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Total Synthesis of Indolizidine Alkaloids via Nickel-Catalyzed (4 + 2) Cyclization

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Cite This: https://dx.doi.org/10.1021/acs.orglett.9b04479 Read Online

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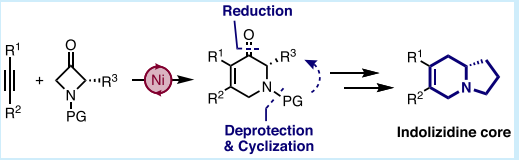
ABSTRACT: A Ni-catalyzed (4 + 2) cycloaddition of alkynes and azetidinones toward piperidinones was used as key reaction in the enantioselective synthesis of naturally occurring indolizidine alkaloids. The reaction benefits from the use of an easily accessible azetidinone as an advanced and divergent intermediate to build the indolizidine core. This methodology has been applied in the total syntheses of (+)-septicine, (+)-ipalbidine, and (+)-*seco*-antofine to illustrate the applicability of the general approach.



Indolizidine alkaloid natural products, such as (+)-septicine (**1**), (+)-*seco*-antofine (**2**), and (+)-ipalbidine (**3**) as well as phenanthroindolizidines (+)-tylophorine (**4**) and (+)-antofine (**5**) (Figure 1), have been the center of much interest for some

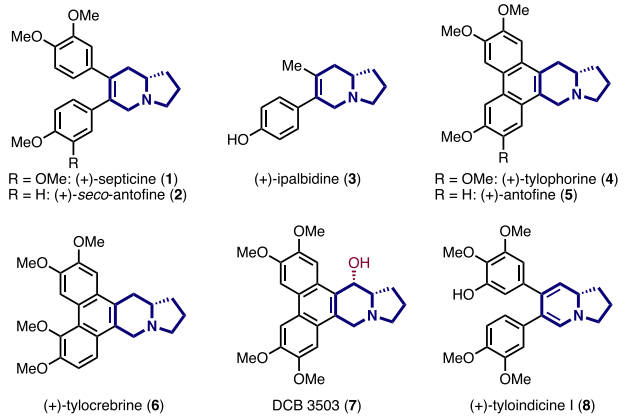


Figure 1. Representative structures of indolizidine alkaloids.

time due to their anticancer,[1−10] anti-inflammatory,[11−14] and antiviral[15,16] properties. Tylophorine (**4**) and antofine (**5**) are popular targets for total synthesis due to their well-characterized various antitumor activities.[17−20] Tylocrebrine (**6**) even entered phase 1 clinical trials as an anticancer drug candidate, though its progress halted due to central nervous system toxicity.[21,22] Despite this setback, interest in this family of compounds has been greatly renewed due to the recent discovery of their unique potency against multidrug-resistant cancer (MDR) cell lines. For example, the synthetic analog DCB 3503 (**7**) and tyloindicine I (**8**) were shown to be potent against a variety of MDR cancer cells in the NCI's 60 cell line assay.[7,23] Perhaps even more exciting is that preliminary data suggest their mechanism of action is novel.[7,24]

The natural alkaloids have been isolated from diverse plant families such as *Tylophora* (Asclepiadaceae) and *Ficus* (Moraceae).[25] However, given their potential in the treatment of MDR cancer, effective synthetic routes to these natural products and, perhaps more importantly, their synthetic analogs have been developed. A closer look reveals that the majority of these methods focus on building phenanthroindolizidines by utilizing phenanthrene-based starting materials.[14,16,26−41] As such, access to indolizidine derivatives, such as the *seco*-analogs of **4** and **5**, remains difficult.[42−48]

