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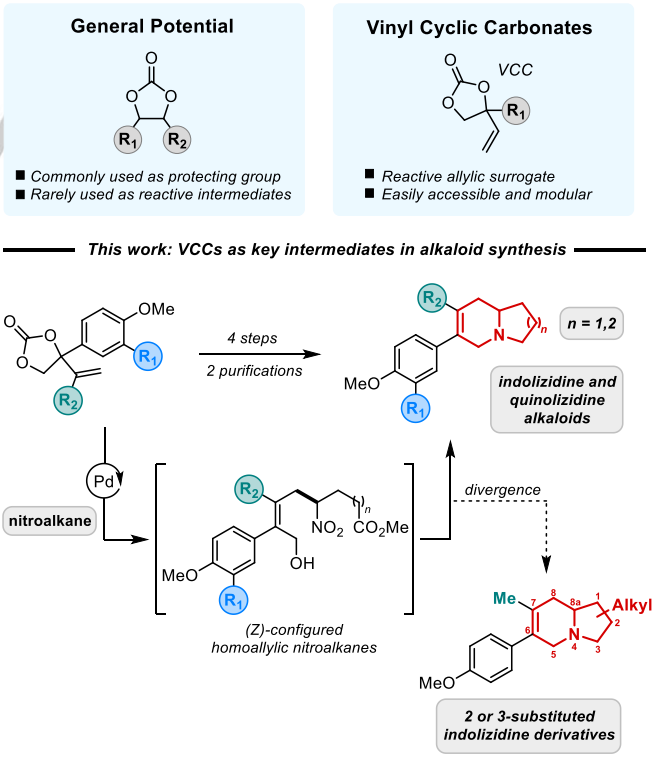
Formal Synthesis of Indolizidine and Quinolizidine Alkaloids from Vinyl Cyclic Carbonates

Àlex Cristòfol,[a] Christian Böhmer[a] and Arjan W. Kleij*[a,b]

Abstract: Cyclic carbonates have long been considered relatively inert molecules acting as protecting groups in complex multistep synthetic routes. This study shows that a concise, yet modular synthesis of indolizidine and quinolizidine alkaloids can be developed from vinyl-substituted cyclic carbonate (VCC) intermediates. Through a highly stereoselective palladium-catalyzed allylic alkylation reaction, these alkaloid motifs can be assembled in four synthetic and only two column purification steps. The combined results help to further advance functionalized cyclic carbonates as useful and reactive intermediates in natural product synthesis.

For many years, cyclic carbonates have been considered to be a category of relatively inert molecules with their main application being protecting groups of diols in synthetic organic chemistry.[1] This has been particularly useful in polyhydroxylated molecules such as sphingolipids or carbohydrates, and in these latter cases the cyclic carbonate productively served to improve the selectivity in glycosylation reactions.[2] Despite their excellent potential as protecting groups, this intrinsic kinetic stability has hampered their use as reactive intermediates in synthetic campaigns towards more complex organic molecules. Therefore, the synthesis of complex natural products using cyclic carbonates as reactive intermediates has indeed remained scarce.[3] This is noteworthy as their oxazolidinone (cyclic carbamate) analogues have been extensively used in natural product synthesis as chiral auxiliaries.[4]

