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

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Keywords

cocculidine; benz[g]indolizinone; benz[e]indolizinone; cycloisomerization; Erythrina alkaloids; heterocycles; Schrock catalyst; molybdenum; 3-demethoxyerythratidinone

Novel nitrogen-containing rings (azacycles) are particularly valuable in the arenas of alkaloid synthesis and medicinal chemistry. To that end, our group has been engaged in the development of cycloisomerization strategies of pyridine propargylic carbinols (e.g., **1**, Figure 1) for the generation of indolizinones and indolizines using both Pt(II)- and In(III)-catalysts.[i] Similarly, others have shown that a wide variety of π-acids can mediate the cycloisomerization of pyridine propargylic carbinols to indolizines. [ii] Unfortunately, benzannulated variants of these underutilized scaffolds (especially benz[e]indolizinones or benz[g]indolizinones) that would arise from quinoline or isoquinoline carbinols, respectively (see **2** and **3**, Figure 1), are not formed efficiently under the metal promoted cycloisomerization conditions that were effective for the synthesis of indolizines and indolizinones. In this communication, we demonstrate that benzindolizinones can be produced in high yields by the cycloisomerization of quinoline or isoquinoline carbinols mediated by protic solvents (e.g., ethanol or *n*-propanol), which presumably form a H-bonding network that activates the substrate.

Surprisingly, the benzindolizinone framework has gone virtually unexplored, with only scattered reports of benz[e]indolizinones [iii] and only a single report of the isomeric benz[g]indolizinone[iv] appearing in the literature prior to the work that is described herein. To demonstrate the utility of the unique azacyclic products that can now be effectively realized using protic solvent mediated cycloisomerization, we have applied the benz[g]indolizinone scaffold to short syntheses of the *Erythrina* alkaloids[v] (±)-3-demethoxyerythratidinone (**4**)[vi] and (±)-cocculidine (**5**).[vii]

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 carbinols to yield indolizines and indolizinones.[viii,ix] This observation suggested a potential

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route to access benzindolizinones given that the metal-mediated cycloisomerization conditions (e.g., **6a** to **7a**, Scheme 1) proceed only in low yield (36%) due to a competing ejection of the acetylide unit to give a ketone (e.g., **8a**) and hexyne.[x] Alternatively, as demonstrated by Kim and coworkers, [xi] subjecting quinoline propargylic carbinol **6b** to iodocycloisomerization conditions results in the formation of iodo pyrrolo[1,2-a]quinoline **9** and not the expected benzindolizinone (i.e., **7b**) or its iodinated derivative.

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

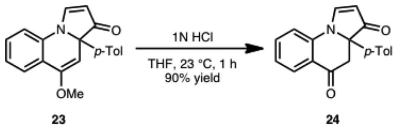
As shown in Scheme 2, aryl, alkyl and alkenyl groups function as migrating groups when terminal alkyne bearing quinoline propargylic carbinol substrates (i.e., **3**) are employed to give the desired products in good to excellent yields. Generally, these reactions were conducted at 100 °C in sealed vessels 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 electronics 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 alkenyl-alkynyl carbinol 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 carbinols to form benz[e]indolizinones appears to arise in situations where significant peri-strain develops en route to the product as demonstrated in Scheme 3. Thus, for internal alkyne substrates (e.g., **6a** and **11**), cycloisomerization proceeds only slowly at 100 °C (e.g., 50% conversion of **6a** to **7a** after heating in ethanol for 40 h). Gratifyingly, increasing the reaction temperature to 120 °C (which necessitated a switch to the higher boiling solvent *n*-PrOH) leads to complete conversion over the same time period. Similarly, aryl substituted carbinol **11** undergoes complete conversion over 9 h at 120 °C to afford a 95% yield of **12**. Importantly, our observation that methyl-substituted quinoline propargyl carbinol substrate **13**, which possesses a terminal alkyne group is slow to react at 100 °C and only proceeds to full conversion upon raising the reaction temperature to 120 °C, demonstrates that the lower reactivity of **6a** and **11** is likely because of peri-strain in slowing the progress of the reaction and not because these are internal alkyne substrates.