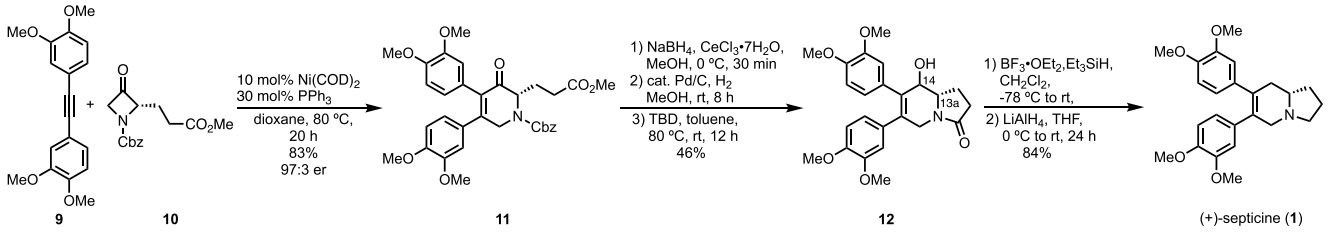
Our group previously developed a method where a Ni(0)/PPh_3 system catalyzes the (4 + 2) cycloaddition of azetidinones and internal alkynes.[49,50] This provides access to a piperidone moiety with high regioselectivity while retaining the chirality of azetidinone substrates. We postulated that this method could be used as general approach to indolizidine alkaloids (as well as their pentacyclic analogs) through reduction and cyclization of the resulting piperidone to create the asymmetric bicyclic core structure. Our azetidinone would serve as advanced and divergent intermediate. Furthermore, this method would complement previous methods that afford phenanthroindolizidine products directly. Herein, we highlight this approach in the total synthesis of (+)-septicine (**1**), and (+)-*seco*-antofine (**2**) and (+)-ipalbidine (**3**).

We chose (+)-septicine as the initial target for proof-of-concept for our convergent synthetic protocol due to the symmetrical nature of the aryl rings. Our approach began with alkyne **9**, which was prepared in three steps from

Received: December 13, 2019

https://dx.doi.org/10.1021/acs.orglett.9b04479
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of (+)-Septicine (1)

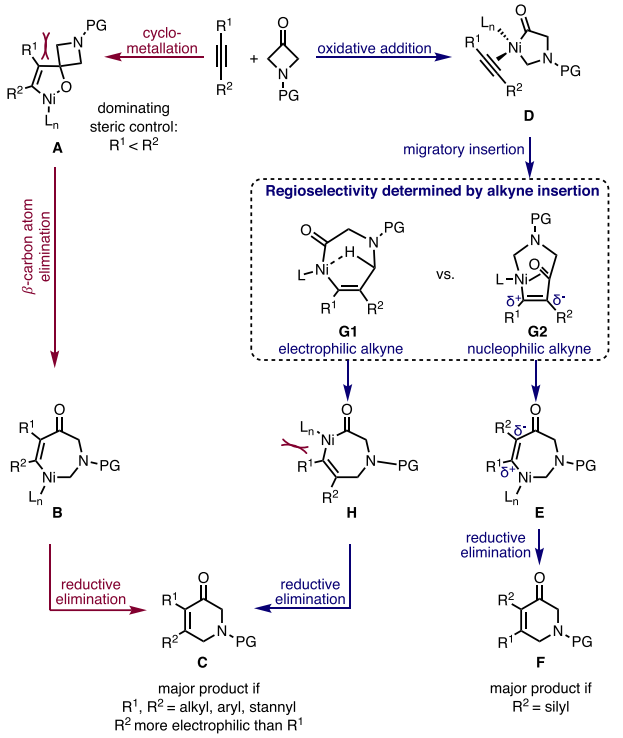


veratraldehyde. Azetidinone **10** served as our divergent intermediate and was synthesized from glutamic acid according to Seebachs's procedure.[51] Both reagents were transformed into 3-piperidinone **11** using our developed Ni-catalyzed (4 + 2)-cycloaddition procedure. Compound **11** has also been previously synthesized using our developed *in situ* generated catalyst system.[50] The stereo information on azetidinone **10** was retained during this transformation (97:3 er, Scheme 1). Piperidinone **11** was reduced under Luche conditions to form the alcohol. Subsequent deprotection using Pd/C and ester aminolysis using triazabicyclodecene (TBD) furnished the cyclized alcohol **12**. Dehydroxylation using Et_3SiH and reduction of the amide with $LiAlH_4$ provided (+)-septicine (**1**) in 12 steps and 8.2% overall yield (Scheme 1).