Though cyclic carbonates have been seldom used in natural product synthesis, an increasing number of research groups have recently started to use vinyl cyclic carbonates (VCCs; see Scheme 1) as reactive partners in transition-metal catalyzed methodological development.[5] In particular, VCCs have been frequently used in allylic substitution chemistry[6] and C–H functionalization reactions.[7] Compared to vinyl epoxides, VCCs are not only more accessible, modular and easier to synthesize from readily available α-hydroxy ketones, but also their reactivity has proven to be different in some cases.[8] Our group has focused on the functionalization of vinyl cyclic carbonates in palladium-catalyzed allylic substitution reactions with different types of nucleophiles.[9] Previously, we reported on a palladium-catalyzed allylic alkylation combining modular VCCs and nitroalkanes as (pro)nucleophiles giving access to highly substituted, homoallylic nitroalkanes with excellent stereocontrol (Scheme 1).[10] We envisioned that this type of readily accessible (*Z*)-configured homoallylic nitroalkanes would provide an excellent starting point for the preparation of indolizidine and quinolizidine alkaloids (Scheme 1) in few overall synthetic manipulations via a double and appropriate cyclization strategy. These two families of alkaloids comprise more than 740 compounds that have been identified and isolated, and are naturally present in many living organisms.[11] In particular, indolizidine and quinolizidine alkaloids containing an aryl-substituent (such as ipalbidine, thylophorine, antofine and cryptoleurine as well as their *seco*-analogues) have received widespread attention due to their biological activities.[12] Several synthetic approaches towards these alkaloids have been reported,[13] but a more unifying and flexible strategy based on a common intermediate could allow simple access to a wider array of indolizidine and quinolizidine targets. Such a development would be of general importance from a synthetic and medicinal development point of view.



Scheme 1. Synthetic approach towards the synthesis of indolizidine and quinolizidine alkaloids using vinyl-substituted cyclic carbonates.

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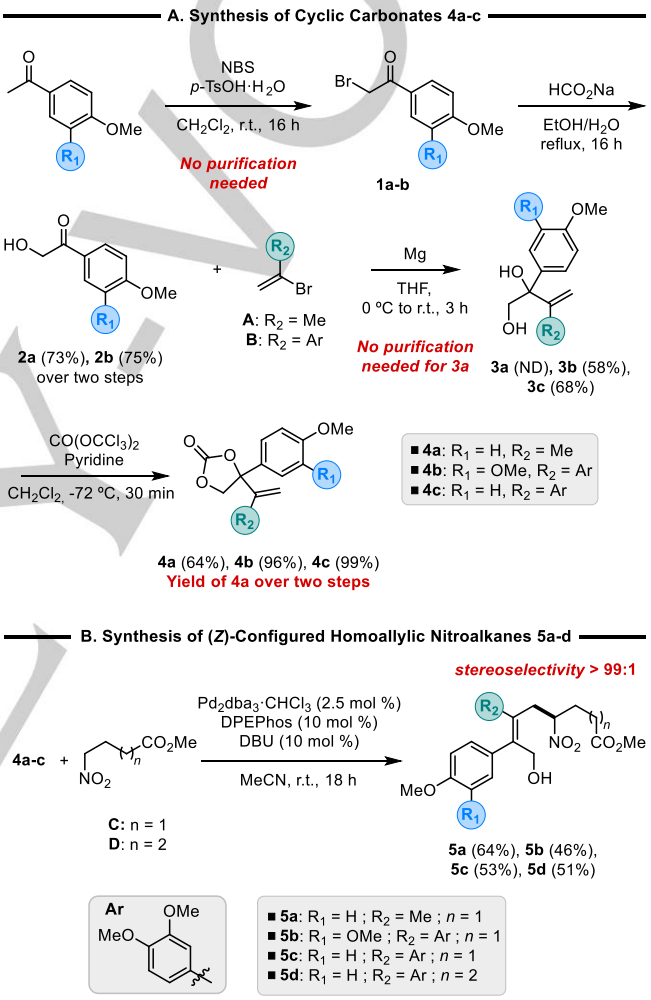
Herein, we report on a highly flexible and general synthesis of indolizidine and quinolizidine alkaloids that takes advantage of the modular and accessible nature of VCCs (Scheme 1). Importantly, our strategy relies on the excellent stereoselectivity achieved in the conversion of VCCs under palladium catalysis,[6c,6h,9] which sets up the formal alkaloid syntheses by providing precursors with the requisite functionalities and double bond configuration. Moreover, by slightly adjusting the synthetic route, we were able to access 2- and 3-substituted indolizidine alkaloids through stereodefined homoallylic nitroalkane intermediates.

