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Multicatalytic Asymmetric Synthesis of Complex Tetrahydrocarbazoles via a Diels–Alder/Benzoin Reaction Sequence

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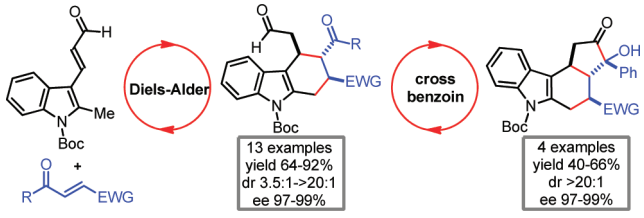
ABSTRACT



Expanding upon the recently developed aminocatalytic asymmetric indole-2,3-quinodimethane strategy, a straightforward synthesis of structurally and stereochemically complex tetrahydrocarbazoles has been devised. The chemistry's complexity-generating power was further harnessed by designing a multicatalytic, one-pot Diels–Alder/benzoin reaction sequence to stereoselectively access *trans*-fused tetracyclic indole-based compounds having four stereogenic centers with very high fidelity.

Polycyclic indole architectures,[1] including tetrahydrocarbazole derivatives,[1e−h] are key structural elements in many natural alkaloids and synthetic biologically active compounds. There is thus great interest in developing catalytic asymmetric methodologies to efficiently access these privileged molecular scaffolds.[1d,2]

Recently, our laboratory discovered a straightforward synthetic route to complex tetrahydrocarbazole derivatives with multiple stereocenters using nontraditional disconnections.[3] The chemistry used the intrinsic synthetic power of the Diels–Alder reaction to provide predictable and single-step access, from simple starting materials, to stereochemically dense cyclohexenyl rings adorned with different molecular architectures (Figure 1). The success of this indole-2,3-quinodimethane strategy[4] relied on the *in situ* generation of intermediates **II**, reactive diene species that were never before used in a catalytic approach. Upon condensation with enal **1** and the formation of the expected electrophilic iminium ion intermediate **I**, the chiral secondary aminocatalyst **A** (diphenylprolinol silylether)[5] induced a tautomerization event toward the reactive species **II**, while selectively directing the [4 + 2] cycloaddition reaction with suitable dienophiles toward a highly enantioselective pathway.

Recognition of the directness and versatility of the aminocatalytic indole-2,3-quinodimethane strategy for the stereocontrolled annulations of indole systems prompted

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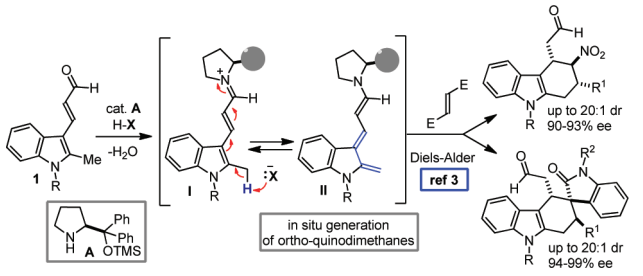
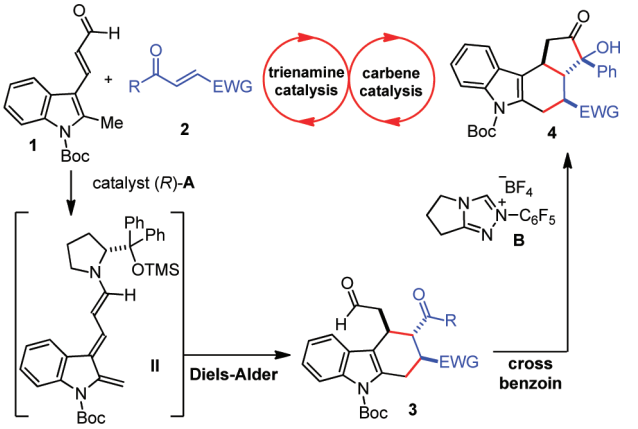


