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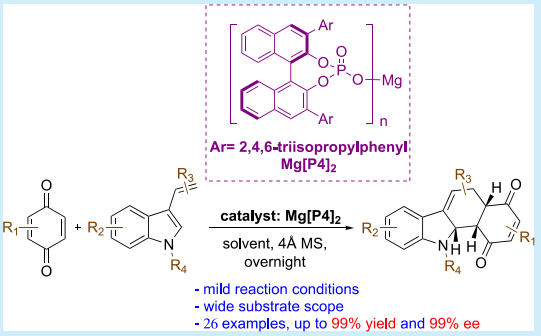
Catalytic Enantioselective Diels−Alder Reactions of Benzoquinones and Vinylindoles with Chiral Magnesium Phosphate Complexes

Yujia Bai, Jinping Yuan, Xiaoyue Hu, and Jon C. Antilla*

Institute for Molecular Design and Synthesis, School of Pharmaceutical Science and Technology, Health Science Platform, Tianjin University, Tianjin 300072, China

Supporting Information

ABSTRACT: Tetrahydrocarbazole and its derivatives have received much attention due to the prevalence of this scaffold in natural products and their use in organic synthesis. We have developed a Diels−Alder reaction of benzoquinones and 3-vinylindoles catalyzed by chiral magnesium phosphate complexes to provide tetrahydrocarbazole derivatives in excellent yields and enantioselectivities (up to >99% yield, 99% ee). This transformation features a wide substrate scope, excellent enantioselectivities, and mild conditions.



Tetrahydrocarbazole has received considerable interest as a building block for the construction of bioactive natural products that often exhibit significant biological activity (Figure 1).[1a,b] Carbazoles and derivatives are also frequently found in organic functional materials as the primary scaffold.[1c−e] It is therefore of particular interest to develop or improve synthetic methods for the *controlled synthesis* of tetrahydrocarbazole derivatives. Diels−Alder type reactions are one of the most powerful transformations for the construction of six-membered ring structures in organic chemistry, rapidly giving access to cyclic and polycyclic compounds that contain multiple stereocenters.[2] We based our work on the [4 + 2] cycloaddition reactions of benzoquinones and 3-vinylindoles, and report an efficient asymmetric Diels−Alder reaction for the formation of tetrahydrocarbazole derivatives.

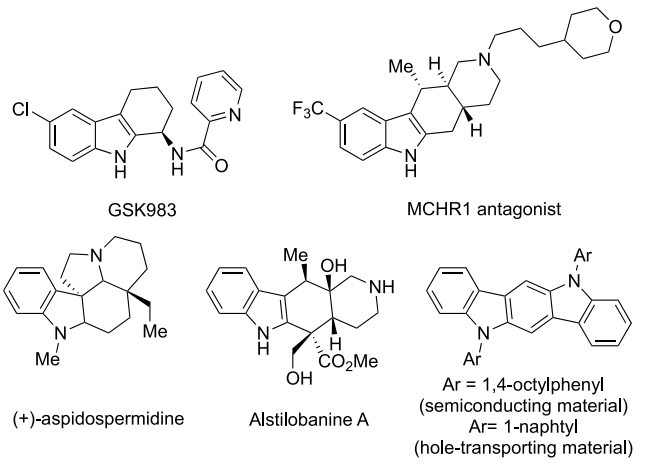


Figure 1. Examples of the tetrahydrocarbazole core in natural products and organic materials.

Chiral phosphoric acid based catalysts derived from substituted BINOL have been previously successfully employed in enantioselective Diels−Alder reactions. In 2006, Akiyama developed an aza-Diels−Alder reaction catalyzed by a chiral phosphoric acid derived from BINOL, using 2-hydroxyphenyl imines with Brassard's diene.[3] In the same year, he also extended his results utilizing imine substrates.[4] Terada also showed a hetero-Diels−Alder reaction of ethyl glyoxylate and dienes to synthesize dihydropyrans in 2009.[5]

