# A Stereoselective Michael—Mannich Annelation Strategy for the Construction of Novel Tetrahydrocarbazoles†

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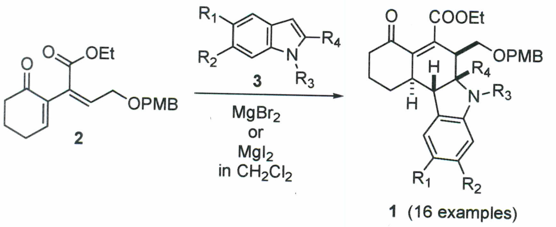
*Supporting Information Placeholder*



**ABSTRACT:** A novel annelation strategy has been devised for stereoselective synthesis of tetrahydrocarbazoles. The pathway features a regio- and stereocontrolled condensation of indole and its substituted derivatives with electron-deficient 1,3-dienes via a Michael–Mannich reaction sequence. An extension of this method to include cross-conjugated allenes as substrates also results in a Michael–Mannich–Michael cascade, incorporating two equivalents of indole with increasing product complexity. The formal $4\pi + 2\pi$ cyclization describes a concise route to polycyclic alkaloids of this family.

Carbazole and tetrahydrocarbazole ring systems are prominent features displayed in many alkaloids. In fact, heteroaromatic 9*H*-carbazoles are widely distributed among plants of the family *Rutaceae*, and are also isolated from microorganisms.[1] The tetrahydrocarbazole motif is common to polycyclic alkaloids, but also serves as a key precursor to the parent carbazoles via mild dehydrogenation. Representative examples show significant biological activity, and, as a result, there is a high level of interest in the development of efficient methods of preparation.[2] Prior art has broadly utilized the multistep Fischer–Borsche procedure for the synthesis of tetrahydrocarbazoles and subsequent oxidations to 9*H*-carbazoles.[3] Recent studies have described transition-metal catalyzed oxidative cyclizations which directly access *N*-substituted carbazoles via aniline derivatives.[4] Transition-metal catalysis has also facilitated the discovery of applications of indoles in C–H activation and intramolecular alkenylation.[5] Asymmetric $\pi$-allyl metal cyclizations[6] have been utilized to afford tetrahydrocarbazoles. Noteworthy benzannulations of 2-alkenyl-, 3-alkenyl- and 2,3-divinyl-substituted indoles have been described.[7] Intense efforts have focused on methods which employ indoles and simple indole derivatives for convergent strategies in the construction of highly substituted carbazoles.[8,9] A recent report has described a one pot, three-component condensation of indoles, ketones and nitroalkenes, which leads directly to functionalized carbazoles via *in situ* air oxidation.[10] On the other hand, hydrogen-bonding catalysis promotes asymmetric Michael reactions of nitroalkenes and 2-propenylindoles to yield complex tetrahydrocarbazoles with good to excellent enantioselectivity.[7a,11]

Cycloadditions have been employed for the synthesis of tetrahydrocarbazoles using, electron-deficient indoles as dienophiles,[12] and inverse electron-demand Diels–Alder reactions of 3-chloro-indole have been described.[13] One report has documented asymmetric induction with chiral thioureas in the Diels–Alder reactions of 3-vinylindole with several dienophiles as a route to enantioenriched tetrahydrocarbazoles.[14] Bäckvall[15] and Matsuo[16] have described stepwise [4+2] cycloadditions of indoles to give useful tetrahydrocarbazole systems, and Zhang and coworkers have recently demonstrated asymmetric induction in the gold-catalyzed formal [4+2] cycloadditions of 3-styrylindoles with *N*-allenamides.[17]

This report communicates studies leading to an efficient synthesis of complex 2,3,4,9-tetrahydro-1*H*-carbazoles (**1**). As illustrated in Figure 1, our investigations have explored a formal $[4\pi+2\pi]$ annelation reaction of electron-deficient 1,3-dienes **2** with indole and substituted indole derivatives **3** to effect a regio- and stereocontrolled cycloaddition.

