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Asymmetric Catalysis of Diels−Alder Reactions with in Situ Generated Heterocyclic *ortho*-Quinodimethanes

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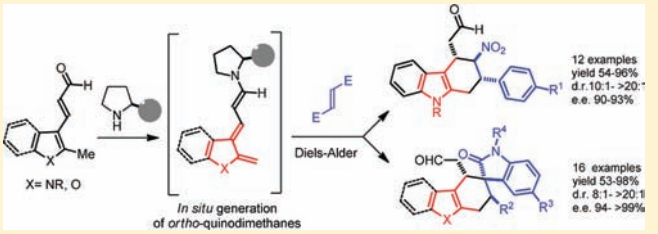
Supporting Information

ABSTRACT: The Diels−Alder reaction is probably the most powerful technology in the synthetic repertoire for single-step constructions of complex chiral molecules. The synthetic power of this fundamental pericyclic transformation has greatly increased with the emergence of asymmetric catalytic variants, and research aimed at further expanding its potential is still exciting and fascinating the chemical community. Here, we document the first asymmetric catalytic Diels−Alder reaction of in situ generated heterocyclic *ortho*-quinodimethanes (*o*QDMs), reactive diene species that have never before succumbed to a catalytic approach. Asymmetric aminocatalysis, that uses chiral amines as catalysts, is the enabling strategy to induce the transient generation of indole-, pyrrole- or furan-based *o*QDMs from simple starting materials, while directing the pericyclic reactions with nitroolefins and methyleneindolinones toward a highly stereoselective pathway. The approach provides straightforward access to polycyclic heteroaromatic compounds, which would be difficult to synthesize by other catalytic methods, and should open new synthetic pathways to complex chiral molecules using nontraditional disconnections.



INTRODUCTION

The Diels−Alder reaction[1] is considered to be the most powerful and reliable synthetic strategy for achieving structural and stereochemical complexity. This is testified to by its many applications in total synthesis.[2] As anticipated a decade ago,[3] further advances in the scope and utility of this transformation were to come, and investigations into further improvement are still a highly active area of modern organic chemistry research. The emergence of catalytic asymmetric variants[4] has even increased the synthetic potential of this pericylic reaction. Many combinations of dienes and dienophiles have been rendered highly stereoselective, providing a predictable and single-step access, from simple starting materials to stereochemically dense cyclohexenyl rings adorned with different molecular architectures. Although the scope of the asymmetric Diels−Alder reaction has greatly expanded, one highly useful class of dienes, *ortho*-quinodimethanes (*o*QDMs),[5] has never been used for a catalytic enantioselective approach. This notable lack stands in sharp contrast to the synthetic utility of *o*QDMs and their heterocyclic counterparts, since those highly reactive dienes provide direct access to complex polycyclic (hetero)aromatic compounds with multiple stereocenters. Indeed, heterocyclic *o*QDMs[6] have been extensively studied over the last 40 years in order to design intra- and intermolecular Diels−Alder reactions for synthesizing target complex molecules, including steroids, alkaloids, and anthracyclines.[7,8] To date, the sporadic examples of enantioselective Diels−Alder reactions of *o*QDMs described in the literature require (over)-stoichiometric amounts of chiral inducers.[9,10] The challenge of designing a catalytic asymmetric strategy mainly depends on the necessity of generating the highly reactive and unstable *o*QDMs dienes in situ, in the presence of the trapping reactant (the dienophile).[5,6] Generally, the dearomatization process that leads to these species (intermediate **I** in Figure 1a) requires harsh reaction conditions and high temperatures, which are not compatible with the action of a chiral catalyst.

In the 1980s, Magnus and colleagues published a series of inspiring studies on the Diels−Alder process of heterocyclic *o*QDMs. These works illustrated the directness and versatility of this approach for the stereocontrolled annulations of indole systems (Figure 1b).[11] The so-called indole-2,3-quinodimethane strategy,[12] designed for the synthesis of indole alkaloids, was based on the mild generation of the indole-2,3-quinodimethane intermediate **III** from a preformed imine. The key tautomerization event was driven by the increased acidity of the proton at the 2-methyl indole moiety, induced by nitrogen quaternarization with methyl chloroformate to form an iminium ion intermediate **II**. Despite the rather mild reaction conditions, the implementation of an enantioselective synthesis of the *cis*-fused tetracyclic products was based upon the use of chiral auxiliaries.[13,14]

One fascinating aspect of chemical research, and scientific progress at large, is that the accumulated knowledge and resulting techniques often provide new tools for attacking longstanding problems using pre-existing strategies.[15] One example is asymmetric

