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# Hexadehydro-Diels–Alder (HDDA)-Enabled Carbazolyne Chemistry: Single Step, de Novo Construction of the Pyranocarbazole Core of Alkaloids of the *Murraya koenigii* (Curry Tree) Family

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Supporting Information

**ABSTRACT:** Here we report the use of the hexadehydro-Diels–Alder (HDDA) reaction for the de novo construction of a benzenoid ring in fused polycyclic heteroaromatic carbazole (i.e., [2,3]-benzoindole) skeletons. The strategy allows creation of highly substituted benzenoids. We also describe the HDDA-enabled chemical synthesis of the natural product alkaloids mahanimbine and koenidine. Trapping of the intermediate carbazolyne with a conjugated enal, proceeding through formal [2+2] cycloaddition, 4$\pi$-electrocyclic ring opening, and 6$\pi$-electrocyclic ring-closing events, constitutes a robust method for producing pyranocarbazoles.

Carbazoles have a long[1] and rich history in the fields of heterocyclic and medicinal chemistries and recently have garnered considerable attention as a chromophoric platform for the development of organic electroluminescent[2] materials. Hundreds of carbazole-containing alkaloid secondary metabolites are known.[3] Collectively these exhibit manifold categories of bioactivity.[4]

Numerous approaches for carbazole synthesis use construction of one of the benzenoid rings as a strategic tactic.[3,5] Methods using condensation, elimination, or oxidative aromatization reactions are common. Cyclizations or cycloadditions involving alkynes or allenes have also been used. These often give rise to the new six-membered carbocycle at precisely the oxidation state of benzene. The examples shown in Figure 1a–c include electrocyclic ring closure,[6] [2+2+2] cyclization of three isolated alkyne units,[7] and the tetradehydro-Diels–Alder[8,9] reaction.

Here we describe a new strategy for carbazole assembly that capitalizes on the hexadehydro-Diels–Alder (HDDA) cascade.[10] The process involves a sequential net 4+2 cycloisomerization reaction between a 1,3-diyne and a diynophile to produce a benzyne intermediate,[11] followed by one of several different modes of trapping reactions.[10−14] This cascade constitutes a powerful and versatile strategy for synthesis of benzenoid derivatives in which the benzene ring itself has been assembled in de novo fashion from the six reacting alkyne carbon atoms. The purely thermal nature of the reaction conditions lends itself to the discovery of new types of aryne trapping reactions that can be complementary to those possible with arynes generated by conventional[15] means.

In the studies we present here, the relevant and enabling intermediate is a carbazolyne (**2**, Figure 1d), a rare member[16] of the family of arynes. We have used a number of different trapping agents Nu–El to capture the intermediate carbazolynes. Collectively, these demonstrate the versatility of this approach for preparing carbazoles bearing a wide variety of substituents and other structural variations. Finally, we further demonstrate the strategic power of this approach[17] through efficient chemical syntheses of the mahanine alkaloids mahanimbine (**12**)[18] and koenidine (**19**)[19] in which three of the four rings in these pyranocarbazoles are constructed in a single operation.

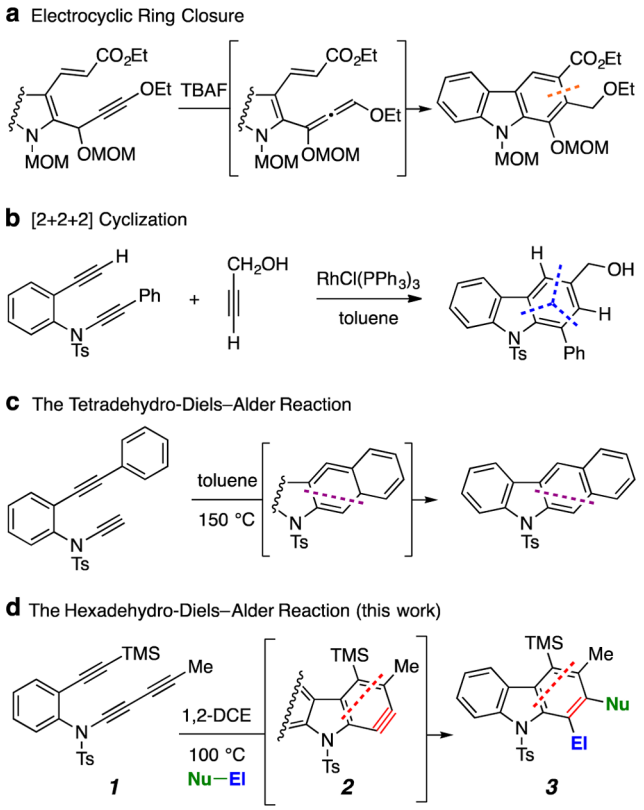


**Figure 1.** (a–c) Three known types of alkyne-containing substrates that produce a benzenoid moiety of carbazoles. (d) The hexadehydro-Diels–Alder (HDDA) cascade of the diynamide substrate **1** produces substituted carbazoles **3** via the carbazolyne **2**.