Figure 1. Aminocatalytic indole-2,3-quinodimethane strategy (previous work used nitroolefins and methyleneindolinones as the dienophiles, see ref 3).

us to further investigate its synthetic potential. In particular, we wondered if the complexity-generating power of the chemistry could be further expanded by integration into a multicatalytic reaction sequence. Tandem or cascade reactions have recently been recognized as powerful tools for delivering dramatic increases in molecular and stereochemical complexity via single-pot operations, without the need for intermediate workup or purification.[6] In addition, the seminal studies by Rovis,[7] Jørgensen,[8] and Enders[9] have shown that it is possible to combine the catalytic activity of secondary amines of type **A** and *N*-heterocyclic carbenes (NHCs, catalysts of type **B** in Scheme 1) to stereoselectively access complex molecules.[6a] Given the compatibility of these two catalysts, we envisioned a direct way to stereoselectively access *trans*-fused tetracyclic indole-based compounds **4** by combining the aminocatalytic-driven in situ formation of indole-2,3-quinodimethane intermediates **II** with an NHC-promoted intramolecular benzoin condensation (Scheme 1).[10] For this to be feasible, we needed to use a well-designed dienophile **2** in the first aminocatalytic step. The multicatalytic system would only be operative if we included a substrate bearing a keto moiety, the chemical handle that is essential for benzoin condensation.

Here we describe the successful realization of this idea, based on the extension of the indole-2,3-quinodimethane strategy to include novel classes of keto-containing dienophiles **2** and the optimization of an unprecedented one-pot Diels–Alder/benzoin reaction sequence. The chemistry provides straightforward access to highly functionalized tetrahydrocarbazoles **3** and **4** bearing multiple stereogenic centers with extremely high regio-, diastereo-, and enantioselectivity.

Scheme 1. Design Plan for the Multicatalytic Asymmetric Diels–Alder/Cross-Benzoin Reaction Sequence to *trans*-Fused Tetracyclic Products (EWG: Electron Withdrawing Group)



The versatility of the aminocatalytic indole-2,3-quinodimethane strategy was initially tested against the enal **1a**/*trans*-1,2-dibenzoylethylene **2a**[11] combination. We chose the *N*-Boc protected 3-(2-methyl-indol-3-yl)acrylaldehyde **1a** because of its previously established ability to coax the *in situ* formation of the key indole-2,3-quinodimethane intermediate **II** upon condensation with the aminocatalyst **A** (20 mol %). The commercially available **2a** was selected as the dienophile. This is because it bears the chemical handle needed to develop the envisioned multicatalytic strategy. Table 1 summarizes selected optimization studies on the Diels–Alder process, which led to the tetrahydrocarbazole **3a**. Extensive details are reported in the Supporting Information (Tables S1–S3).

Initial results confirmed that the indole-2,3-quinodimethane strategy, driven by catalyst **A**, can be successfully extended to other dienophile classes, while maintaining its inherent ability to rapidly build up complex frameworks from simple starting materials and with high stereoselectivity. Evaluation of the standard reaction parameters revealed that both the reaction medium and the acidic additive were crucial factors for improving the catalysis. The best results were achieved when using toluene and a catalytic system made by mixing equimolar amounts of amine **A** with the bulky 2,4,6-trimethylbenzoic acid (TMBA, entry 5). Importantly, the reaction temperature increased the catalyst turnover while minimally affecting the stereoselectivity of the cycloaddition process (entry 6). From a synthetic standpoint, it is worth mentioning that the use of the antipode of catalyst **A** showed the same catalytic profile and stereochemical outcome, granting access to each product enantiomer individually (entry 7).

