Nitrene C–H Bond Insertion Approach to Carbazolones and Indolones. Formal Total Synthesis of (–)-Methyl *N*-Decarbomethoxychanofruticosinate, (–)-Aspidospermidine and (+)-Kopsihainanine A

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Abstract

A new, modular platform for access to 1,2,3,9-tetrahydro-4*H*-carbazol-4-ones (H_4-carbazolones) and 3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-ones (H_2-indolones) is disclosed from readily accessed 2-arylcycloalkane-1,3-diones (6- and 5-membered). These precursors were prepared through a Cu-catalyzed arylation of 1,3-cyclohexanediones with aryl iodides or *via* a ring-expansion of aryl succinoin derivatives. Activation of a single carbonyl group in the diones, a highly regioselective reaction with unsymmetrical 2-arylcyclohexane-1,3-diones, and subsequent azidation gave 3-azido-2-aryl-cycloalk-2-en-1-ones. The regioselectivity was computationally assessed. Finally, a Rh-catalyzed nitrene/nitrenoid insertion into the *ortho*-C–H bond of the aryl moiety, gave the H_4-carbazolones and H_2-indolones, products that are of high synthetic value. One carbazolone synthesized was elaborated to a key intermediate for the formal total synthesis of *N*-decarbomethoxychanofruticosinate, (–)-aspidospermidine, (+)-kopsihainanine A. With 2-aryl-1,3-cycloheptanedione, prepared from cyclohexanone and benzaldehyde, the azidation reaction was accomplished in a facile manner. However, the Rh-catalyzed reaction led to some unusual observations, with an azirine as a major product. DFT computations were performed in order to understand the differences in reactivities of the 5- and 6-membered β-azido enones in comparison to the 7-membered analogue.

Introduction

The indole and dihydroindole moieties, privileged heterocycles, are present in a number of natural products and physiologically important compounds (examples in Figure 1). Because of the high importance of these scaffolds, methodological developments towards them are continually emerging.[1,2] Cyclohexa, cyclopenta, cyclohepta-fused indoles, and dihydroindoles are prominent in a number of natural and synthetic products. Besides, indole-fused cycloalkanones are themselves compounds of interest and many serve as precursors to other compounds.

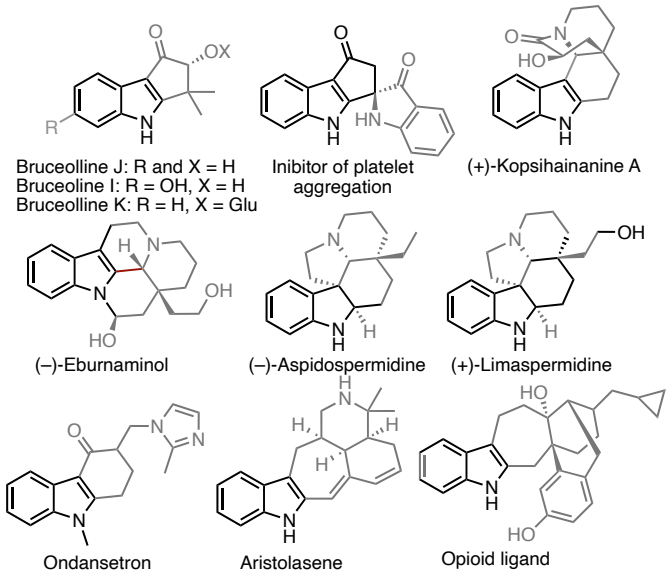
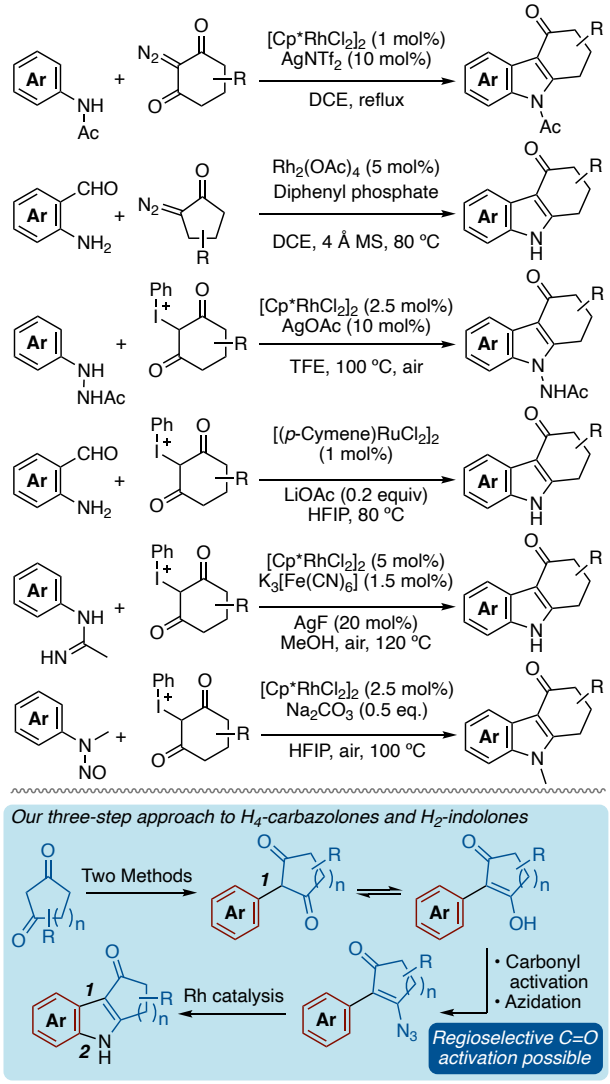