Analogous to the developments using *quinoline* propargylic carbinols to access benz[*e*]indolizinones (Scheme 2), *isoquinoline* propargylic carbinols serve as effective substrates for the synthesis of benz[*g*]indolizinones. As illustrated in Scheme 4, aryl and alkyl groups are competent as migrating groups to afford the benz[*g*]indolizinones in excellent yield. Qualitatively, cycloisomerizations to afford benz[g]indolizinones proceed more quickly than the corresponding formation of benz[e]indolizinones.

As shown in Scheme 5, the benzindolizinone frameworks that can now be effectively accessed may be selectively manipulated. For example, oxidation level adjustments can be performed chemoselectively by exploiting differences in electronic bias between the vinylogous amide, enamide, or alkene groups (see **17, 18**, **20** and **21**, respectively). [xii] Alternatively, iodination can be effected using *N*-iodosuccimide to afford **19** and **22** as the major products from **10e** and **16b**, respectively.[xiii]

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



(1)

As a testament to the utility of the benzindolizinone scaffolds that can now be accessed using our cycloisomerization approaches, we have employed benz[g]indolizinones in syntheses of the *Erythrina* alkaloids 3-demethoxyerythratidinone (**4**) and cocculidine (**5**). The synthesis of **4** (Scheme 6) commenced with the preparation of benzindolizinone **29**, which is available from iodo-isoquinoline **25**[xiv] in three steps. The union of **25** and Weinreb amide **26** provides ketone **27**. [xv] Treatment of **27** with ethynylmagnesium bromide affords propargylic carbinol **28** in 68% yield over the two steps. Cycloisomerization of **28** to the desired benzindolizinone (**29**) proceeds in quantitative yield over 1 h by heating the propargylic alcohol substrate in ethanol. Of note, enantiopure **28** (>99% ee; obtained by preparative chiral HPLC) [xvi] affords enantiopure **29** (>99% ee) demonstrating excellent enantiospecificity in the chirality transfer for the cycloisomerization step. Following a survey of various reduction protocols (including hydrogenation and the use of hydride reagents such as sodium borohydride and diisobutyl aluminium 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 single pot 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.[xvii] Diketone **30** was then converted to (±)-3-demethoxyerythratidinone (**4**) using a base-mediated aldol condensation as previously reported by Simpkins and coworkers.[xviii] Thus, the synthesis of **4** was achieved in five steps from **25** and **26**.

Using a similar approach to that employed in the synthesis of **4**, we have prepared cocculidine (**5**) as illustrated in Scheme 7 in five steps from iodoisoquinoline **31**[xix] and Weinreb amide **32**.[xx] The sequence began with the coupling of **31** and **32** to afford ketone adduct **33**. Ethynylation of **33** proceeds in quantitative yield but with modest diastereoselectivity (1.2:1 d.r.) to give **34** as the major product. Because the mixture of

propargylic alcohol diastereomers is not easily separated using flash chromatography, the mixture was subjected to the cycloisomerization conditions to give a quantitative yield of the diastereomeric benzindolizinone products (i.e., **35b** and its diastereomer). The diastereomers can be readily separated at this stage to give 53% yield of **35b**. On the basis of the observations made during the cycloisomerization of enantiopure **28** to **29** (Scheme 6), we believe that excellent chirality transfer from the propargylic stereocenter in **34** to the ring fusion position in **35b** occurs even in the presence of the methoxy bearing stereocenter. In line with our previous studies, the enamide and enamine double bonds of benzindolizinone **35b** can be readily reduced (in the presence of the terminal olefin group) to give **36b**. Following a survey of numerous direct and indirect ring closing tactics,[xxi] we found that a carbonyl-ene ring closing metathesis reaction using the Schrock molybdenum complex **37**[xxii,xxiii] provided the best way to convert **36b** to cocculidine (**5**). This synthesis constitutes the shortest reported synthesis of cocculidine, which highlights the significance of the benzindolizinone framework as a starting point for the synthesis of the *Erythrina* alkaloids. Synthetic **5** provided spectral data that is in full agreement with that reported previously. Furthermore, its structure was unambiguously confirmed by single crystal X-ray analysis (see Figure 2 for an ORTEP representation of **5**).