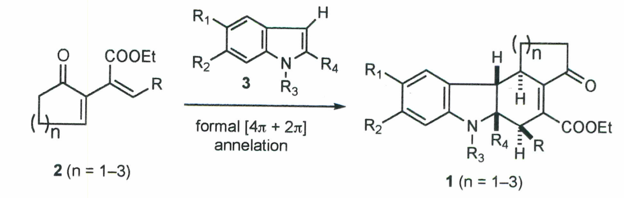


**Figure 1.** Tetrahydrocarbazoles via condensations of **2** and **3**.

These efforts have been substantially advanced by our prior report of cross-coupling methodology for the preparation of unsymmetrical $\alpha$-linked bisenone systems.[18] In this fashion,

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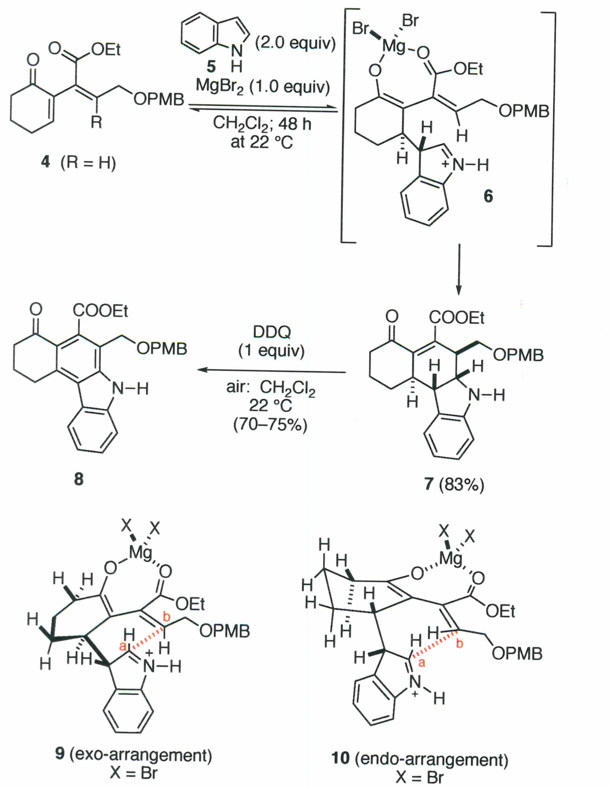
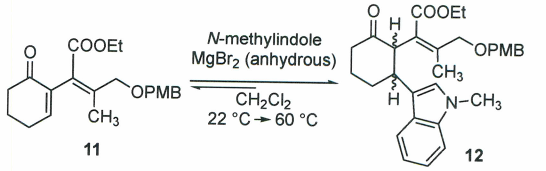
† We dedicate this paper to Professor Al Padwa on the occasion of his 80th birthday.

we have readily obtained the differentiated and cross-conjugated α,β-unsaturated dicarbonyl system **4**. The anticipation of increased reactivity of **4** via Lewis acid catalysis enhances regioselectivity and underscores the role of the ketone carbonyl as a preferred site of coordination. On this basis, the condensation of indole with enone **4** (Scheme 1) in the presence of anhydrous $MgBr_2$ (1 equiv) at 22 °C, has afforded the tetrahydrocarbazole **7** (83% yield) as a single diastereoisomer. Stereochemical assignments in **7** are based upon extensive NOESY-NMR studies (see Supporting Information). We postulate a reaction mechanism which is initiated by the nucleophilicity of C-3 of indole and the activated Michael acceptor enone of **4**. The production of an extended enolate **5** leads to intramolecular capture of the iminium intermediate in a Michael–Mannich cascade.