It is worth mentioning that the hydroxy group at C14 is desired for high anticarcinogenic activity.[36,52] Moreover, the additional polarity was proposed to reduce CNS toxicity by reducing transition into the blood−brain barrier.[22] Several syntheses were since designed to include functionalizations at C14.[33,35,36] However, inclusion of this functional group leads to increased sensitivity to acids, and we noticed partial racemization at C13a of ketone **11** during the Luche reduction, when HCl was used during workup. Similar instabilities have previously been observed.[53,54] We therefore recommend the use of mild acids, such as NH_4Cl, to avoid acid catalyzed epimerization.

A key element to expand our approach to indolizidine alkaloids with different aryl substituents, such as (+)-ipalbidine and (+)-*seco*-antofine, is the regiocontrolled cycloaddition of unsymmetrical alkynes into the C_{sp3}−C_{sp2} bond of azetidinone **10**. We previously observed regiocontrol in Ni-catalyzed cycloadditions with unsymmetrical alkynes where the larger group was distal to the carbonyl carbon (**C**, Scheme 2) unless silyl or stannyl substituted alkynes were employed. In these cases, the larger silyl and stannyl substituents are adjacent to the carbonyl carbon in the product (**F**, Scheme 2). Though we originally proposed a mechanism that involved minimizing steric interactions in an initial oxidative addition between the alkyne and the azetidinone carbon and subsequent *β*-carbon-elimination (red pathway, Scheme 2), computational studies suggest a mechanism involving oxidative addition of the C_{sp3}−C_{sp2} bond of azetidinone alone (blue pathway, Scheme 2) rather than oxidative coupling with the alkyne.[55] The regioselectivity was then determined by the alkyne insertion (**G1** vs **G2**, Scheme 2) and, furthermore, the alkyne either acted as an electrophile or a nucleophile. When the alkynes possess only alkyl or aryl substituents, the alkyne acts as an electrophile in the insertion step, and the more nucleophilic Ni−C_{sp3} carbon forms a bond with the more electrophilic carbon (i.e., the aryl substituted carbon in unsymmetrical alkyl/aryl alkynes) to form metallacycle **H** via intermediate **G1**. Minimizing steric interactions between the alkyne substituent

Scheme 2. Proposed Mechanism of Cycloaddition



and the ligand (intermediate **H**) also contributes to the regioselectivity. However, silyl and stannyl substituents increase the electron density of the alkyne carbons resulting in an alkyne insertion where the alkyne acts as nucleophile to attack the electron-deficient carbonyl carbon and inserts into the other Ni−C bond, namely the Ni−C(O) bond, to form metallacycle **E** via intermediate **G2**.

With this in mind, we used both steric and electronic factors to our advantage to develop a regioselective synthesis of (+)-ipalbidine and (+)-*seco*-antofine. Ni-catalyzed (4 + 2) cycloaddition of alkyne **14** and azetidinone **10** yielded desired piperidinone **15** with high regioselectivity (10:1 rr). The regioselectivity was analyzed by ^1H NMR spectroscopy using the crude reaction mixture, and the desired regioisomer was supported by 2D NOE correlation. Importantly, a lower reaction temperature was necessary to avoid alkyne trimerization.

In a similar approach to (+)-septicine, Luche reduction of piperidinone **15** to alcohol **16** and subsequent deprotection and cyclization and deoxygenation afforded intermediate **18**.

Finally, demethylation using BBr_3 yielded (+)-ipalbidine (**3**) in 8.4% total yield (Scheme 3A).

In an attempt to synthesize (+)-*seco*-antofine, we utilized alkyne **19** to access piperidone **22**. However, the marginally unsymmetrically methoxy substituted alkyne **19** underwent