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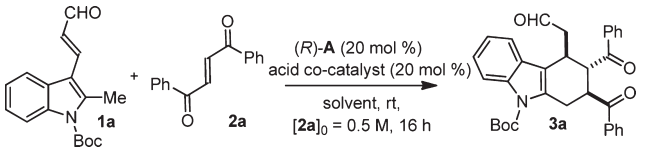
(10) Previous studies showed how carbene catalysis could be combined with distinct aminocatalytic activation modes driven by amine **A**. References 7a, 8, and 9a deal with iminium ion activation. Reference 7b deals with enamine activation. Here, we provide the first demonstration that the reactivity of an extended enamine (the trienamine intermediate **II**) can also be integrated into a multicatalytic process.

(11) Wang, Y.; Li, H.-M; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, Li. *J. Am. Chem. Soc.* **2007**, *129*, 6364.

Table 1. Selected Optimization Studies[a]



entry	solvent	acid	yield[b] (%)	dr[c]	ee[d] (%)
1	toluene	–	<5	nd	nd
2	toluene	$PhCO_2H$	38	5.6:1	97
3	DCE	$PhCO_2H$	48	6.3:1	94
4	toluene	o-NO_2-$PhCO_2H$	42	8:1	97
5	toluene	TMBA	52	8:1	96
6[e]	toluene	TMBA	84	8:1	98
7[f]	toluene	TMBA	85	8:1	98[f]

[a] Reactions performed mixing **1a** (0.12 mmol), **2a** (0.1 mmol), (*R*)-**A** (0.02 mmol), and acid (0.02 mmol) in 0.2 mL of the solvent at ambient temperature for 16 h. [b] Yield of the isolated compound **3a**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction performed at 40 °C over 48 h. [f] The (*S*) enantiomer of amine **A** was used, leading to the opposite antipode of product **3a**. DCE = 1,2-dichloroethane, TMBA = 2,4,6-trimethylbenzoic acid.

The conditions in entry 6 were selected to examine the scope of the Diels–Alder process by evaluating a variety of keto-containing dienophiles **2**. Figure 2 summarizes the results. There appears to be significant tolerance toward structural and electronic variations of substitution patterns on the dienophiles. Different substituents at the aromatic moiety of the symmetric *trans*-1,2-dibenzoylethylene derivatives were well-tolerated, regardless of their electronic properties. The corresponding tetrahydrocarbazoles **3a**–**d** were obtained in good yield and very high levels of stereocontrol (up to 8:1 dr, 97–99% ee). We also explored the influence of an unsymmetrical substitution pattern on both sides of the dienophile double bond. We successfully extended the chemistry to include nonsymmetrical *trans*-benzoylacrylic esters (R = aryl, EWG = ester moiety), achieving an almost perfect level of chemo-, diastereo-, and enantioselectivity (products **3e**–**l** in Figure 2).

The catalytic system also maintained its efficiency when applied on a synthetically useful scale (1.0 mmol), leading to the formation of the adducts **3c** and **3e** with comparable yield and optical purity (results between brackets refer to a 0.1 mmol scale). We also found that the stereochemistry of the cycloadducts **3** appeared to be insensitive to the double bond geometry of **2**. Indeed, starting from a *trans*- or *cis*-configured dienophile, the corresponding tetrahydrocarbozole **3f** was forged with the same relative and absolute configuration. This is because, under the reaction conditions, a scrambling of the double bond occurs prior to the cycloaddition.[12] It is noteworthy that the indole-2,3-quinodimethane strategy can also be applied to benzoyl acrylonitrile (EWG = CN), with the corresponding product **3m** formed with perfect regioselectivity. Finally, we