Figure 1. Examples of compounds containing an indole or a dihydroindole core.

It is therefore not surprising that over the years a number of methods have evolved to access H_4-carbazolones and H_2-indolones (see Table S1 in the Supporting Information). Classical approaches are Fischer indolization/oxidation[3–5] or indolization with 1,3-cyclohexanediones,[6,7] and Friedel-Crafts acylations.[8] Photochemical ring closure of β-*N*-aryl enaminones (with 100–400 W UV lamps) with an oxidant or with NaOMe yielded H_4-carbazolones,[9–11] but these procedures were generally inefficient for H_2-indolones. In applications of hypervalent iodine reagents, PIFA-mediated cyclization of α-aryl enaminones yielded H_4-carbazolones,[12] and Koser's reagent has been used to prepare H_4-carbazolones and H_2-indolones from β-*N*-aryl enaminones.[13] However, $AgSbF_6$ was a critical additive in the latter approach in order to access radical intermediates. In a single example, 3-((2-fluorophenyl)amino)cyclohex-2-en-1-one, was converted in a low yield to H_4-carbazolone by reaction with LDA at 75 ºC.[14] In other approaches, four H_4-carbazolones were obtained by a two-step reaction of aryl hydroxyl amines with dimedone and 1,3-

cyclohexandione,[15] and ring expansion of *N*-tosylindole-substituted cyclobutanols with NBS yielded *N*-tosyl H_4-carbazolones in modest yields.[16,17]



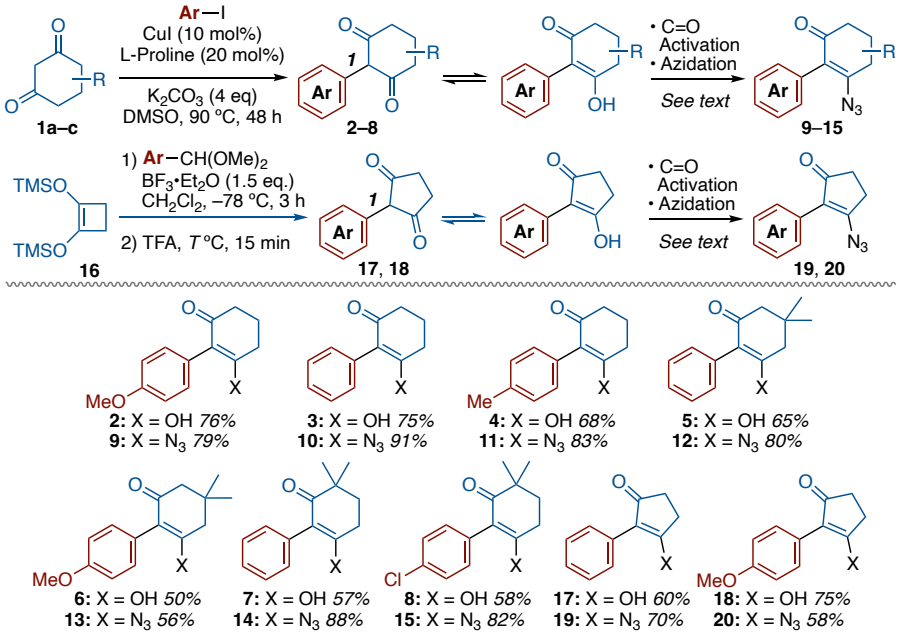
Scheme 1. Rh- and one Ru-catalyzed approaches to H_2-indolones and H_4-carbazolones.