**Scheme 1. The Michael–Mannich Annelation of Indole with Enone 4**



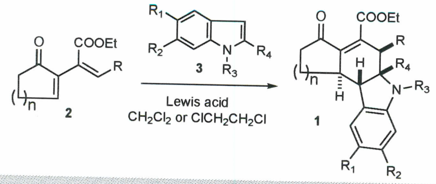
In fact, the product **7** reflects the result of an inverse electron-demand Diels–Alder reaction via an *exo*-transition state (TS). Although an asynchronous cycloaddition[19] is also plausible, we have assumed a reaction coordinate that progresses via an initial Michael addition. Our modelling has indicated that a feasible orientation for cyclization is achieved in the bonding arrangement leading to **9** versus **10**. The *exo*-arrangement **9** provides a half-chair TS with *trans*-diaxial hydrogens at sites (a) and (b), whereas the *endo*-arrangement **10** reveals a boat-like TS for bond formation. DFT computational studies, optimized with B3LYP/6-31G(d), have provided further details. These studies have indicated that the estimated TS energy for an asynchronous TS via **10** is approximately 6.0 kcal/mol higher than the *exo*-arrangement. In addition, the product **7** is 3.1 kcal/mol more stable than the corresponding diastereomeric carbazole resulting from **10**. Facile DDQ oxidation (1 equiv) leads to the aromatic C-ring of the carbazole alkaloids prior to removal of the PMB ether to yield **8**. Additional quantities of DDQ result in cleavage of the PMB to yield the corresponding alcohol of **8** (Scheme 1). Experimental evidence for a stepwise rationale is suggested from reactions of enone **11**, incorporating β,β-disubstitution of the unsaturated moiety. Utilizing similar reaction conditions, a modest yield of the Michael adduct **12** is obtained as an inseparable mixture of *cis*- and *trans*-diastereomers without advancing the Mannich cyclization.

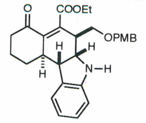
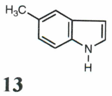
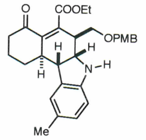
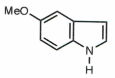
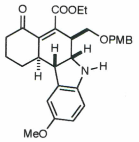
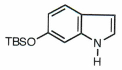
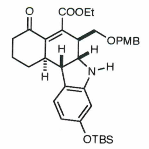
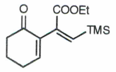
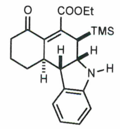
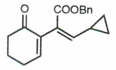
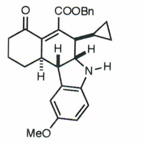
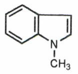
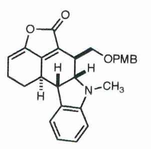
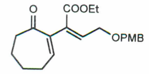
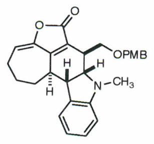
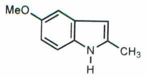
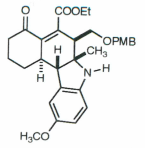
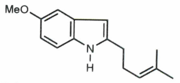
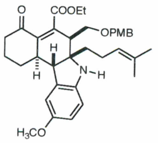
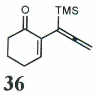
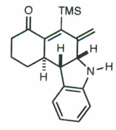
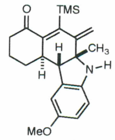
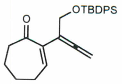
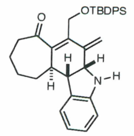
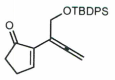
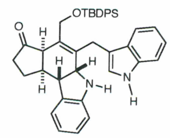
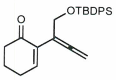
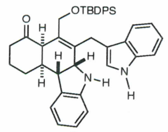