However, when one considers the use of chiral phosphate metal catalysts with multiple coordination sites being possible, often as alkali and alkaline-metal salts, one can realize why chiral phosphates as ligands for asymmetric catalysis could be attractive.[6] Inanaga's group pioneered the utilization of chiral lanthanide phosphates and a series of other chiral phosphates in asymmetric Diels−Alder reactions.[7] Later, Feng[8] and Zhu[9] reported the hetero-Diels−Alder reactions with other chiral BINOL derived catalysts. In addition, our group used metal phosphates as catalysts to develop new enantioselective Diels−Alder reactions.[10] The Ricci group has reported that chiral thioureas, a bifunctional acid−base organocatalyst system, catalyze the D−A reaction of 3-vinylindoles with different representative dienophiles for obtaining optically active tetrahydrocarbazole derivatives.[11] However, effective catalysts have rarely been reported for the generation of optically active tetrahydrocarbazole derivatives in D−A reactions.[12] This inspired our exploration of a catalytic system for preparing

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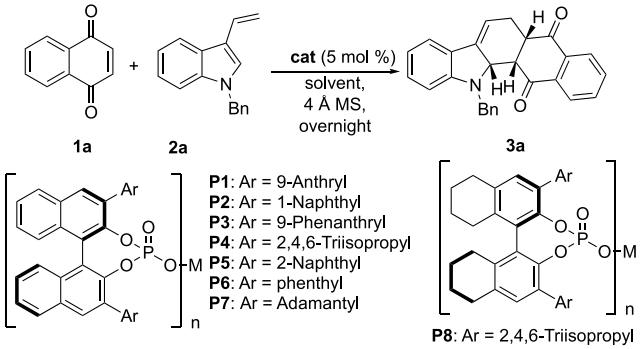
enantioselective tetrahydrocarbazole skeletons utilizing the Diels–Alder reaction.

We initiated our study for the asymmetric Diels–Alder reaction by utilizing benzoquinone and 3-vinylindoles as starting materials (ratio of **1a**/**2a** = 1:1.5). We screened various chiral metal BINOL phosphate catalysts (5 mol %) in ether. Metal phosphates of calcium and magnesium were found to be superior after an extensive initial discovery. The reaction successfully gave the desired product **3a** in full conversion and in good isolated yields (Table 1, entries 1–11). Catalyst

Table 1. Optimization of Reaction Conditions[a–c]



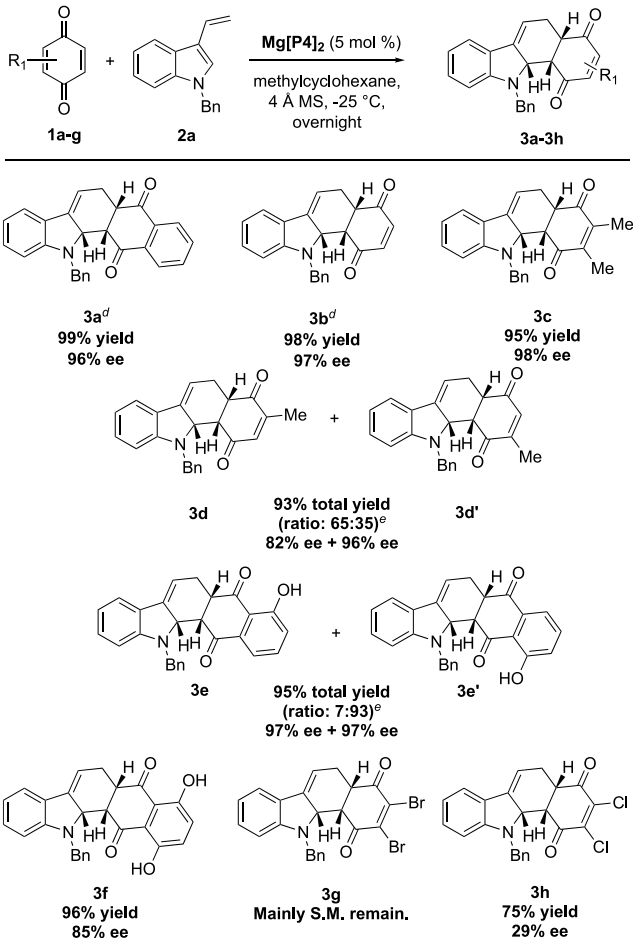
entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	Ca[**P1**]$_2$	ether	90	17
2	Ca[**P2**]$_2$	ether	85	7
3	Mg[**P2**]$_2$	ether	87	4
4	Ca[**P3**]$_2$	ether	92	24
5	Mg[**P3**]$_2$	ether	94	47
6[d]	Mg[**P3**]$_2$	ether	91	20
7	Mg[**P4**]$_2$	ether	94	78
8	Mg[**P5**]$_2$	ether	90	53
9	Mg[**P6**]$_2$	ether	92	25
10	Mg[**P7**]$_2$	ether	85	10
11	Mg[**P8**]$_2$	ether	93	38
12	Mg[**P4**]$_2$	hexane	87	74
13	Mg[**P4**]$_2$	cyclohexane	92	79
14	Mg[**P4**]$_2$	methylcyclohexane	93	83
15[e]	Mg[**P4**]$_2$	methylcyclohexane	76	7
16[f]	Mg[**P4**]$_2$	methylcyclohexane	94	61
17[g]	Mg[**P4**]$_2$	methylcyclohexane	91	96
18[h]	Mg[**P4**]$_2$	methylcyclohexane	94	85
19[i]	Mg[**P4**]$_2$	methylcyclohexane	90	75
20[j]	Mg[**P4**]$_2$	methylcyclohexane	84	62