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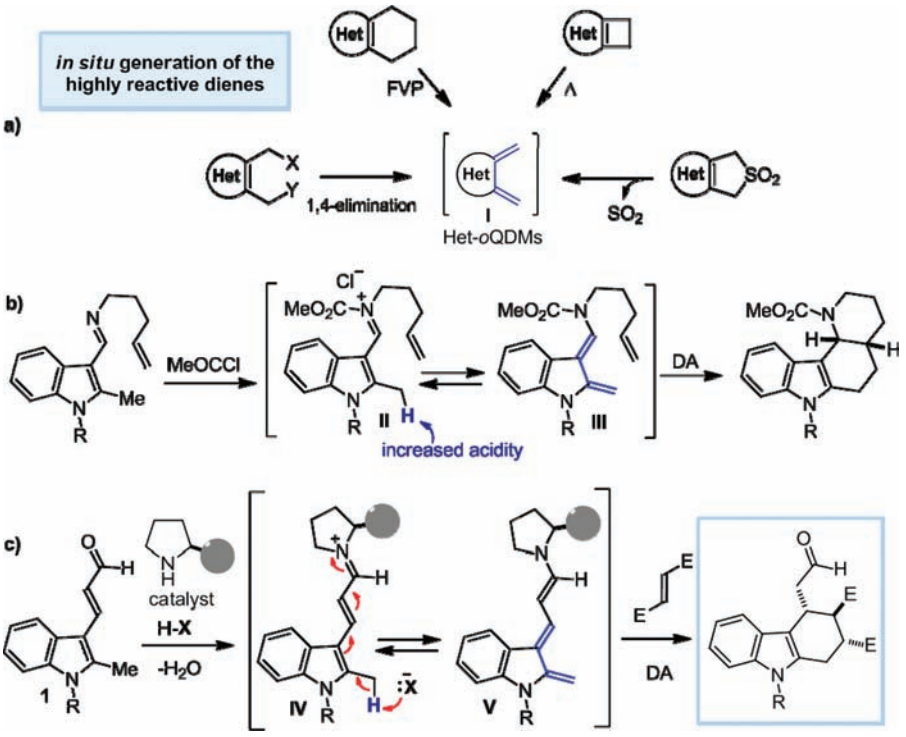


Figure 1. *ortho*-Quinodimethanes (*o*QDMs) as dienes of the Diels−Alder reaction. (a) Traditional methods for the generation of *o*QDM intermediates **I** generally require harsh reaction conditions, high reaction temperatures, and difficult-to-make starting materials, that is, 1,4-eliminations, flash vacuum pyrolysis (FVP) of cyclohexene-fused heterocycles, thermal ring-opening of aryl-cyclobutene derivatives, and cheletropic extrusion of sulfur dioxide. (b) Original annulation developed by Magnus and colleagues in 1981, based on the indole-2,3-quinodimethane intermediate **III** formation through imine tautomerization. (c) Design blueprint for an asymmetric catalytic Diels−Alder reaction with in situ generated indole-2,3-quinodimethane using aminocatalysis as the enabling strategy. Het, heteroaromatic; DA, Diels−Alder; E, electron-withdrawing group; H-X, acid.

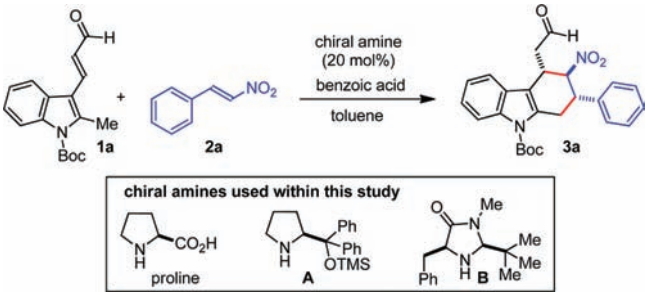
aminocatalysis,[16] which exploits the ability of chiral amine catalysts to reversibly condense with carbonyl compounds.[17,18] Exploiting fundamental and well-established mechanistic patterns,[19] and mainly using the chemistry of simple enamine and iminum ion intermediates,[20] this approach has greatly expanded the chemist's ability to asymmetrically functionalize unmodified carbonyl compounds.[21] We recently wondered whether the synthetic plan engineered by Magnus and co-workers[11−14] could be brought to fruition by capitalizing on this modern perspective, after 30 years of chemistry progress and innovation. Could the underlying principle of the indole-2,3-quinodimethane strategy (Figure 1b) be used to design a catalytic asymmetric Diels−Alder reaction, using enantioselective aminocatalysis as the enabling strategy? Specifically, we sought to generate in situ the desired diene derivative **V** directly from a simple starting material, such as an easily available β-indolyl unsaturated aldehyde of type **1** and a chiral secondary amine catalyst (Figure 1c). To meet this challenge, we recognized two critical issues. We needed to identify a chiral catalyst that, upon condensation with enal **1** and the formation of the expected electrophilic iminum ion intermediate **IV**, (i) could facilitate the tautomerization toward the reactive species **V**, (ii) while selectively directing the [4 + 2] cycloaddition reaction with a suitable dienophile toward a highly enantioselective pathway.

