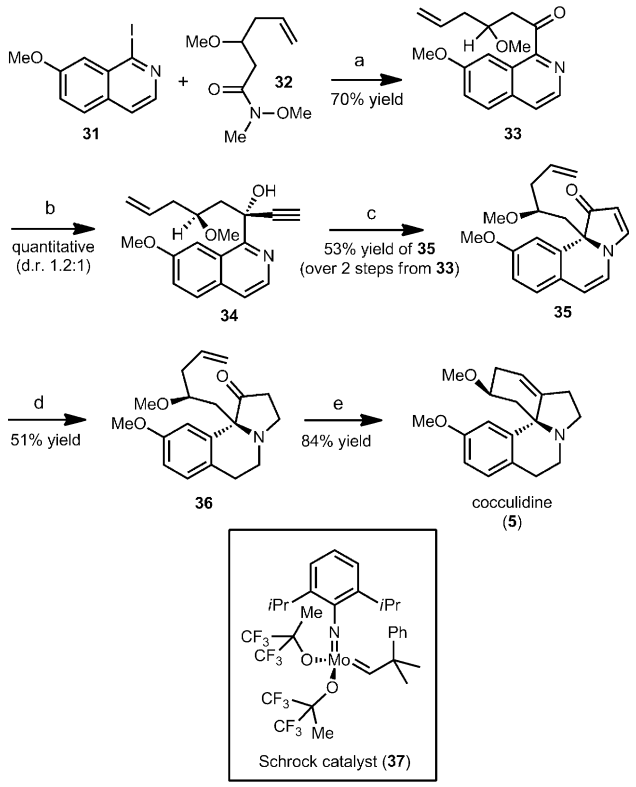
(1)

As a testament to the utility of the benzindolizinone scaffolds that can now be accessed by our cycloisomerization approaches, we employed benz[*g*]indolizinones in syntheses of the *Erythrina* alkaloids 3-demethoxyerythratidinone (**4**) and cocculidine (**5**). The synthesis of **4** commenced with the preparation of benzindolizinone **29**, which is available from iodoisoquinoline **25**[14] in three steps (Scheme 7). The union of **25** and Weinreb amide **26** provided ketone **27**.[15] The treatment of **27** with ethynylmagnesium bromide afforded the propargylic tertiary alcohol **28** in 68% yield over the two steps. Cycloisomerization of **28** to the desired benzindolizinone **29** proceeded in quantitative yield in 1 h upon heating in ethanol. Notably, enantiomerically pure **28** (>99% *ee*; obtained by preparative HPLC on a chiral phase)[16] afforded enantiomerically pure **29** (>99% *ee*), which demonstrates the excellent enantiospecificity of the cycloisomerization step. Following a survey of various reduction protocols (including hydrogenation and the use of hydride reagents, such as sodium borohydride and diisobutylaluminum hydride), we found that under carefully controlled conditions, an ionic reduction of both the enamine and vinylogous-amide moieties of **29** could be effected with attendant deprotection of the pendant ketone group in a one-pot process to give **30**. Overall, this cycloisomerization/reduction sequence provides a powerful alternative to the Pictet–Spengler approach that has historically been employed for the synthesis of intermediates such as **30** in many syntheses of *Erythrina* alkaloids.[17] Diketone **30** was then converted into (±)-3-demethoxyerythratidinone (**4**) by a base-mediated aldol condensation as previously reported by Simpkins and co-workers.[18] Thus, the synthesis of **4** was achieved in five steps from **25** and **26**.

By a similar approach to that employed in the synthesis of **4**, we prepared cocculidine (**5**) in five steps from iodoisoquinoline **31**[19] and Weinreb amide **32**[20] (Scheme 8). The sequence began with the coupling of **31** and **32** to afford the ketone adduct **33**. The ethynylation of **33** proceeded in quantitative yield but with modest diastereoselectivity (d.r. 1.2:1) to give **34** as the major product. Because the mixture of diastereomers of the propargylic alcohol could not be separated easily by flash chromatography, the mixture was subjected to the cycloisomerization conditions to give the diastereomeric benzindolizinone products **35** and its diastereomer in quantitative yield. The diastereomers could be readily separated at this stage to give **35** in 53% yield. On the basis of the observations made during the cycloisomerization of enantiomerically pure **28** to **29** (Scheme 7), we believe that excellent chirality transfer from the propargylic stereocenter in **34** to the ring-fusion position in **35** occurs even in the presence of the methoxy-substituted stereocenter. In line with our previous studies, the vinylogous-amide and enamine double bonds of benzindolizinone **35** were readily reduced (in the presence of the terminal alkene group) to give **36**. A survey of numerous direct and indirect ring-closing tactics[21] led us to conclude that a carbonyl–ene ring-closing metathesis reaction with the Schrock molybdenum complex **37**[22,23] provided the best way to convert **36** into cocculidine (**5**). This shortest reported synthesis of cocculidine highlights the significance of the benzindolizinone framework as a starting point for the