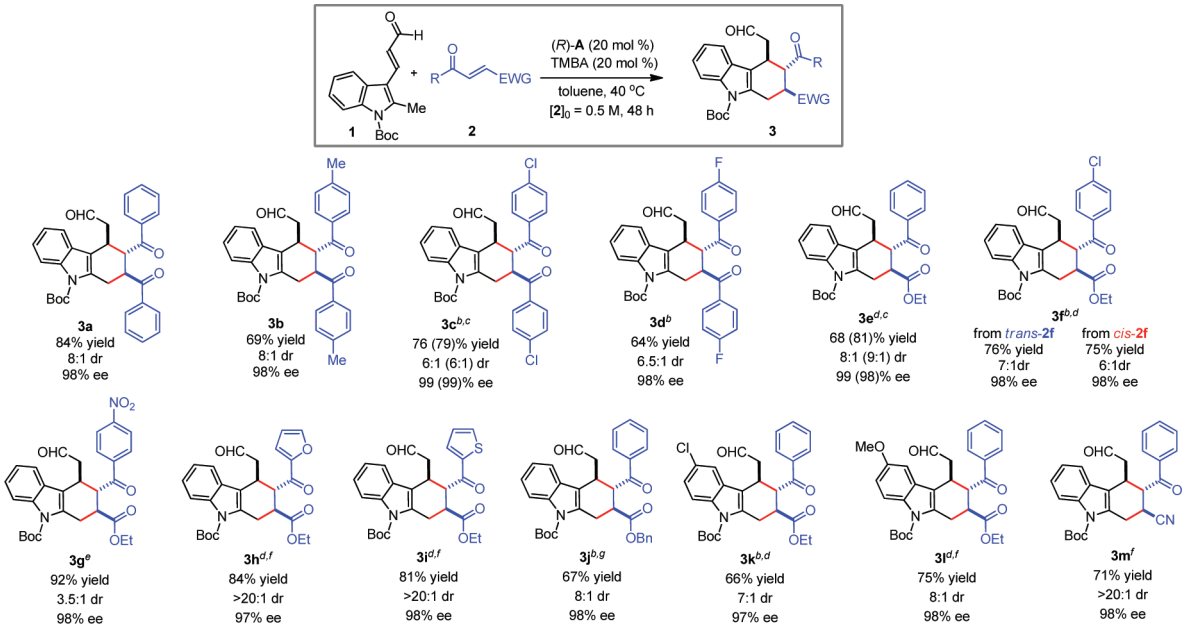
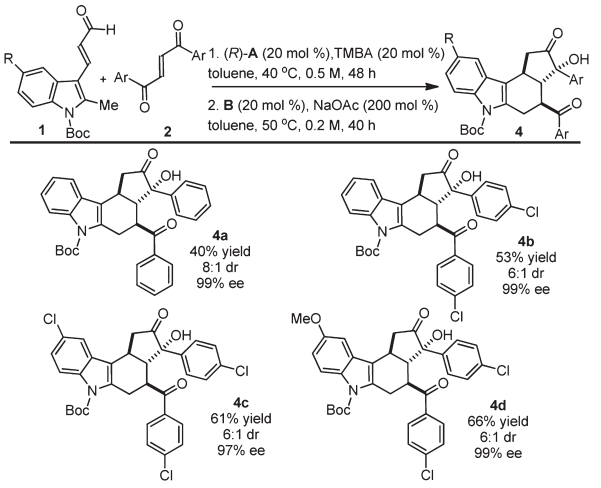


Figure 2. Extending the aminocatalytic indole-2,3-quinodimethane strategy to new classes of dienophiles. [a]Unless noted otherwise, reactions performed at 40 °C with **1** (0.12 mmol), **2** (0.1 mmol), **A**, and TMBA (0.02 mmol) in toluene (0.2 mL) for 48 h. Yields refer to the sum of the isolated diastereoisomers **3** and reflect the degree of conversion. [b]Yield of the isolated single, major diastereoisomer. [c]1 mmol scale reaction: results between brackets refer to 0.1 mmol scale reaction. [d]Reaction at 50 °C. [e]2,6-Bis(trifluoromethyl) benzoic acid (20 mol %) was used. [f]Yield and ee were determined after in situ homologation of aldehydes **3h**–**i**,**l**–**m** with a Wittig reagent (PPh_3=$CHCO_2Et$, 0.14 mmol, rt, 16 h). [g]Reaction at 60 °C.

showed that different substituents on the indole core of enal **1** were well tolerated. Substitution at the 5-position efficiently provided diene precursors for the highly stereoselective Diels–Alder reaction with *trans*-benzoylacrylic esters, leading to products **3k** and **3l**.