As a focused study to develop this concept for the synthesis of targeted natural product congeners, the scope of our reaction has been explored for a related series of polycyclic systems. A compilation of results is summarized in Table 1. In the course of these investigations, a number of Lewis acid catalysts have been examined, including anhydrous salts of $CuBr_2$, $ZnBr_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Eu(fod)_3$, $Yb(OTf)_3$ and $Sc(OTf)_3$.[20] Generally, all of these choices failed to induce productive annelations whereas the use of anhydrous $MgBr_2$ or $MgI_2$ in $CH_2Cl_2$ or 1,2-dichloroethane solutions selectively afforded the desired adducts. Reactions are not observed upon the introduction of coordinating solvents such as diethyl ether or THF. Similarly, the use of chiral (*S*)-Binol[21] or pybox ligand 2,2′-isopropylidene-bis(4*S*)-4-*tert*-butyl-2-oxazoline[22] for Lewis acid coordination also extinguished the anticipated reactivity. Table 1 permits a comparison of $MgBr_2$ and $MgI_2$ catalysis. Qualitatively faster reactions are observed with the use of anhydrous $MgI_2$ (1 equiv) as compared to anhydrous $MgBr_2$ (1 equiv) at 22 °C. However, the nucleophilicity of the iodide diminishes yields of the ethyl esters while producing small amounts of side products (compare Table 1, entries 1–5). Substitution in the starting indole **2** ($R_1$ or $R_2$) features the series of 5-methyl, 5-methoxy and 6-*tert*-butyldimethylsilyloxy (OTBS) derivatives, leading to the expected products **14**, **16**, and **18** (Table 1, entries 1–6). Although studies have focused on the incorporation of a protected hydroxylmethyl substituent ($CH_2OPMB$), the successful inclusion of labile cyclopropyl and trimethylsilyl groups in the 1,3-diene component (Table 1, entries 7 and 8) is indicative of the breadth of the reaction. These examples proceed without the need for N–H protection of the indole. On the other hand, less reactive *N*-methylindole ($R_3$ = Me) (entries 9 and 10) has required the use of $MgI_2$. These experiments occur with annelation and subsequent dealkylation of the ethyl ester to yield the complex butenolides **24** (80%) and **26** (35%) (30% of the ethyl ester of **26** is also obtained). Two examples have detailed reactions of C-2 substituted indoles **27** and **29** (entries 11 and 12). The annelation products **28** and **30** are isolated in modest yields (40%), displaying a quaternary carbon at the ring fusion. The latter attempts also introduced a number of uncharacterized byproducts, contributing to the reduced yields.

The annelation has been extended to the series of conjugated allenic, cyclic enones of Scheme 2. The allenic substrates are prepared in one step via the Stille cross-coupling of the propargylic stannanes **31** and **32** with α-iodoenones **33**, **34**, and **35** by direct application of our previous report.[23] In this fashion, the reactive allenic enones **36, 37, 38,** and **39** are generated in 51% to 69% yields, and subsequent condensations with indoles occurred smoothly at 22 °C to 50 °C. This high-value transformation efficiently assembles the unsaturated tetracycle **41** (72%) from **37** via the Mannich reaction of **40** (Scheme 2). Similarly, the TMS substituent of **36** is tolerated for the formation of **42** and **43** (Table 1, entries 13 and 14). In these cases, reduced steric hindrance in the Mannich ring closure leads to the isolation of diastereomers indicating cyclizations proceeding from *syn*- and *anti*-Michael adducts. The extended conjugation of these adducts has suggested the possibility of a Michael–Mannich–Michael cascade. In the event, our incorporation of excess indole, as shown in entries 16 and 17 of Table 1, provides for subsequent 1,6-conjugate addition from the initial annelation products to yield **45** (70%) and **46** (70%), respectively. These findings have illustrated an elegant, two-step construction of molecular complexity from the starting α-iodo-enones **33** and **34**, resulting in diastereoselective generation of novel polycyclic alkaloids. Unambiguous stereochem-