Catalytic and stoichiometric metals have been used for cyclization of β-*N*-aryl enaminones. Methods include use of CuI/NaH in HMPA (105–170 °C),[18] CuI/L-proline/KOH in DMSO at 90 °C,[19] catalytic and stoichiometric $Pd(OAc)_2$,[20,21] and Pd/Cu co-catalysts.[22,23] Reductive-cyclization of 2-(2-nitrophenyl)-1,3-cycloalkanediones is also a route to indole-fused cycloalkanones.[24–28] A Pd^{II}-catalyzed amino cyclization and addition to a nitrile in an alkyne-tethered malononitrile has been used to produce *N*-mesyl carbazolones bearing various substituents and a nitrile α-to the carbonyl moiety.[29]

In relation to this work, Rh and Ru catalysts have recently been investigated, but these only yield H_4-carbazolones or their N-substituted derivatives (Scheme 1).[30–35] Our currently described work stemmed from our desire to develop a simple, scalable, modular synthetic platform that can result in rapid diversification. Furthermore, we were interested in methodology with applicability to 5-, 6-, and possibly 7-membered systems.

Results and Discussion

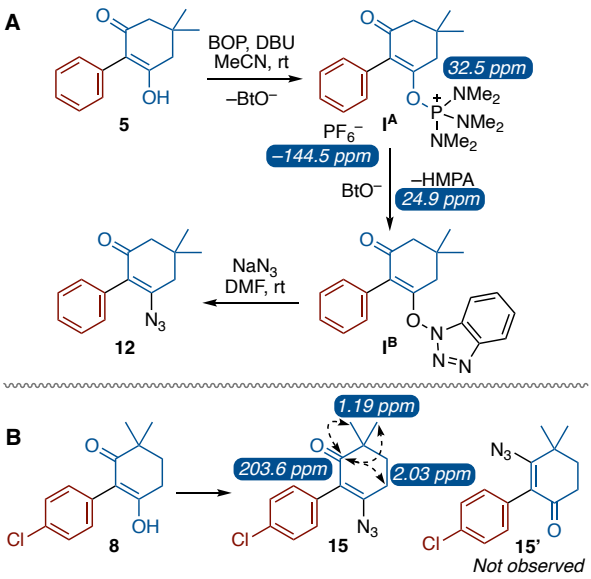
Despite the various approaches to H_4-carbazolones and H_2-indolones, many involve harsh conditions and/or functional group incompatibility issues, and the Rh-catalyzed methods in Scheme 1 are specific to H_4-carbazolones. Herein, we describe a modular and unified method to H_4-carbazolones and H_2-indolones, and our three-step approach is also shown in Scheme 1.



Scheme 2. Synthetic routes to 2-arylcyclohexane- and 2-arylcyclopentane-1,3-diones, and their subsequent conversion to β-azido enones.

In our approach, step 1 *en route* to H_4-carbazolones, involved a CuI/L-proline-catalyzed arylation of 1,3-cyclohexanediones **1a–c** with aryl iodides (Scheme 2).[36,37] However, the subsequent one-pot conversion of the ensuing 2-arylcyclohexane-1,3-diones (or the enols) **2–8** to the azides **9–15** required optimizations. For the unsubstituted substrates **2–4**, tosylation with *p*-TsCl/Et_3N in CH_2Cl_2, at 0 °C, and azidation of the crude tosylates with NaN_3 in DMF, at room temperature, was very effective. For precursors **5–8**, bearing substituents on the cyclohexyl ring,

carbonyl group activation was performed with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and DBU in MeCN, at room temperature. We have extensively studied the use of BOP for the activation of amido carbonyl groups in nucleosides,[38] and for the preparation of 4-azidocoumarins from 4-hydroxycoumarins.[36] Thus, activation of one carbonyl group in substrates **2**–**8** with BOP followed by azidation of the crude products with NaN_3 in DMF, at room temperature, gave azides **12**–**15** in generally good yields.



Scheme 3. Panel A: a plausible mechanism for the activation of the 1,3-dione moiety and azidation. Panel B: selective activation of the less hindered carbonyl group.