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

i. a Smith CR, Bunnelle EM, Rhodes AJ, Sarpong R. Org. Lett. 2007; 9:1169. [PubMed: 17309277] b Bunnelle EM, Smith CR, Lee SK, Singaram WS, Rhodes AJ, Sarpong R. Tetrahedron. 2008; 64:7008. [PubMed: 22593605] c Hardin AR, Sarpong R. Org. Lett. 2007; 9:4547. [PubMed: 17845052]

ii. Ag(I)-catalysis: Bai Y, Zeng J, Ma J, Gorityala BK, Liu XW. J. Comb. Chem. 2010; 12:696. [PubMed: 20831266] A report detailing both Ag(I)- and Au(I)-catalysis: Seregin IV, Schammel AW, Gevorgyan V. Org. Lett. 2007; 9:3433. [PubMed: 17637023] Au(III)-catalysis: Yan B, Liu Y. Org. Lett. 2007; 9:4323. [PubMed: 17854200] Seregin IV, Gevorgyan V. J. Am. Chem. Soc.

2006; 128:12050. [PubMed: 16967938] Cu(I)-catalysis: Yan B, Zhou Y, Zhang H, Chen J, Liu Y. J. Org. Chem. 2007; 72:7783. [PubMed: 17718578] Kel'in AV, Sromek AW, Gevorgyan V. J. Am. Chem. Soc. 2001; 123:2074. [PubMed: 11456838]

iii. See references 1a and 2e

iv. Eicher T, Krause D. Synthesis. 1986:899.

v. a Amer ME, Shamma M, Freyer AJ. J. Nat. Prod. 1991; 54:329. and references therein. b Dyke, SF.; Quessy, SN. The Alkaloids. Rodrigo, RGA., editor. Vol. 18. Academic Press; New York: 1981. p. 1-98.

vi. Isolation from natural source: Barton DHR, Gunatilaka AAL, Letcher RM, Lobo AMFT, Widdowson DA. J. Chem Soc., Perkin Trans. I. 1973:874. For previous total and formal syntheses of 4, see: Tsuda Y, Nakai A, Ito K, Suzuki F, Haruna M. Heterocycles. 1984; 22:1817.Zhang F, Simpkins NS, Blake AJ. Org. Biomol. Chem. 2009; 7:1963. [PubMed: 19590794] Joo JM, David RA, Yu Y, Lee C. Org. Lett. 2010; 12:5704. [PubMed: 21090648] Allin SM, Streetly GB, Slater M, James SL, Martin WP. Tetrahedron Lett. 2004; 45:5493.Chuang KV, Navarro R, Reisman SE. Chem. Sci. 2011; 2:1086.Gao S, Tu YQ, Hu X, Wang S, Hua R, Jiang Y, Zhao Y, Fan X, Zhang S. Org. Lett. 2006; 8:2373. [PubMed: 16706529] Wang Q, Padwa A. Org. Lett. 2006; 8:601. [PubMed: 16468721] Irie H, Shibata K, Matsuno K, Zhang Y. Heterocycles. 1989; 29:1033.Danishefsky SJ, Panek JS. J. Am. Chem. Soc. 1987; 109:917.Wasserman HH, Amici RM. J. Org. Chem. 1989; 54:5843.Tanaka H, Shibata M, Ito K. Chem. Pharm. Bull. 1984; 32:1578.Moon JT, Jung JA, Ha SH, Song SH, Park SJ, Kim J, Choo DJ, Lee YS, Lee JY. Synth. Commun. 2011; 41:1282.Cassayre J, Quiclet-Sire B, Saunier J-B, Zard SZ. Tetrahedron Lett. 1998; 39:8995.Hosoi S, Ishida K, Sangai M, Tsuda Y. Chem. Pharm. Bull. 1992; 40:3115.Tsuda Y, Sakai Y, Nakai A, Kaneko M, Ishiguro Y, Isobe K, Taga J, Sano T. Chem. Pharm. Bull. 1990; 38:1462.Ishibashi H, Sato T, Takahashi M, Hayashi M, Ishikawa K, Ikeda M. Chem. Pharm. Bull. 1990; 38:907.Chikaoka S, Toyao A, Ogasawara M, Tamura O, Ishibashi H. J. Org. Chem. 2003; 68:312. [PubMed: 12530854]

vii. For isolation of 5 from its natural source, see: Bhakuni DS, Uprety H, Widdowson DA. Phytochemistry. 1976; 15:739. [b] For a previous syntheses of 5, see: Ju-Ichi M, Fujitani Y, Ando Y. Chem. Pharm. Bull. 1981; 29:396.