Herein, we document how this design blueprint was translated to experimental reality, leading to the development of the first asymmetric catalytic Diels−Alder reaction of in situ generated heterocyclic *o*QDMs with two distinct classes of olefinic dienophiles, nitroolefins and methyleneindolinones. The chemistry allows direct access to functionalized tetrahydrocarbazoles[22] with three stereogenic centers with extremely high regio-, diastereo-, and enantio-control, and can be extended to the synthesis of polycyclic pyrrole- or furan-based compounds.

RESULTS

In our initial experiments, we examined the reactivity of N-Boc protected 3-(2-methyl-indol-3-yl)acrylaldehyde **1a** toward the [4 + 2] cycloaddition with the electron-deficient *trans*-β-nitrostyrene **2a**. We chose compound **1**, a 2-methylindole bearing an α,β-unsaturated aldehyde substitution pattern in position 3, instead of the 2-methylindole 3-carboxaldehyde used by Magnus as the imine precursor.[23] This is because we wished to make the strategy catalytic. The amine, following the Magnus approach, is consumed by becoming part of the product as a substituent in the Diels−Alder adduct (from intermediate **III**, Figure 1b). Conversely, in our design plan, the use of the α,β-unsaturated aldehyde **1**, after activation by a chiral amine catalyst, would afford a cycloadduct (from intermediate **V**, Figure 1c) bearing an enamine substituent. This would subsequently release the amine through iminium ion hydrolysis, providing the necessary condition for the catalyst turnover. Pursuing this prospect, we investigated the effect of different chiral secondary amine catalysts in the model reaction. Extensive optimization studies are reported in Tables S1−5 in the Supporting Information, with selected results summarized in Table 1. There was no background reaction when aldehyde **1a** and nitrostyrene **2a** were combined without any catalyst, indicating an inherent lack of reactivity

Table 1. Optimization of the Asymmetric Catalytic Diels–Alder Reaction of in Situ Generated Indole-2,3-quinodimethane[a]



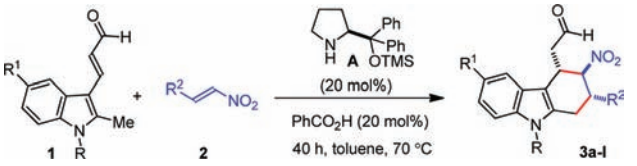
entry	catalyst	benzoic acid [mol %]	t [h]	T [°C]	yield [%][b]	dr[c]	3a ee [%][d]
1			15	40	<5		
2	proline		15	40	<5		
3	**A**		15	40	19	4:1	90
4	**B**	20	15	40	<5		
5	**A**	20	15	40	33	12:1	91
6[e]	**A**	20	15	40	44	15:1	93
7[e]	**A**	20	40	60	69[f]	15:1	94
8[e]	**A**	20	40	70	76[f]	16:1	93
9[e]	**A**	20	40	70	75[f]	16:1	92[g]
10[e]	**A**	20	40	80	76[f]	15:1	90
11[e]	**A**[h]	10	40	70	65[f]	15:1	92

[a] Boc: *tert*-butyloxycarbonyl. General reaction conditions: unless otherwise specified, reactions were carried out on a 0.1 mmol scale using 1.2 equiv of **2a** and $[\mathbf{1a}]_0$ = 0.5 M in toluene. [b] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] Diastereomeric ratios (dr) were determined by means of ^{1}H NMR analysis of the crude mixture. [d] Enantiomeric excess (ee) values were determined after $NaBH_4$ reduction of compound **3a** to the corresponding alcohol and HPLC analysis on commercially available chiral stationary phases. [e] Reactions carried out on a 0.1 mmol scale using 1.5 equiv of **1a** and $[\mathbf{2a}]_0$ = 0.5 M in toluene. [f] Yield of the isolated product **3a**. [g] The (*R*) enantiomer of amine **A** was used, leading to the opposite antipode of product **3a**. [h] Reaction performed over 64 h using 10 mol % of catalyst **A**.