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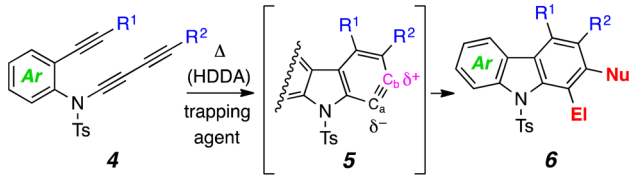
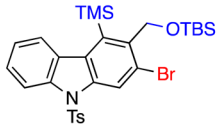
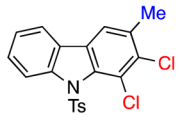
**Table 1. HDDA Construction[a] of Carbazoles 6 from Triyne Substrates 4 via Trapping of the Carbazolynes 5**



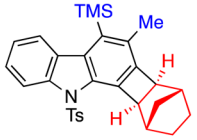

**Product (trapping agent, isolated yield)**



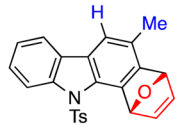

**6a** ($NEt_3$•HBr,[b] 87%)



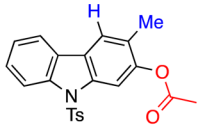

**6b** ($Li_2CuCl_4$,[c] 94%)



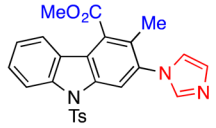

**6c** (norbornene,[d] 37%)



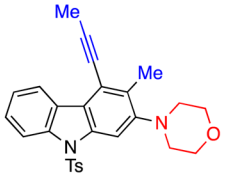

**6d** (furan,[c] 72%)



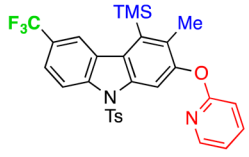

**6e** (acetic acid,[b] 71%)



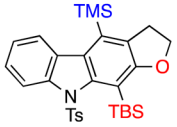

**6f** (imidazole,[c] 79%)



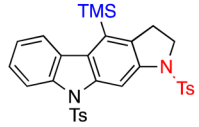

**6g** (morpholine,[c] 78%)




**6h** (2-pyridone,[d] 97%)




**6i** (internal OTBS, 72%)



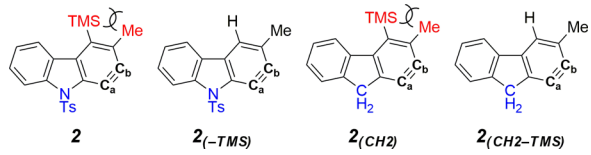

**6j** (internal NHTs, 72%)

[a]Reactions were carried out in 1,2-dichloroethane (DCE), chloroform, or THF at temperatures of 90−100 °C (see Supporting Information) with an initial concentration of **4** = 0.02 M. [b]2 equiv of external trapping agents used. [c]5 equiv of external trapping agents used. [d]10 equiv of external trapping agents used.

In Table 1 we have shown examples of the types of carbazoles that can be prepared using this HDDA approach. Many different types of trapping agents, both internal (tethered) and external, are effective, and often highly so. Various substituents $R^1$ and $R^2$ are accommodated on the alkyne termini [e.g., TMS, H, $CO_2Me$, and alkynyl (on the diynophile) and alkyls (on the diyne)], and the benzene ring in the triyne **4** can carry an additional substituent (e.g., **6h**). Taken together, these types of modifications can be envisioned to allow for considerable flexibility in the substitution pattern that can be accessed in the carbazole products **6**.

For trapping reactions that involve inequivalent trapping atoms or groups, the nucleophilic component could add to either $C_a$ or $C_b$ in the electrophilic carbazolynes **5**. However, we never observed an isomeric product arising from attack of the nucleophile at $C_a$ (cf. **6a**, **6e**, **6f**, **6g**, and **6h**).[20] This essentially perfect level of regioselectivity is deserving of comment. Aryne **5** ($R^1$ = TMS and $R^2$ = Me; i.e., **2** in Figure 1) is computed [DFT: SMD($ClCH_2CH_2Cl$)/M06-2X/6-31G(d)] to be significantly distorted, having a very large difference of 24° (see Table 2) between the intra-annular angles at its nominally sp-