viii. Hardin Narayan AR, Sarpong R. Green Chem. 2010; 12:1556. [PubMed: 21572597]

ix. Kim I, Choi J, Lee S, Lee GH. Synlett. 2008:2334.

x. See reference 1a

xi. Choi J, Lee GH, Kim I. Synlett. 2008:1243.

xii. For a related reduction of indolizinones, see: Narayan ARH, Sarpong R. Org. Biomol. Chem. 2012; 10:70. [PubMed: 22072189]

xiii. For related iodination of pyrrolones, see: McNab H, Monahan LC. J. Chem. Soc. Perkin Trans. 1. 1989:419.

xiv. Metzger A, Schade MA, Knochel P. Org. Lett. 2008; 10:1107. [PubMed: 18288850]

xv. Duggan ME, Perkins JJ, Meissner RS, Patent US. 6211191:2001.

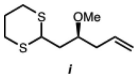
xvi. This chromatographic resolution was performed using SFC separation on an IC column (2 × 25 cm) with 15% isopropanol(0.1% DEA)/CO_2, 100 bar with a 60 mL/min flow rate. The separation was performed by Lotus Separations LLC, Princeton, New Jersey. We are indebted to Christina Kraml and Daniel Sanner for their generous assistance.

xvii. For a discussion of approaches to Erythrina alkaloids, see: Reimann E. Prog. Chem. Org. Nat. Prod. 2007; 88:1., and references therein.

xviii. See Ref. 6c.

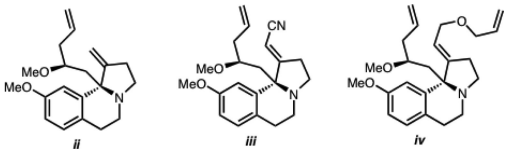
xix. Prepared from 7-methoxyisoquinolin-1(2H)-one in one step. See: Eloy F, Deryckere A. Helv. Chim. Acta. 1969; 52:1755.

xx. For details on the synthesis of **32** from dithiane **i** (3 steps), see the Supporting Information.



i

xxi. Among the tactics that were surveyed were ring closing metathesis from diene **ii** and nitrile **iii**, as well as relay ring closing metathesis using vinyl allyl ether **iv**. Complete details will be reported in a full account of this work.



xxii. For the original reports on the synthesis of the Schrock complex, see: Schrock RR, Murdzek JS, Bazan GC, Robbins J, DiMare M, O'Regan M. J. Am. Chem. Soc. 1990; 112:3875.Bazan GC, Oskam JH, Cho H-N, Park LY, Schrock RR. J. Am. Chem. Soc. 1991; 113:6899.Bazan GC, Schrock RR, Cho H-N, Gibson VC. Macromolecules. 1991; 24:4495.

xxiii. For original report on carbonyl olefin metathesis, see: Fu GC, Grubbs RH. J. Am. Chem. Soc. 1993; 115:3800.

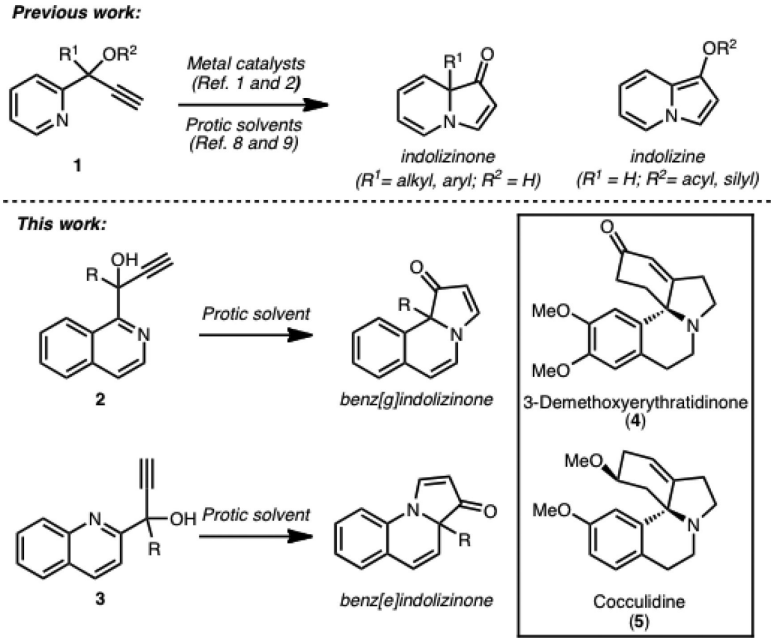
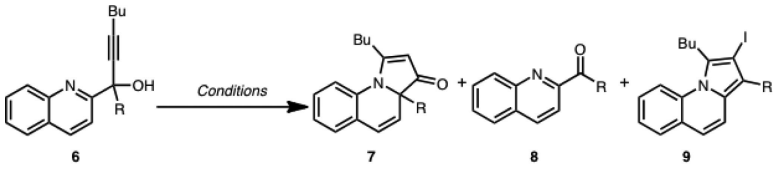