The carbonyl group activation by BOP was a mechanistic curiosity with important implications in the overall utility of this approach. Therefore, we first assessed a plausible mechanism *via* $^{31}P\{^1H\}$ NMR (see Scheme 3A and Figure S1 in the Supporting Information). The spectrum of BOP in CD_3CN (0.15 M) showed resonances for P^+ at δ = 43.7 ppm (s) and PF_6^- at δ = –144.5 ppm (sept). To this solution 1.0 eq. of substrate **5** was added and a spectrum was acquired, where no change was observed. Then, upon addition of 2.0 eq. of DBU, within 2 min two new resonances were observed at δ = 32.5 ppm and δ = 24.9 ppm. The former was more intense and was in the same range of other phosphonium ions we have observed.[38,39] The latter was less intense and corresponded to HMPA. After *ca.* 70 min the two new resonances were of nearly equal intensity and over time the HMPA resonance increased while that for the new phosphonium ion

decreased. On the basis of these data, we propose the mechanism shown in Scheme 3 where polar intermediate $\mathbf{I}^{A}$ is formed initially and is converted to the less polar benzotriazolyl derivative $\mathbf{I}^{B}$ by reaction with BtO^{-}. Both $\mathbf{I}^{A}$ and $\mathbf{I}^{B}$ are expected to react with azide ion.

A second very important discovery was in relation to the regioselectivity in the carbonyl group activation. With precursors **7** and **8** that contain an unsymmetrically functionalized cyclohexanedione moiety, the carbonyl group remote from the substituted carbon atom underwent *exclusive* activation. In the reaction of dione/enol **8**, a single azide regioisomer was obtained, and HMBC correlations were utilized for structure establishment. Key interactions between the carbonyl group and gem-dimethyl groups as well as the allylic methylene protons are shown in Scheme 3B (additional information was obtained by X-ray analysis, *vide infra*).

This observation led us to evaluate the energy differences between isomeric intermediates $\mathbf{I}^{C}$ and $\mathbf{I}^{D}$ by DFT (Figure 2). The initial structures were generated in GaussView 5 and were optimized at the B3LYP/6-311 G++ (d,p) level using Gaussian 09. In MeCN, $\mathbf{I}^{C}$ was lower in energy than $\mathbf{I}^{D}$ by 8.8 kcal/mol (the isomeric enolates only differ by 0.9 kcal/mol). Because an alternative approach is *via* enol sulfonates, reactions with $ArSO_2Cl$ are also anticipated to occur at the less sterically impeded carbonyl group. As with $\mathbf{I}^{C}$ and $\mathbf{I}^{D}$, DFT analysis showed a similar trend with a smaller difference of 3.2 kcal/mol (in CH_2Cl_2) between the two tosylate isomers (Figure S2 in the Supporting Information). Thus, should a need arise, we postulate that sterically bulky $ArSO_2Cl$ will enable discrimination in the regiocontrolling activation step.

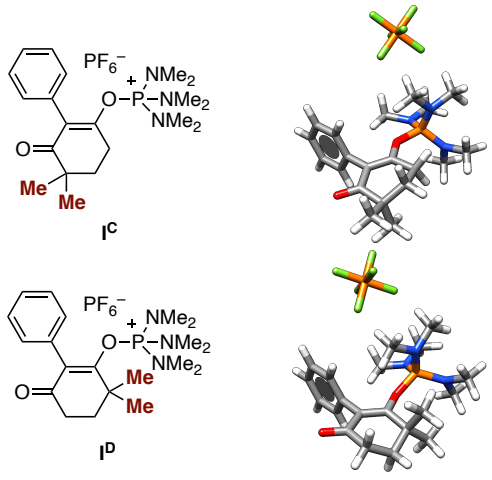
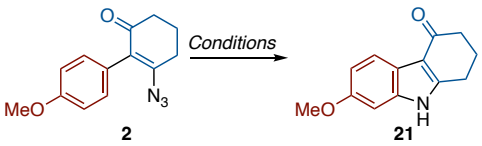


Figure 2. DFT computed structures of two regioisomeric phosphonium ion intermediates that can be obtained by carbonyl group activation of a 2-arylcyclohexane-1,3-dione.

Diones/enols **17** and **18**, precursors to H_2-indolones, were obtained by reaction of dimethyl acetals of aryl aldehydes with bis-silylated succinoin derivative **16** (Scheme 2).[40–42] Precursor **17** was converted to the intermediate tosylate by reaction with *p*-TsCl/Et_3N in CH_2Cl_2, at 0 °C. However, azidation with NaN_3 in DMF at room temperature, returned azide **19** in only a 42% yield. Because azidation of 3-chloro-2-phenylindan-1-one has been reported to be exothermic,[43] the azidation reaction was conducted at 0 °C. This change gave a significantly elevated yield of azide **19**. Application of a similar tosylation/azidation protocol to precursor **18** gave azide **20**.