The synthesis of VCCs **4a-c** was accomplished in four steps (Scheme 2A) starting from commercially available and inexpensive acetophenone derivatives. First, α-bromination was carried out with *N*-bromosuccinimide (NBS) under acidic conditions. Although compounds **1a-b** are commercially available, we preferred to use the freshly prepared reagents, as these compounds tended to decompose. Subsequent hydrolysis of crude **1a-b** with aqueous sodium formate solution gave the desired α-hydroxyketones **2a-b** in good yields. Compared to other methods, this approach worked best in terms of yield and reproducibility (see Table S1 in the Supporting Information for more details). With α-hydroxyketones **2a-b** in hand, Grignard reactions with freshly prepared organomagnesium reagents from alkenyl bromides **A** and **B** afforded 1,2-diols **3a-c**. A slight excess of organomagnesium reagent had to be used due to deprotonation of the free alcohol group. Therefore, purification of **3b-c** (containing R_2 = 3,4-dimethoxyphenyl) was needed to remove the non-volatile 3,4-dimethoxystyrene by-product, in contrast to gaseous propene generated from alkenyl bromide **A**. Finally, facile formation of the cyclic carbonate using triphosgene in the presence of pyridine at low temperature concluded the preparation of VCCs **4a-c**.

Once the synthesis of VCCs **4a-c** was completed, the stereoselective, catalytic formation of homoallylic nitroalkanes was examined (Scheme 2B). Using already established conditions for this transformation,[10] we successfully prepared compounds **5a-d** from VCCs **4a-c** and nitroalkanes **C-D** in 46-64% yield while maintaining excellent stereocontrol in the olefin moiety. Importantly, the stereochemical configuration around the double bond achieved in this step is crucial to provide the requisite geometry for the subsequent cyclization steps affording the 1,2,3,6-tetrahydropyridine ring present in the indolizidine and quinolizidine core.

The synthesis of the desired indolizidine and quinolizidine alkaloids was then carried out from compounds **5a–d**, which were first reduced to their diols using DIBAL-H at ambient temperature (Scheme 3). The resulting nitrodiol intermediates **6a–d** were further reduced with activated zinc under acidic conditions to efficiently yield the polar aminodiol intermediates **7a–d**. After screening of various conditions (see Table S2 in the Supporting Information for more details), we found that *in situ* generated SO_2F_2 under basic conditions smoothly enabled the formation of the bicyclic system. We believe that the hard electrophilicity of SO_2F_2 may provide suitable conditions for a charge-controlled reaction, which may not be the case if other electrophiles are employed. This unprecedented intramolecular double cyclization strategy represents a useful example of the utilization of SO_2F_2 to drive the overall chemoselectivity while allowing the efficient cyclization of an amino alcohol group.[14] These unique conditions proved to be more generally applicable and allowed to generate OMe-ipalbidine (**8a**), septicine (**8b**), seco-antofine (**8c**) and julandine (**8d**) in a reproducible and effective manner. Additionally, we confirmed the structure of julandine (**8d**) by X-ray analysis (Scheme 3).[15] Moreover, alkaloids **8a–d** have been previously used to access ipalbidine and the other phenantroindolizidine and phenantroquinolizidine alkaloids in a single step.[16]



Scheme 2. Synthesis of VCCs **4a-c** and their transformation into stereodefined homoallylic nitroalkanes **5a-d**. Ar = 3,4-$(OMe)_2C_6H_3$, NBS = *N*-bromosuccinimide, *p*-TsOH·H_2O = *p*-toluenesulfonic acid monohydrate, THF = tetrahydrofuran, ND = not determined, dba = dibenzylideneacetone, DPEPhos = bis[(2-diphenylphosphino)phenyl] ether, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Next, we investigated the introduction of substituents on the cyclopentane ring of the indolizidine core to provide access to novel alkaloid scaffolds. Since previous methods for such alkaloid synthesis start from proline or related pyrrolidine compounds which are difficult to functionalize,[12b] we envisioned a potential divergent approach that would allow to accommodate substituents