**Table 1. Michael–Mannich Annelation Reactions**

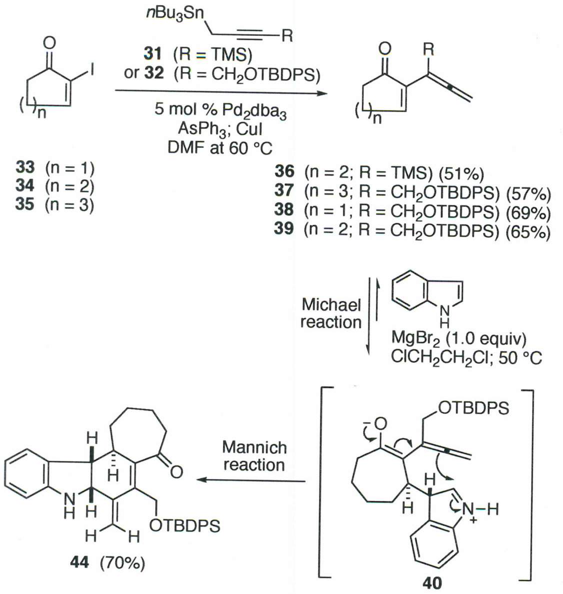


| entry | enone | indole | conditions | product yield (%)[a] |
|---|---|---|---|---|
| 1 | enone **4** | **5** | MgI$_2$ (36 h) at 22 °C | <br>**7** (59) |
| 2 | enone **4** | <br>**13** | MgBr$_2$ (48 h) at 22 °C | <br>**14** (80) |
| 3 | enone **4** | **13** | MgI$_2$ (24 h) at 22 °C | **14** (50) |
| 4 | enone **4** | <br>**15** | MgBr$_2$ (24 h) at 22 °C | <br>**16** (73) |
| 5 | enone **4** | **15** | MgI$_2$ (16 h) at 22 °C | **16** (70) |
| 6 | enone **4** | <br>**17** | MgBr$_2$ (24 h) at 22 °C | <br>**18** (59)[b] |
| 7 | <br>**19** | **5** | MgBr$_2$ (36 h) at 22 °C | <br>**20** (76) |
| 8 | <br>**21** | **15** | MgBr$_2$ (24 h) at 22 °C | <br>**22** (75) |
| 9 | enone **21** | <br>**23** | MgI$_2$ (24 h) at 22 °C | <br>**24** (80) |
| 10 | <br>**25** | **23** | MgI$_2$ (36 h) at 22 °C | <br>**26** (49) |
| 11 | enone **4** | <br>**27** | MgBr$_2$ (24 h) at 22 °C | <br>**28** (40) |
| 12 | enone **4** | <br>**29** | MgBr$_2$ (48 h) at 22 °C | <br>**30** (38) |
| 13 | <br>**36** | **5** | MgBr$_2$ (36 h) at 22 °C | <br>**42** (60)[c] |
| 14 | **36** | **27** | MgBr$_2$ (48 h) at 22 °C | <br>**43** (38)[d] |
| 15 | <br>**37** | **5** | MgBr$_2$ (4 h) at 50 °C | <br>**44** (70)[e] |
| 16 | <br>**38** | **5** (3.0 equiv) | MgBr$_2$ (4 h) at 50 °C | <br>**45** (72) |
| 17 | <br>**39** | **5** (3.0 equiv) | MgBr$_2$ (4 h) at 50 °C | <br>**46** (60)[f] |

[a] Isolated yields of the purified product are obtained after flash silica gel chromatography. [b] An additional amount (15–20%) of the corresponding phenol is obtained due to TBS cleavage. [c] Less than 8% yield of the "all *syn*" diastereomer of **42** is identified (dr 88:12), based on the proton integrations of NMR signals. This minor isomer coelutes with indole in the HPLC analysis, and is not purified further. [d] The "all *syn*" diastereomer of **43** is isolated in 16% yield (dr 70:30). [e] The "all *syn*" diastereomer of **44** is also isolated in 13% yield (dr 84:16). [f] Equal amounts of two *trans*-fused tetrahydrodecalin diastereomers are also isolated (10% yield of each isomer).

ical assignments of **45** have been established by a single crystal X-ray diffraction study.[24]

**Scheme 2. Cyclizations of Allenic Enones**



In summary, a novel synthesis of complex tetrahydrocarbazoles has utilized a regio- and stereocontrolled annelation achieved via the asynchronous [4 + 2] cycloaddition of indoles with electron-deficient α-linked bisenone derivatives.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglettxxxxxx

General information, experimental procedures and characterization data, $^1$H and $^{13}$C NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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