Using azide **9**, a variety of conditions were evaluated for cyclization to indole **21**. These data are displayed in Table 1. Whereas good conversion was attained with catalytic $RuCl_3 \bullet 3H_2O$ in DME, the reaction was sensitive to temperature and solvent (entries 1–3). Product yield was greatly improved with $Rh_2(O_2CC_7H_{15})_4$ as catalyst, but this reaction was also sensitive to solvent (entries 4–7). $Rh_2(O_2CCH_3)_4$ and CuI proved to be quite inferior to $Rh_2(O_2CC_7H_{15})_4$ (entries 8 and 9). Dirhodium(II) catalysts have been employed in the synthesis of carbazoles from biaryl azides,[44] indole-2-carboxylates from β-aryl-α-azidoacrylates,[45] and pyrroles from *ortho*-azido stilbenes as well as *ortho*-azido-β-alkylstyrenes (2 examples).[46] The examples herein involve conversions of β-azido enones to products that can be further functionalized (*vide infra*).

Table 1. Conditions evaluated for the formation of indole 21.[a]



Entry	Conditions	*T* °C, *t* h	Yield[b]
1	2 mol% $RuCl_3 \bullet 3H_2O$, DME	60, 4	*60%*
2	2 mol% $RuCl_3 \bullet 3H_2O$, DME	85, 1	*48%*
3	2 mol% $Rh_2(O_2CC_7H_{15})_4$, 100 wt% 4 Å MS, PhMe	60, 1	*77%*
4	10 mol% $RuCl_3 \bullet 3H_2O$, 100 wt% 4 Å MS, PhMe	60, 18	*44%*
5	5 mol% $Rh_2(O_2CC_7H_{15})_4$, 100 wt% 4 Å MS, PhMe	60, 1	*84%*
6	5 mol% $Rh_2(O_2CC_7H_{15})_4$, 100 wt% 4 Å MS, MeCN	60, 1	*51%*
7	5 mol% $Rh_2(O_2CC_7H_{15})_4$, 100 wt% 4 Å MS, TFE	60, 1	*22%*
8	5 mol% $Rh_2(O_2CCH_3)_4$, 100 wt% 4 Å MS, PhMe	60, 5	*49%*
9	10 mol% CuI, 100 wt% 4 Å MS, PhMe	60, 5	*35%*

[a]Reactions were conducted with 0.2 mmol of azide **9** in 2 mL of solvent.

[b]Yield is of isolated and purified product.

Using conditions in entry 5 of Table 1, precursors **9**–**20** were all smoothy converted to H_4-carbazolones and H_2-indolones in generally high yields (Figure 4). HMBC and X-ray analyses allowed for additional insight into the highly regioselective carbonyl group activation discussed above. Key HMBC correlations between the carbonyl group in H_4-carbazolone **27** to the methyl as well as non-benzylic methylene protons, and one indolyl carbon atom to the benzylic as well as non-benzylic methylene protons are shown in Figure 4. X-ray analysis of H_4-carbazolone **27** provided unequivocal confirmation of the regioselective carbonyl group activation leading to this product. A crystal structure of H_2-indolone **28** was also obtained.

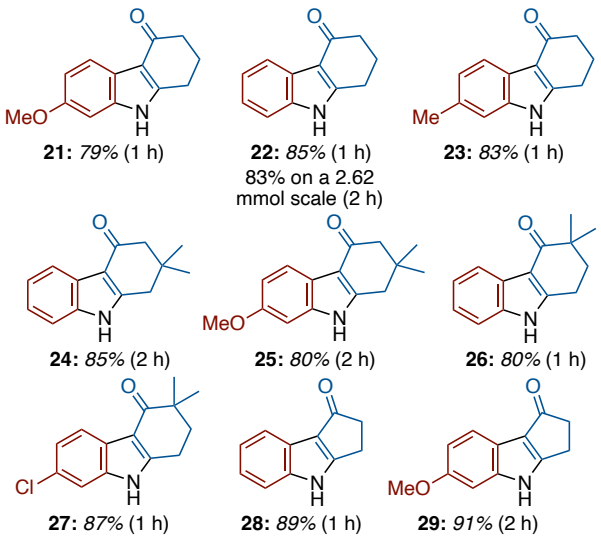


Figure 3. H_4-Carbazolones and H_2-indolones that were prepared.