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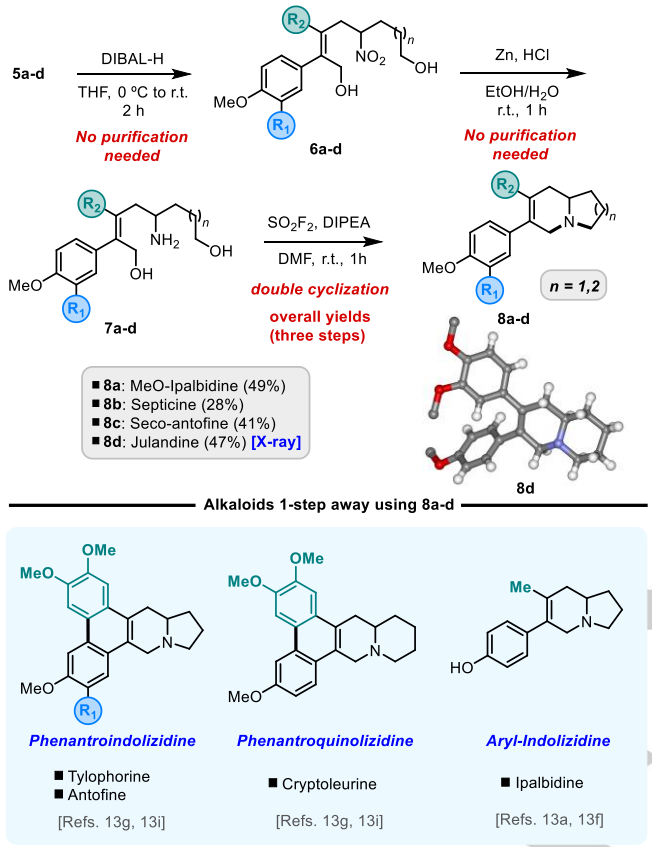
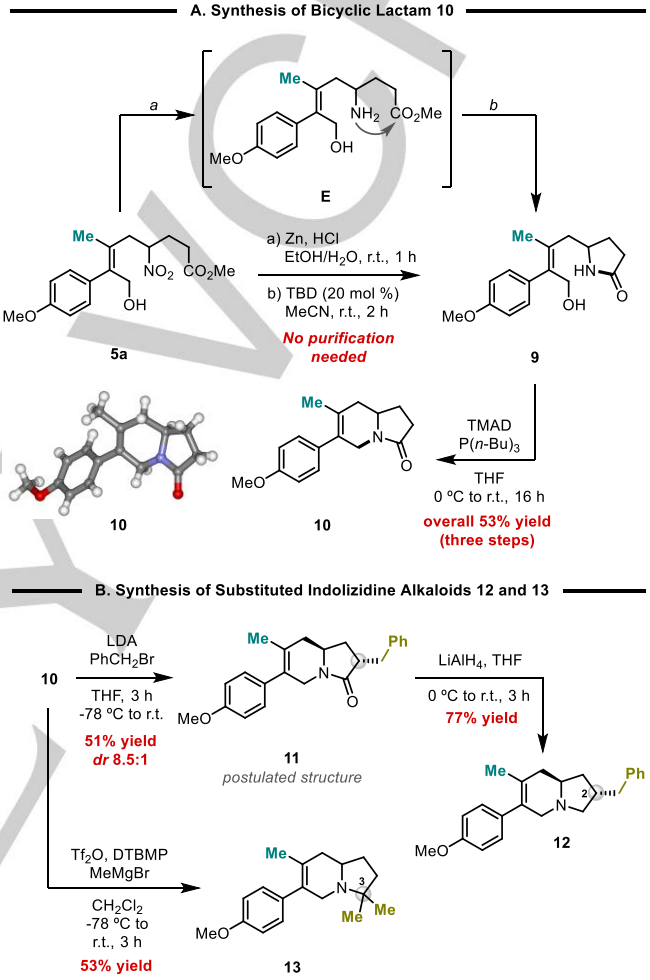
at positions 2 and 3 of the indolizidine core in an efficient and step-economical manner. Therefore, a straightforward reduction of the NO_2 group in compound **5a** with activated zinc under acidic conditions gave clean access to aminoester intermediate **E** (Scheme 4).



Scheme 3. Synthesis of indolizidine and quinolizidine alkaloids. DIBAL-H = diisobutylaluminum hydride, DIPEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide.