**Table 2. Computed (DFT) Geometric Distortion of 2 vs Analogous Benzynes Lacking the TMS and/or Having the Electronegative *N*-Toluenesulfonyl Moiety Replaced by a Methylene Group**




**2** **$2_{(-TMS)}$** **$2_{(CH2)}$** **$2_{(CH2-TMS)}$**

| angle (deg) | 2 | $2_{(-TMS)}$ | $2_{(CH_2)}$ | $2_{(CH_2-TMS)}$ |
|---|---|---|---|---|
| ∠a | 114.8° | 117.7° | 120.8° | 125.3° |
| ∠b | 138.8° | 136.0° | 134.1° | 129.9° |
| ∠b−∠a | 24.0° | 18.3° | 13.3° | 4.6° |

hybridized atoms $C_a$ vs $C_b$. It is now well established[21] that this ring-distortion allows one to account for (or predict in advance) the sense of the regioselectivity shown by unsymmetrical trapping agents of the Nu−El class. Consistent with this, the nucleophilic portion of the trapping agent (Nu) shows a high preference for adding to $C_b$, the atom having higher in-plane p-character and, accordingly, greater electrophilicity ($\delta^+$) in the reactive, strained alkyne. This is portrayed in **5** at the top of Table 1.

To gain a better sense of the factors that contribute to the highly biased geometry of these carbazolynes, we also calculated the extent of distortion in several analogs of **2**. These are shown in Table 2. The remote TMS substituent is more than an innocent bystander. Its removal results in a reduction of the ring distortion (see $\mathbf{2}_{(-TMS)}$, where b−a = 18.3°), presumably a response to the change in the buttressing force the TMS imposes on its adjacent substituents. Nonetheless, the trapping of **5** ($R^1$ = H and $R^2$ = Me) with, for example, acetic acid also proceeded with high regioselectivity, giving **6e** as the only observed product. To understand the impact of the electronegative NTs substituent adjacent to carbon a, the geometries of the methylene replacement analogs $\mathbf{2}_{(CH2)}$ and $\mathbf{2}_{(CH2\text{-}TMS)}$ were also computed. These show, in turn, a substantial reduction in the extent of the internal distortion (b−a = 13.3° and 4.6°, respectively), which shows that the inductive effect of the NTs is a major contributor to the polarization of the alkyne in carbazolyne **2**. A similar effect has been observed for the computed geometric distortions of 6,7-indolyne vs 4,5-indanyne.[21b]

We then explored whether this type of reaction could serve as an enabling strategy for the synthesis of mahanine alkaloids such as mahanimbine (**12**, Scheme 1) and koenidine (**19**, Scheme 2). These natural substances are found in *Murraya koenigii* (the curry tree) and have been ingested by humans, including for medicinal purposes, for eons. Koenidine was recently reported to show insulin sensitizing and blood glucose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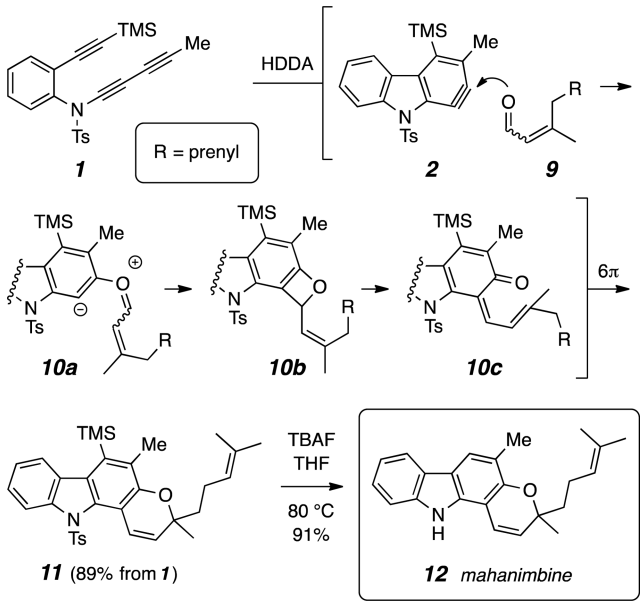
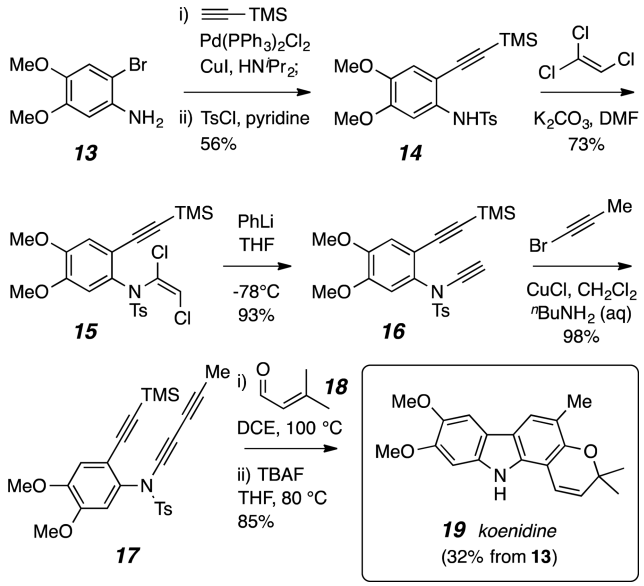
**Scheme 1. Key Step in the Enal Trapping of Benzyne 2, Establishing the Tetracyclic Pyranocarbazole Core Structure of Mahanimbine (12)**