Figure 1.

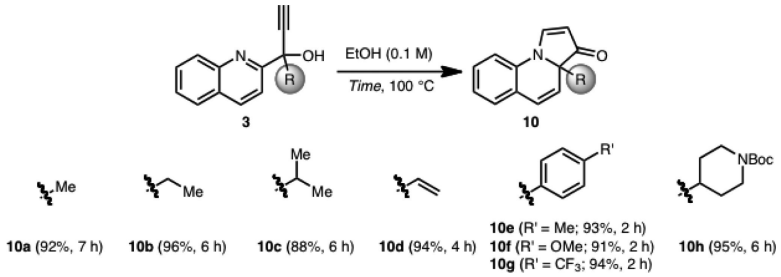
Cycloisomerization approaches to indolizines, indolizinones and benzindolizinones.



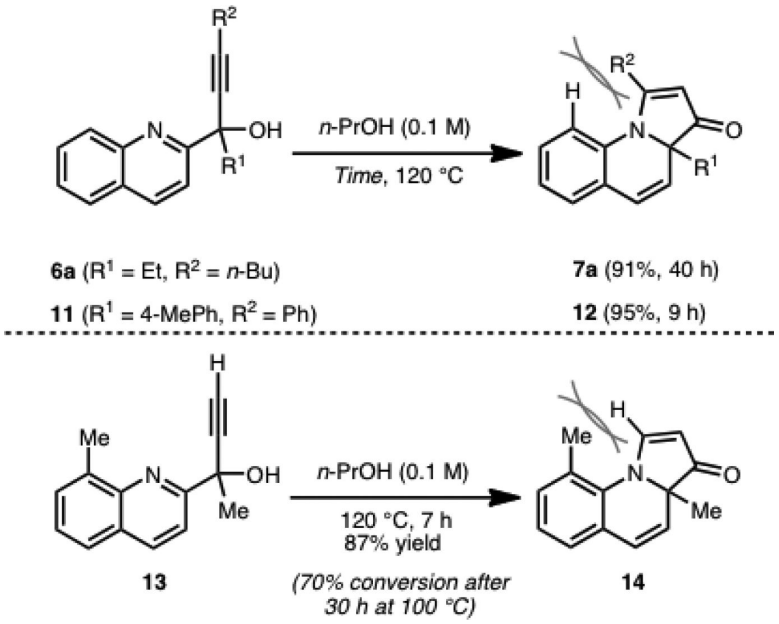
6		7	8	9
6a (R = Et)	$PtCl_2$ (5 mol %) JohnPhos (10 mol %) Cs_2CO_3 (10 mol %) PhH, 100 °C, 48 h (Ref. 1a)	36%	52%	n.a.
6b (R = Me)	I_2 (2 equiv) DCM, 23 °C	n.d.	n.d.	83%
6a (R = Et)	***n*-PrOH (solvent) 120 °C, 40 h**	**91%**	**n.d.**	**n.a.**

Scheme 1.