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), 5 mol % catalyst, and 1.0 mL of ether with 4 Å MS as an additive under argon at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Without 4 Å MS as an additive. [e]Run at −78 °C. [f]Reaction temp: −50 °C. [g]Reaction temp: −25 °C. [h]Reaction temp: 0 °C. [i]Reaction temp: 50 °C. [j]Reaction temp: 75 °C.

screening revealed that Mg[**P4**]$_2$ could provide the product **3a** with the highest enantiomeric excess (94% yield, 78% ee). In addition, a variety of common organic solvents were explored for the optimum conditions (entries 12–14). To our delight, methylcyclohexane was found to be the most suitable solvent for this transformation, allowing for a 93% yield and 83% ee of **3a** (entry 14). We also discovered that activated 4 Å molecular sieves (MS) (entries 6–7), and lowering the temperature (entries 15–20), were additional advantageous conditions, significantly improving the ee value. Eventually, the best enantioselectivity was obtained when using methylcyclohexane as the solvent at −25 °C (entry 17).

We next we turned our attention to the substrate scope of benzoquinones for the Diels–Alder reaction under the optimized reaction conditions (Scheme 1, **3a**–**3h**). A series

Scheme 1. Substrate Scope of Benzoquinones 1a–i[a–c]



[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), 5 mol % catalyst and 1.0 mL methylcyclohexane with 4 Å MS as an additive under argon at room temperature. dr >95:5. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The absolute configurations were determined by comparison of the data with literature values from the Ricci group.[11a] [e]The ratios of two products were determined by HPLC.

of benzoquinones bearing differing substituents were evaluated as substrates. The desired products **3a**–**3f** were obtained in 92–99% yields and 82–98% ee. Among these substrates, we found that **1d** and **1e** were expectedly converted each into two regioisomers (**3d**/**3d′** and **3e**/**3e′**) with high yields and excellent enantioselectivities. Benzoquinones with a methyl group (**1d**) or a hydroxyl group (**1e**) are suitable reaction partners for this transformation. Under the control of the catalyst, we found the ratio of these two regioisomers was changed dramatically (from 86:14 to 7:93). Although we cannot separate the two regioisomers, the chiral metal phosphate catalyst appears to have a clear effect on the reaction mechanism. With halogen groups on the benzoquinones lower efficiency and/or enantioselectivity was found (**3g** and **3h**). There is possible speculation that the halogen atoms