**Scheme 2. Synthesis of Koenidine (19)**



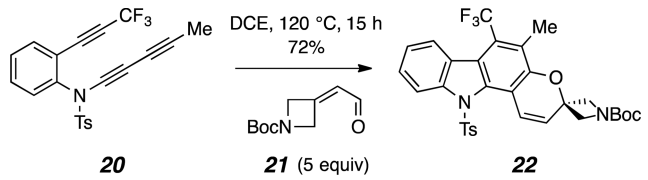

lowering properties in mice.[22] Each of the carbazoles **12** and **19** bears a fused pyran ring, a hallmark of many of the carbazoles found in *Murraya koenigii*, indigenous to Asia.

Enals were recently reported to produce benzopyrans (or chromenes) by trapping *o*-benzyne.[23] If the engagement of the benzyne by the nucleophilic carbonyl oxygen atom in the enal initiates the capture event, then the distortion present in a benzyne like **2** should dictate the proper outcome required for assembly of the requisite skeleton for mahanimbine (**12**) and koenidine (**19**). In the event (Scheme 1), when triyne **1** was heated in the presence of citral (**9**, 2.0 equiv), a very clean transformation to **11** allowed its isolation in 89% yield after chromatographic purification. This reaction proceeds, presumably, through the intermediate 1,3-zwitterion **10a**, benzoxetene **10b**, and alkenyl quinonemethide **10c**, prior to the ultimate electrocyclic ring closure to the pyran. This transformation proceeds with 100% atom efficiency and is mediated solely by thermal energy; no reagents or catalysts are used. Removal of the TMS and Ts groups in **11** proved to be trivial under the action of tetrabutylammonium fluoride (TBAF) in THF at 80 °C, which smoothly provided **12**.

To prepare koenidine (**19**), the triyne **17**, the dimethoxy analog of **1**, was required. The preparation of this substrate, starting from the commercially available bromide **13**, is shown in Scheme 2. This is representative of the strategy used to prepare each of the HDDA substrates used in this study (see the Supporting Information for those details). Particularly noteworthy is the construction of the ynamide bond[24] in **16** via the 1,2-dichlorovinylsulfonamide **15**.[25] In our hands this strategy proved to be more reproducible and serviceable for the sulfonamide **14** than one using the ethynyl iodonium salt HC≡C(Ph)I$^+$TfO$^-$.[26] Heating **17** with *β*,*β*-dimethylacrolein followed by TBAF treatment to strip away the TMS and Ts groups completed this efficient synthesis of koenidine.

Finally and as evidence of the potential that this benzyne plus enal trapping reaction has for the construction of additional types of polycyclic skeletons, we show the reaction between the triyne **20** (which happens to bear a trifluoromethyl substituent[27] on the diynophile) and the designer exocyclic enal **21**[28] (Scheme 3). When heated at 120 °C for 15 h,[29] the spirocyclic pyran **22** was smoothly produced.

**Scheme 3. Example of Use of an Exocyclic Enal, 21, To Introduce the Spirocyclic Pyran Subunit in the Product, 22**




In summary, we have shown that an HDDA cascade is a general strategy for the preparation of substituted carbazoles. The intermediate, unsymmetrical carbazolynes can be captured by a variety of nucleophilic trapping agents with perfect regioselectivity. Factors that contribute to the distortion of these intermediate arynes have been probed through a simple DFT study. Efficient reactions of carbazolynes with 3,3-disustituted enals comprise a key strategy for construction of the tetracyclic pyranocarbozole rings of the alkaloids mahanimbine (**12**) and koenidine (**19**). The de novo construction of a highly substituted, central benzenoid ring constitutes a significant strategic advance.[12i,30]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09628.

New compound preparation, spectroscopic characterization data, and copies of $^1$H and $^{13}$C NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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