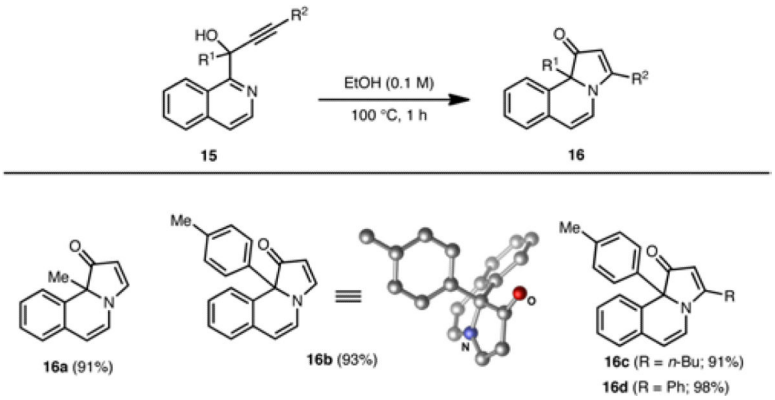
Development of effective cycloisomerization conditions for benzindolizinone formation



Scheme 2.
Migrating group scope for benz[e]indolizinone formation

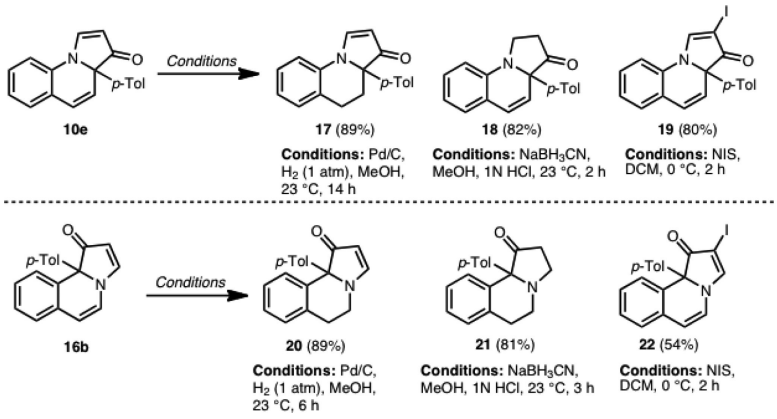


Scheme 3.
The influence of peri-strain on reactivity

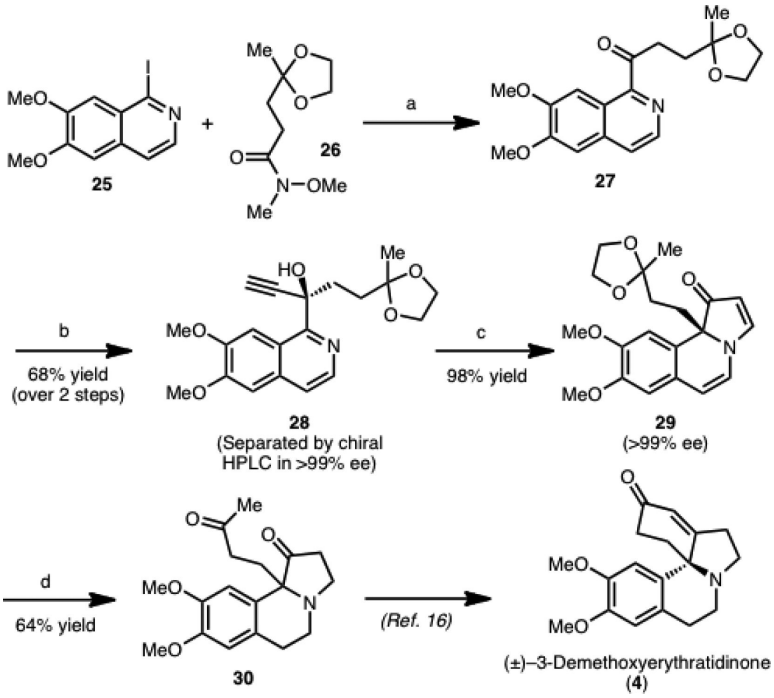


Scheme 4.

Cycloisomerization of isoquinoline propargylic carbinols. (ORTEP of **16b** shown at 50% probability of thermal ellipsoids. Hydrogens removed for clarity).