We expected that intermediate **E** would spontaneously cyclize to lactam product **9**, but the conversion after 16 h in refluxing MeOH was surprisingly low. The desired cyclization could be accelerated using a catalytic amount of triazabicyclodecene (TBD). Hereafter, a Mitsunobu reaction gave access to the cyclohexene ring of the indolizidine motif. Unfortunately, standard Mitsunobu conditions using DEAD and PPh_3 led to a complex mixture. However, using the less frequently used combination of tetramethylazodicarboxamide (TMAD) and tributylphosphine [P(*n*-Bu)$_3$] in THF afforded the desired bicyclic lactam **10** in 84% yield (see Table S3 in the Supporting Information for more details).[17] We further confirmed the structural assignation of the key bicyclic lactam intermediate **10** by X-ray analysis (Scheme 4).[18] From this intermediate, it was possible to introduce substituents at the 2- and 3-position of the indolizidine motif in a straightforward fashion. First, by taking advantage of the nucleophilic nature of the generated lithium enolate, it was possible to introduce a benzyl substituent at the 2-position (cf., intermediate **11**) with a diastereomeric ratio of 8.5:1. Subsequent reduction of the lactam with $LiAlH_4$ provided indolizidine alkaloid **12** in good yield. On the other hand, activation of the lactam with triflic anhydride at -78 ºC using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a bulky base, and subsequent double alkylation with excess MeMgBr afforded the 3,3-dimethyl indolizidine derivative **13**.[19]



Scheme 4. Synthesis of substituted indolizidine derivatives. TBD = triazabicyclodecene, TMAD = tetramethylazodicarboxamide, LDA = lithium diisopropylamide, Tf_2O = triflic anhydride, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

In conclusion, we have developed a flexible and general synthetic route for the synthesis of indolizidine and quinolizidine alkaloids from readily available vinyl-substituted cyclic carbonates (VCCs). A palladium-catalyzed allylic alkylation reaction of VCC building blocks provides useful stereodefined homoallylic nitroalkane intermediates,[20] which can be conveniently transformed into indolizidine or quinolizidine alkaloids in three additional synthetic and one purification step(s). Moreover, this synthetic route allows a divergent approach towards the synthesis of a wider variety of 2- and 3-substituted indolizidine derivatives through the intermediacy of a bicyclic lactam. This work thus further exemplifies that suitably substituted cyclic carbonates can

serve as key intermediates in natural product and fine chemical synthesis.

Acknowledgements

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Keywords: alkaloids • indolizidine • palladium • quinolizidine • vinyl cyclic carbonate

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[15] For details see CCDC-1951370.

[16] For ipalbidine, see refs. 13a and 13f. For cryptoleurine and tylophorine, see refs. 13g and 13i. For antofine, see ref. 13g.

[17] We believe that the failure in using standard DEAD and PPh_3 lies in the low basicity of the anion of the hydrazine dicarboxylate intermediate to deprotonate the lactam NH proton, which acted as a nucleophile instead. Therefore, we switched to diamide reagents whose hydrazine dicarboxamide intermediates should be more basic to deprotonate the lactam NH proton, and thus, partially suppress the nucleophilic attack of the hydrazine dicarboxamide intermediate. In a similar way, this is in accordance with the results reported by Roush and coworkers: C. Allais, W. R. Roush, *Org. Lett.* **2017**, *19*, 2646-2649.

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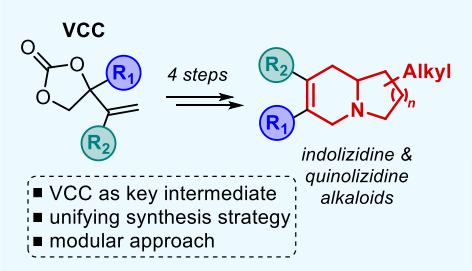
Raising alkaloids: A flexible synthesis of indolizidine and quinolizidine alkaloids is facilitated by stereoselective conversions of vinyl cyclic carbonates under Pd catalysis furnishing key stereodefined homoallylic nitroalkane intermediates. The vinyl cyclic carbonate substrates are showcased as modular and accessible reagents useful in natural product synthesis.



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