https://dx.doi.org/10.1021/acs.orglett.9b04479
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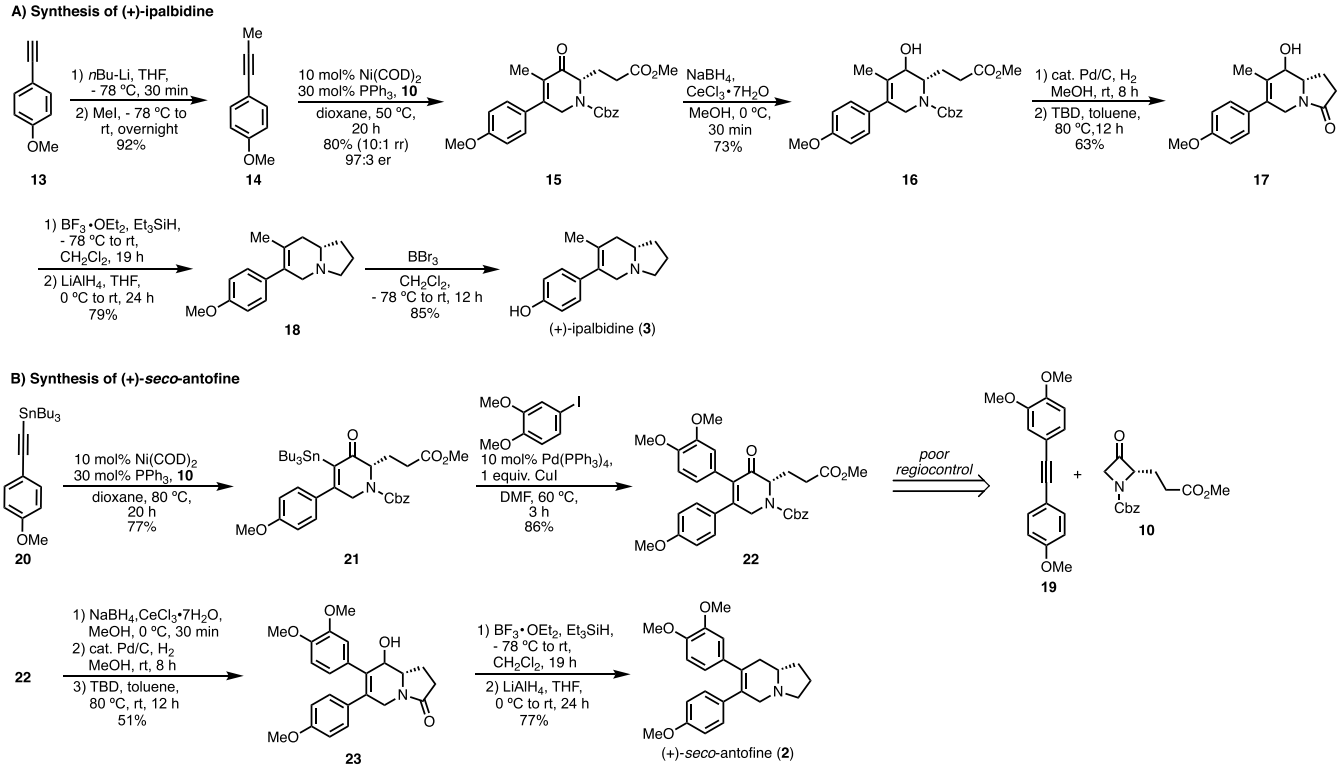
Scheme 3. Synthesis of (+)-Ipalbidine (3) and *Seco*-antofine (2)



cycloaddition with unsurprisingly poor regioselectivity. As such, we utilized alkyne **20** that included a bulky stannyl group, which would electronically dictate and override the steric preference. The Ni-catalyzed insertion into azetidinone **10** proceeded with high regioselectivity resulting in the stannyl group being proximal to the carbonyl group as only observed regioisomer. A subsequent Stille coupling was used to install the unsymmetrical additional arene moiety of (+)-*seco*-antofine resulting in piperidinone **22** (Scheme 3B). In accordance to previous pathways, cyclization of the appendix and removal of excess oxygen functionalities resulted in (+)-*seco*-antofine (**2**) in 7.7% overall yield.

In summary, we leveraged our Ni-catalyzed (4 + 2)-cycloaddition of alkynes and azetidinones to yield chiral piperidinones with high regio- and stereoselectivities in the facile synthesis of natural occurring indolizidine alkaloids. This approach allows for the syntheses of nonphenanthroindolizidine-based alkaloid products. Efforts to increase the efficiency of this approach are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04479.

Experimental considerations, synthetic procedures, HPLC traces, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Institute of Health (GM076125) for financial support. We thank Professor Sigman at the University of Utah for the use of their SFC-instrument. We thank Brianna Esslinger for thoughtful discussions.

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