Scheme 2. Multicatalytic Diels–Alder/Cross-Benzoin Reaction Sequence to *trans*-Fused Tetracyclic Products



With suitable conditions elaborated for a productive pericyclic step, we turned our attention to implementing a multicatalytic Diels–Alder/benzoin reaction sequence. We initially tried to have both the aminocatalyst **A** and the NHC precursor **B** from the outset of the process. However, the Diels–Alder reaction was very sluggish in the presence of a base, which was required to in situ form the active carbene catalyst.[13] Consequently, the achiral triazolium salt **B** and sodium acetate were added in a sequential one-pot manner at an elevated temperature after completion of the Diels–Alder reaction. The resulting multicatalytic process involved an amino-catalyzed pericyclic pathway under trienamine activation[14] of enals **1**, followed by a *N*-heterocyclic carbene-catalyzed intramolecular crossed-benzoin reaction. It led directly to the densely functionalized *trans*-fused tetracyclic indole-based compounds **4** with four stereogenic centers with very high fidelity (Scheme 2). While symmetric dibenzoylethylene derivatives worked well in the multicatalytic sequence, *trans*-benzoylacrylic esters led to complex product mixtures. This is probably because of a transesterification event between the ester group and the newly generated OH group under basic conditions.

(12) NMR spectroscopy confirmed a quick isomerization event, with the *trans* dienophile being the final active species of the pericyclic process.

(13) The absence of an acid cocatalyst resulted in a very sluggish Diels–Alder reaction; see Table 1, entry 1. The complete progress towards the optimized conditions for the multicatalytic sequence is detailed in Table S4 within the Supporting Information.

(14) Diels–Alder reactions via trienamine intermediates: (a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (b) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *37*, 8638. (c) Jiang, H.; Gschwend, B.; Albrecht, L.; Hansen, S. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *33*, 9032.

(15) Crystallographic data for compound **4b** are available free of charge from the Cambridge Crystallographic Data Centre, accession number CCDC 862664.

(16) The optical purity of products **4** reflects the stereoselectivity of the Diels–Alder process, leading to precursors **3**.

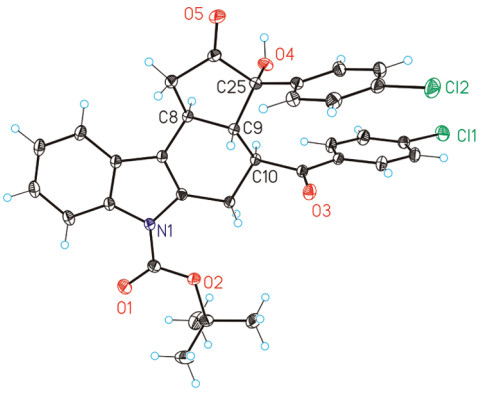


Figure 3. Single crystal X-ray diffraction data for **4b**.

An X-ray crystal structure analysis of the dichloro-substituted cycloadduct **4b** unambiguously allowed the determination of the stereochemical outcome of the multicatalytic process (Figure 3).[15] An *exo*-selective Diels–Alder process[3,14b] is followed by a completely stereoselective benzoin condensation, proceeding through a substrate-directed pathway.[16]

The amino-catalytic indole-2,3-quinodimethane strategy can rapidly build up complex frameworks from simple starting materials. We have shown how its potential can be expanded to include a variety of different dienophiles. The implementation of a multicatalytic, one-pot Diels–Alder/benzoin reaction sequence, based upon the unprecedented combination of trienamine and carbene catalysis, led to the highly stereoselective preparation of complex tetrahydrocarbazole derivatives.

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Supporting Information Available. Complete experimental procedures, compound characterization, HPLC traces, and NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.