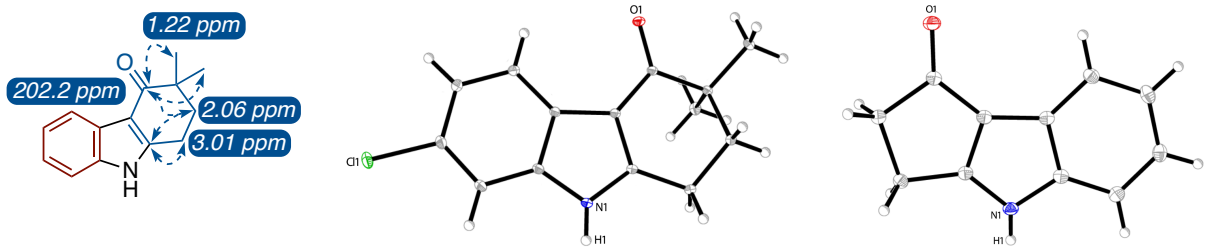
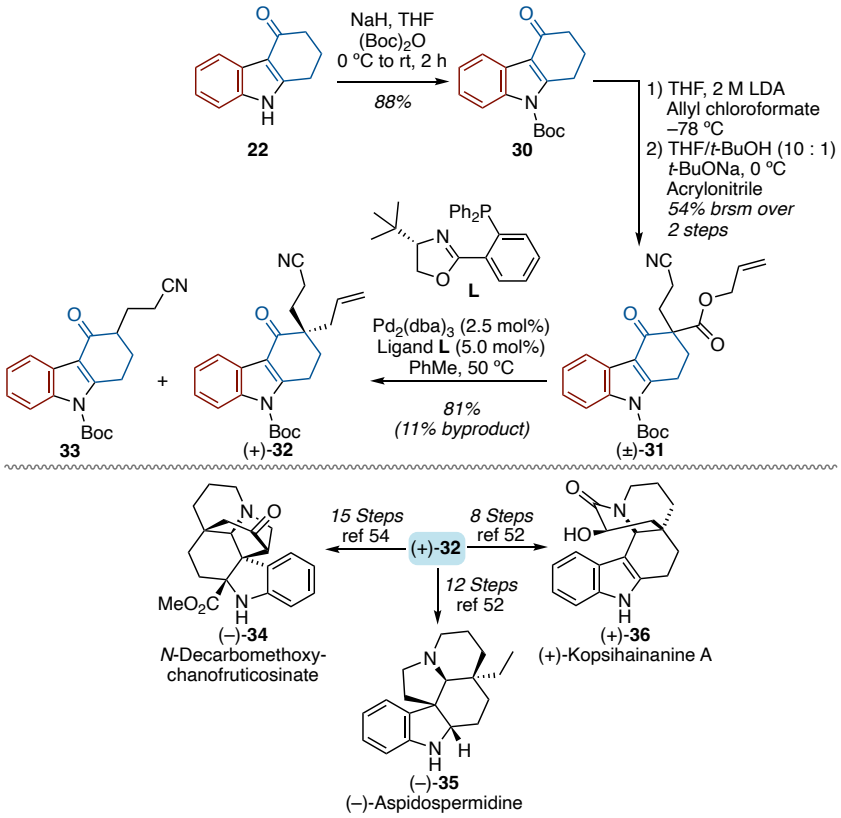


Figure 4. HMBC correlations observed in product 26, and crystal structures of products 27 and 28 (thermal ellipsoids are shown at the 30% probability level).

Facile access to H_4-carbazolones obtained *via* the methodology led us to consider the formal total synthesis of natural products. Enantioselective decarboxylative allylation[47–49] has been key to the synthesis of several indole-containing compounds.[50–55] Because an electron-withdrawing substituent was shown to be best for decarboxylative allylation,[50] H_4-carbazolone **22** synthesized

here, in a 58% yield over three steps, was subjected to *N*-Boc protection (Scheme 4, 88%),[51,56] A two-step acylation and conjugate addition, without purification of the intermediate, resulted in the precursor (±)-**31** (54% over 2 steps, based upon recovered precursor **30**). Decarboxylative-allylation with PHOX ligand **L** gave product (+)-**32** (81%) and the separable decarboxyl-protiated byproduct **33** (11%).