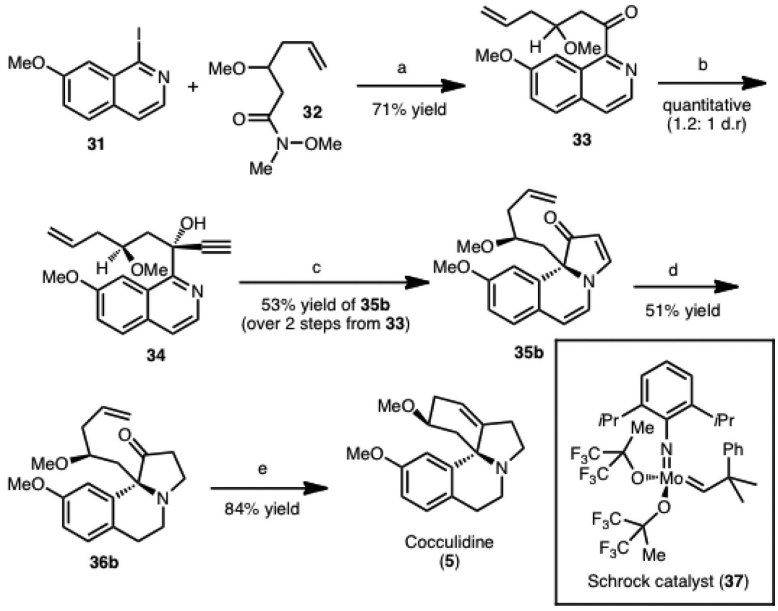


Scheme 5.
Selective manipulation of benzindolizinones.



Scheme 6.

Synthesis of (±)–3-demethoxyerythratidinone (**4**). Reagents and conditions: a) *i*-PrMgCl, **25**, THF, 0 °C, 2 h; **26**, THF, 0 °C to rt, overnight; b) HCCMgBr (2 equiv), THF, rt, 2 h, 68% over two steps; c) EtOH, 100 °C, 1 h, 98%; d) TFA, MeOH, $NaBH_3CN$ (2.3 equiv), 0 °C; acetone; 1 M HCl, 64%. THF = tetrahydrofuran, TFA = trifluoroacetic acid.



Scheme 7.

Synthesis of (±)-cocculidine (**5**). Reagents and conditions: a) *i*-PrMgCl, **25**, THF, -10 °C, 1 h; **32**, THF, 0 °C to rt, overnight, 71%; b) HCCMgBr (1.1 equiv), THF, -10 °C to rt, overnight, quantitative (1.2 : 1 dr); c) EtOH, 100 °C, 1 h, 99% combined yield (53% yield of **35b** over two steps); d) TFA, MeOH, $NaBH_3CN$ (2.1 equiv), 0 °C, 2 h, 51%; e) **37**(1.02 equiv), PhH, 30 °C, 15 h, 84%; THF = tetrahydrofuran, TFA = trifluoroacetic acid, PhH = benzene.

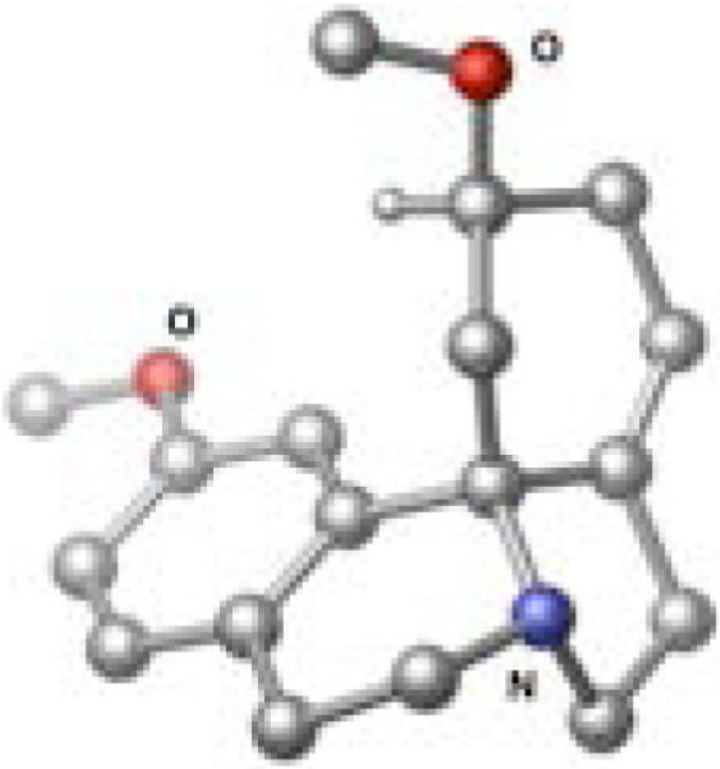


Figure 2.

ORTEP representation of the X-ray crystallography data for cocculidine (Thermal ellipsoids shown at the 50% probability level. Most hydrogens removed for clarity)