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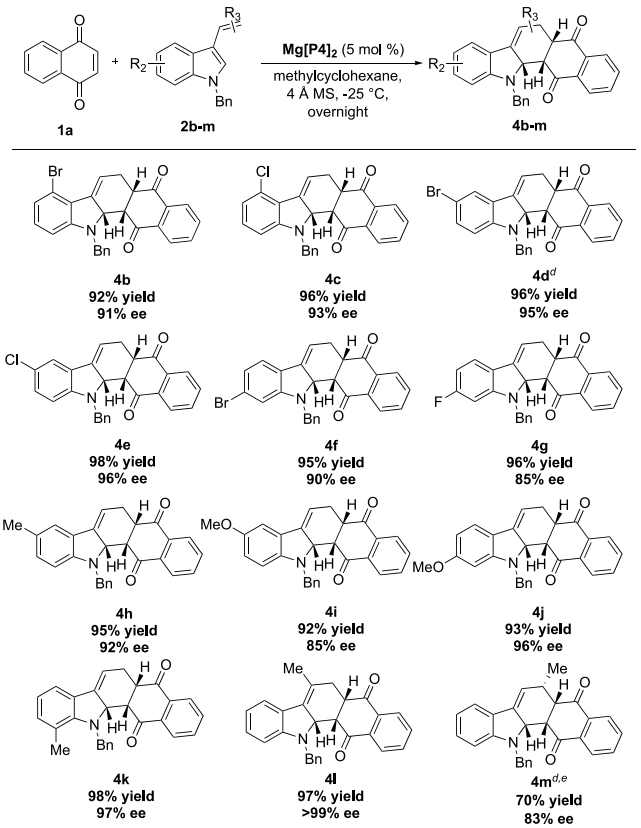
interfered with the interaction between substrates and the catalyst.

Subsequently, we varied the structure of the 3-vinylindoles to investigate the generality of this transformation (Scheme 2, 4b−4m). A halogen group (F, Br, Cl) at the 4-, 5-, 6-, and 7-position of the indole nucleus was well tolerated (4b−4g), furnishing the desired products with 85−96% ee. The use of electron-donating groups (Me, OMe) on the indole induced remarkably high selectivity for the respective products (4h−4l, up to >99% ee). To investigate the effect of different alkenyl isomers on the stereoselectivity of the reaction, we utilized propenyl groups on the indole in the 3-position. The *E*/*Z* mixture of diene **2m** underwent the cycloaddition reaction, giving the product **4m** as a single diastereoisomer with relatively good enantioselectivity. The decreased ee value (83%) of the product **4m** provided experimental evidence for the possible speculation that the methyl group in the isomer might cause unfavorable interactions in the transition state en route to **4m**.

Further substrate modification of the *N*-protected groups on the 3-vinylindoles was investigated in Scheme 3. The protecting groups on nitrogen atoms have a significant effect on this reaction: the products with *N*-benzyl groups resulted in higher ee values. Use of the PMB group or a *tert*-butyl substituted benzyl group gave the desired products (4p−4r) in good ee and yield. However, the use of a 4-chlorobenzyl group led to a slightly lower ee (4r). We assumed that a possible interference via H-bond interaction with the catalyst Mg[**P4**]$_2$ and 3-vinylindole could explain the lower ee in the N−H indole (**2n**) case (product **4n**). The ee value of **4o** was presumably lower due to the steric hindrance formed by the proximity of the PMP group to the reaction site. In addition, an electron-donating group could render the diene more reactive, leading to changes in the reaction.