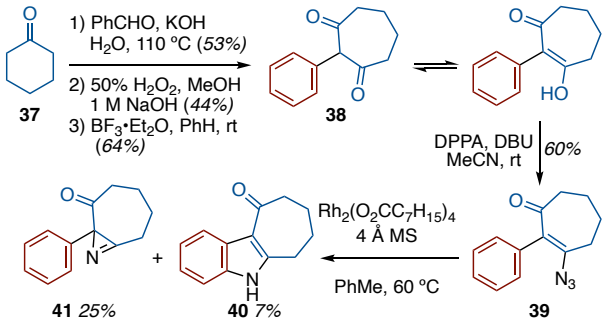


Scheme 4. Synthesis of a key intermediate in the synthesis of indole natural products.

N-Boc derivative (+)-**32** is a precursor to (–)-methyl *N*-decarbomethoxychanofruticosinate (**34**) without altering the indole protecting group.[54] On the other hand, a simple, high-yield interchange of the *N*-Boc group in compound (+)-**32** to *N*-Bn[50,51] yields a precursor to (–)-aspidospermidine (**35**)[52] and (+)-kopsihainanine A (**36**).[52] Also, a precursor to mersicarpine, leuconodine B and D, melodinine E, and rhazinilam can be obtained through a Witkop-Winterfeldt oxidative indole ring cleavage of *N*-Boc protected compound **30** (not shown).[56]

We then proceeded to evaluate the overall methodology for the synthesis of 6,7,8,9-tetrahydrocyclohepta[*b*]indol-10(5*H*)-one (H_4-cycloheptaindolone). Starting from cyclohexanone (**37**), the mono benzylidene derivative was synthesized using PhCHO.[57–59] This was then

epoxidized with H_2O_2/NaOH,[58] and the epoxide was subjected to a ring opening and rearrangement with BF_3•Et_2O to yield 2-phenylcycloheptane-1,3-dione (**38**).[59,60] Conversion of compound **38** to the β-azido enone required experimentation. In the tosylation/azidation approach impurities were observed to form in the tosylation step and this worsened during the azidation. With the BOP/DBU-mediated activation, multiple byproducts made an appearance and the azidation was not attempted. However, use of $(PhO)_2PON_3$ (DPPA) and DBU gave good conversion to the β-azido enone **39**.

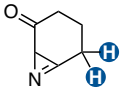
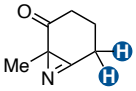
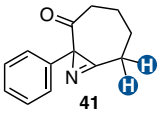


Scheme 5. Synthesis of 2-phenylcycloheptane-1,3-dione, conversion to the α-phenyl-β-azidocycloheptenone, and reaction with $Rh_2(O_2CC_7H_{15})_4$.

Exposure of α-phenyl-β-azidocycloheptenone **39** to $Rh_2(O_2CC_7H_{15})_4$ under the previously described conditions gave unexpected results. The minor product was the anticipated H_4-cycloheptaindolone **40** with NMR data comparable to those previously published[8] (see Table S1 for this comparison). In $CDCl_3$, the major product clearly showed the presence of five aromatic protons [at 500 MHz: δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H)], indicating the absence of reaction at the aryl C–H bond. Also, this compound showed some solvent-dependent NMR shifts of the alkyl protons (see the Supporting Information). The observed HRMS values for this compound were 200.1068 ($[M + H]^+$, calculated 200.1075) and 222.0888 ($[M + Na]^+$, calculated 222.0889). These collective data led to the conclusion that the major product in the reaction of the 7-membered precursor was azirine **41**. It was difficult to obtain literature NMR data for comparisons and two cyclohexyl azirines were identified for this purpose. The chemical shifts of methylene protons alpha to the azirine ring proved to be diagnostic and these are shown in Table 2.

To gain further confidence in the structural assignment of **41**, the ^{1}H NMR chemical shifts were computed using DFT at the B3LYP/6-311+G(2d,p)//M06-2X/6-31+G(d,p) level of theory (please see Table 19 in the Supporting Information). The aliphatic hydrogen atoms showed a mean absolute error (MAE) of 0.06, and the chemical shifts of the methylene protons alpha to the azirine showed absolute errors of 0.02 and 0.05 ppm.

Table 2. Comparison of the chemical shifts of three azirines.