Scheme 7. Synthesis of (±)-3-demethoxyerythratidinone (**4**). Reagents and conditions: a) *i*PrMgCl, **25**, THF, 0°C, 2 h; **26**, THF, 0°C→RT, overnight; b) HCCMgBr (2 equiv), THF, room temperature, 2 h; c) EtOH, 100°C, 1 h; d) TFA, MeOH, $NaBH_3CN$ (2.3 equiv), 0°C; acetone; 1 M HCl. TFA = trifluoroacetic acid.



Scheme 8. Synthesis of (±)-cocculidine (**5**). Reagents and conditions: a) *i*PrMgCl, **31**, THF, −10°C, 2 h; **32**, THF, −50°C→RT, overnight; b) HCCMgBr (1.1 equiv), THF, −10°C→RT, overnight; c) EtOH, 100°C, 1 h (99% combined yield of **35** and its diastereomer); d) TFA, MeOH, $NaBH_3CN$ (2.1 equiv), 0°C, 2 h; e) **37** (1.02 equiv), PhH, 30°C, 15 h.

synthesis of the *Erythrina* alkaloids. Synthetic **5** provided spectral data that are in full agreement with those reported previously. Furthermore, its structure was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).[24]

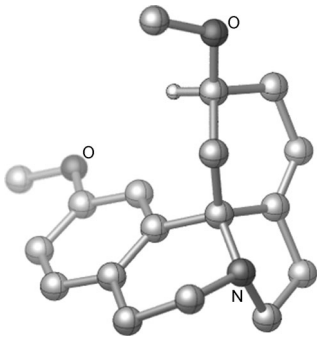


Figure 1. ORTEP representation of the X-ray crystallography data for cocculidine. (Thermal ellipsoids are shown at the 50% probability level. Most hydrogen atoms have been removed for clarity.)

In conclusion, we have described the development of protic-solvent-mediated conditions for the synthesis of benz[*e*]indolizinones and benz[*g*]indolizinones from quinoline propargylic alcohols and isoquinoline propargylic alcohols, respectively. These unusual heterocycles can be manipulated selectively to afford partially saturated variants (e.g., benzindolizidinones). These observations have been applied to short syntheses of the *Erythrina* alkaloids (±)-3-demethoxyerythratidinone and (±)-cocculidine. Our synthesis of (±)-cocculidine also provides a rare example of the utility of the Schrock molybdenum complex **37** for a carbonyl–ene ring-closing reaction in the context of natural products synthesis. Our future studies are aimed at the application of benzindolizinone azacycles in the synthesis of other complex natural products.

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Keywords: cycloisomerization · *Erythrina* alkaloids · heterocycles · molybdenum · Schrock catalysts

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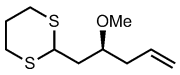
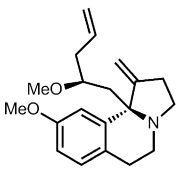
[20] For details on the synthesis of enantiomerically enriched **32** from dithiane **I** (3 steps), see the Supporting Information.

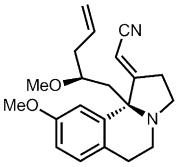


I

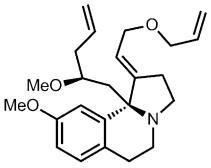
[21] Among the approaches that were surveyed were ring-closing metathesis of diene **II** and nitrile **III**, as well as relay ring-closing metathesis of the bisallylic ether **IV**. Complete details will be reported in a full account of this research.



II



III



IV

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[24] CCDC 955159 (**16b**) and 955160 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