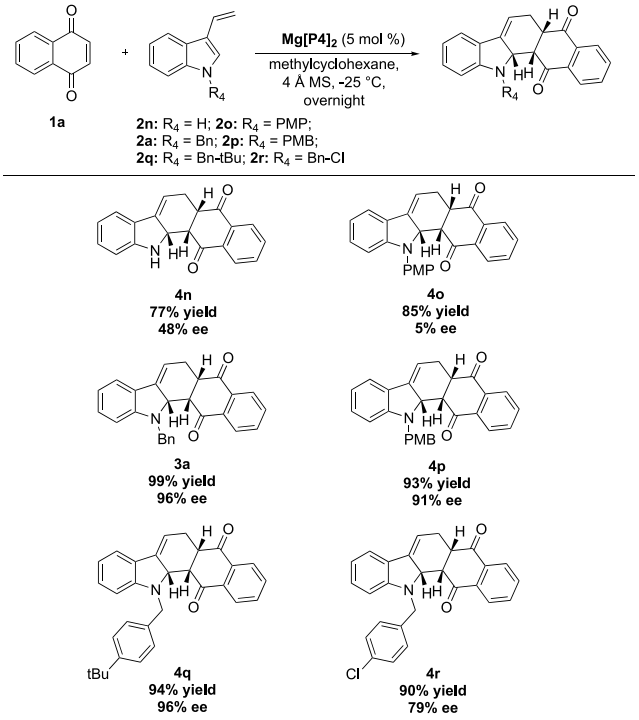
On the basis of the above study, and the presumed catalyst structure, we speculate a possible transition state for the asymmetric Diels−Alder reaction catalyzed by the chiral magnesium phosphate salt (Scheme 4). The carbonyl group of benzoquinone would be presumed to coordinate with Mg^{2+} to obtain the tetrahydrocarbazole intermediate in which the

Scheme 2. Substrate Scope of 3-Vinylindoles 2b−m[a,b,c]



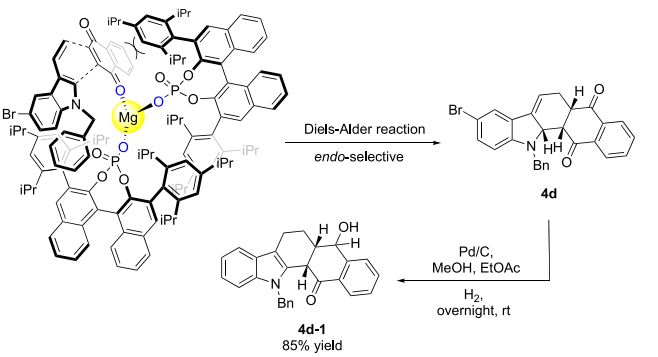
[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), 5 mol % catalyst, and 1.0 mL of methylcyclohexane with 4 Å molecular sieve as an additive; dr >95:5. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The relative configuration determined by NOESY spectroscopy (detail in Supporting Information). [e]Reaction carried out at −25 °C for 48 h.

Scheme 3. Substrate Scope of N-Protected Group of 3-Vinylindoles[a,b,c]



[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), 5 mol % catalyst, and 1.0 mL of methylcyclohexane with 4 Å MS as an additive. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Scheme 4. Proposed Transition State for the Magnesium Phosphate Salt Catalyzed Asymmetric D−A Reaction



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benzene ring of the dienophile is shielded by the TRIP group, while leaving the C=C double bond open for the 3-vinylindole approach to form *endo* product **4d**. Additionally, the benzyl group was in proximity to the other TRIP group. These analyses can explain the stereoselective outcomes of the asymmetric D–A reaction catalyzed by Mg[**P4**]$_2$. Since the product **4d** was found to be fairly easily aromatized in air over time, its derivative **4d-1** was obtained directly by a reduction reaction to make the tetrahydrocarbazole skeleton more stable (Shown below in Scheme 4).

In conclusion, we have developed a mild Diels–Alder reaction catalyzed by a chiral metal magnesium phosphate complex with high enantioselectivity and efficiency. It provides a suitable method for the formation of tetrahydrocarbazole derivatives as exemplified in a number of investigations into the substrate scope. Simultaneously, a proposed monoactivation is invoked as a possible explanation of the origin of stereoselectivity in this interesting reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01437.

Experimental details, experimental preparations, characterization, NMR spectra, chiral HPLC conditions, and other data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jantilla@tju.edu.cn.

ORCID

Jon C. Antilla: 0000-0002-8471-3387

Notes

The authors declare no competing financial interest.

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