Compound	Proton chemical shifts
	In $CDCl_3$ at –50 °C:[61,62] δ = 3.30 and 3.47 ppm
	In $CDCl_3$ at rt:[61,62] δ = 3.15 and 3.36 ppm
 **41**	In $CDCl_3$ at rt: δ = 2.96 and 3.25 ppm In DMSO at rt: δ = 3.10 and 3.25 ppm

In order to understand the plausible origins of the reactivity differences between the 5- and 6-membered β-azido enones (**3** and **17**) in comparison to the 7-membered analogue (**38**), natural bond orbital (NBO) analyzed charges on the olefinic carbon atoms were assessed by DFT computation using the B3LYP hybrid density functional with the 6-311++ G(d,p) basis set, in toluene solvent (please see Figure S3 in the Supporting Information). In this comparison, the NBO charges on the vinylic carbons atoms of the 5- and 6-membered enones were very comparable, but different from those of the 7-membered analogue. The β-carbon atoms of the 5- and 6-membered systems were more electropositive than that of the 7-membered enone. Likewise, the α-carbon atoms were more electronegative in the 5- and 6-membered enones as compared to the 7-membered analogue. Notably, the carbonyl group was conjugated with the olefin in the 5- and 6-membered enones, whereas it was out-of-plane in the 7-membered enone.

Next, the nitrene intermediates (not the Rh nitrenoids) were assessed computationally from various starting conformations (please see Figure S4 in the Supporting Information). In this comparison, the nitrenes from the 5- and 6-membered β-azido enones (**3** and **17**) showed significant planarization of the atoms involved in the cyclization, with electronic delocalization. In fact, in the 6-membered case the cyclized product structure emerged from the minimization

(geometry optimization) exercise. With the nitrene from the 7-membered β-azido enone (**38**), such a planarization and electronic delocalization was not observed. In a comparison of the NBO charges on the nitrogen atom and the vinyl carbons of the 5- and 7-membered nitrenes, these were quite different. From the DFT computed structures, the N to =Cα and the N to *ortho*-aryl carbon distances were compared in these two cases. In the 5-membered enone, the N to =Cα distance was 2.43 Å and the N to *ortho*-aryl carbon atom distance was 2.69 Å. In the 7-membered enone, the N to =Cα distance was a much shorter 1.59 Å, whereas the N to *ortho*-aryl carbon atom distance was 3.35 Å (please see Figure S5 in the Supporting Information). Such subtle features likely contribute to the preferential formation of the unstable aziridine **41** over the indole derivative **40** from the 7-membered β-azido enone.

CONCLUSIONS

In summary, we have developed a unified method for the synthesis of H_4-carbazolones and H_2-indolones from easily accessed 2-arylcycloalkane-1,3-diones. Carbonyl group activation and azidation, performed as a one-pot approach, and $Rh_2(O_2CC_7H_{15})_4$ mediated annulation results in the desired products. With 4,4-dialkyl-2-arylcyclohexane-1,3-diones, the less-hindered carbonyl group undergoes exclusive activation and azidation, and the basis for this regioselectivity has been explored computationally. Because single regioisomers of substituted H_4-carbazolones can be obtained, H_4-carbazolones differentially functionalized at either the cyclohexyl unit, or the indole, or both can be readily accessed. This will be a diversification point for the synthesis of natural products and their analogues, as well as other important indole-based compounds. Interestingly, the chemistry diverges in the case of the β-azido enone obtained from 2-phenylcycloheptane-1,3-dione, where the indole derivative was a minor product in the cyclization step and formation of an azirine predominated. DFT computations revealed substantial differences in the β-azido enones and nitrenes from the 5- and 6-membered ring systems as compared to the 7-membered one. These differences likely play out in the exclusive cyclization of the 5- and 6-membered β-azido enones to the indole derivatives, whereas the 7-membered β-azido enone predominantly led to a labile azirine. Further iterations of the concepts disclosed herein are considerations in these laboratories.

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Conflicts of Interest

There are no conflicts to declare.

Author Contributions

M. K. L. conceived the work, provided advise for the synthesis and at critical junctures, wrote the manuscript, and prepared a significant portion of the Supporting Information on the basis of the Ph.D. thesis of D. S. D. S. performed the benchwork, obtained NMR data, performed most of the interpretations, produced a Ph.D. thesis, supplied copies of the NMR spectra as well as the free induction decay files for the Supporting Information, and edited the manuscript and Supporting Information to rectify errors transferred from the thesis. P. P. performed the computational analyses in collaboration with M. K. L., assisted with complex NMR experiments, and with some NMR interpretations. M. C. N. performed the X-ray crystallographic analyses. P. H. W. performed the HRMS analyses of a number of compounds, and along with A. M. P., S. P. T, and A. E. K. H. performed the DFT analysis on the ^{1}H chemical shifts of compound **41**.

Data Availability Statement

Experimental details, additional data on the computational analyses, copies of NMR spectra, X-ray crystallographic data, and free-induction decay files can be found in the Supporting Information. CCDC Nos. 2282186-2282187 contain the supplementary crystallographic information files for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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