between the chosen reagents (Table 1, entry 1). Among the catalysts tested (entries 2–4), only the diphenylprolinol silyl-ether **A** (20 mol %, reaction carried out in toluene), independently developed by Jørgensen et al.[24] and Hayashi et al.[25] in 2005, afforded the desired product **3a**, albeit in less than 20% yield after 15 h and with a rather poor diastereomeric ratio (dr). The level of enantioselectivity (enantiomeric excess, ee = 90% for the major diastereoisomer), however, prompted us toward further optimizations. We thus chose catalyst **A** as the most suitable candidate for inducing the in situ generation of *ortho*-quinodimethane intermediate of type **V** while securing high levels of stereocontrol.

Further optimizations of the standard reaction parameters revealed that the nature of the acidic additive and the stoichiometry of the reagents were the crucial factors for improving the catalysis.[26] When the reaction was carried out in the presence of benzoic acid as additive (20 mol %, equimolar amount with respect to the amine **A**),[26a] both reactivity and diastereoselectivity were positively influenced, leading to the Diels–Alder product **3a** with a 15:1 diastereomeric ratio, while maintaining

Table 2. Generality of the Diels–Alder Reaction with Nitroolefin Substrates[a]



entry	R	R^1	R^2	3	yield [%][b]	dr[c]	ee[d] [%]
1	Boc	H	Ph	**a**	76	16:1	93
2	Boc	OMe	Ph	**b**	84	11:1	92
3	Boc	Cl	Ph	**c**	80	17:1	90
4	Me	H	Ph	**d**	80	17:1	92
5	H	H	Ph		0		
6	Boc	H	p-MeC_6H_4	**e**	72	>20:1	92
7	Boc	H	p-ClC_6H_4	**f**	83	>20:1	92
8	Boc	H	p-$MeOC_6H_4$	**g**	54	>20:1	93
9[e]	Boc	H	p-$NO_2C_6H_4$	**h**	88	10:1	92
10	Boc	H	o-BrC_6H_4	**i**	96	11:1	92
11	Boc	H	2-furanyl	**j**	55	17:1	92
12	Boc	H	3-thiophenyl	**k**	64	>20:1	92
13	Boc	H	CH_2CH_2Ph	**l**	22	14:1	92

[a] General reaction conditions: reactions performed on a 0.1 mmol scale using 20 mol % amine **A**, 20 mol % benzoic acid, 1.5 equiv of **1**, and $[\mathbf{2}]_0$ = 0.5 M in toluene at 70 °C over 40 h. Results represent the average of two runs per substrate. All the reactions have also been performed using (*R*)-**A** as the catalyst to afford the opposite enantiomer of compounds **3**; see Table S8 in the Supporting Information for details. [b] Yield of the isolated compound **3**. The yields reflect the degree of conversion. [c] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of the crude mixture. [d] Enantiomeric excess (ee) values were determined after $NaBH_4$ reduction of compounds **3** to the corresponding alcohols and HPLC analysis on commercially available chiral stationary phases. [e] The reaction required 16 h for completion.

the high enantioselectivity (entry 5). The use of an excess of aldehyde **1a** (1.5 equiv) further increased the reactivity of the catalytic system (entry 6).[26b] Evaluation of the reaction media confirmed that the catalytic process performed better in toluene. Other solvents such as chloroform, tetrahydrofuran, ethyl acetate, and acetone significantly diminished the chemical yield (see Table S2 in the Supporting Information for further details). Importantly, the reaction temperature increased the catalyst turnover while minimally affecting the stereoselectivity of the cycloaddition process (entries 7–10). The best compromise between the chemical yield and the stereocontrol was achieved when performing the Diels–Alder reaction at 70 °C, using 20 mol % of both the amine **A** and benzoic acid in toluene as the solvent (entry 8). Under the optimized conditions, the tetrahydrocarbazole **3a** was isolated after 40 h in 76% yield, with excellent diastereoselectivity (dr 16:1) and very high enantioselectivity (93% ee). The (*R*) enantiomer of the catalyst **A** showed the same catalytic profile and stereochemical outcome, securing access to each product enantiomer individually (entry 9). Lowering the catalyst loading down to 10 mol % resulted in longer reaction times (65% yield after 64 h), although the stereocontrol in the cycloaddition reaction was preserved (entry 11). These results further consolidate the unique ability of catalyst **A** to modulate the equilibrium between the iminium ion intermediate,

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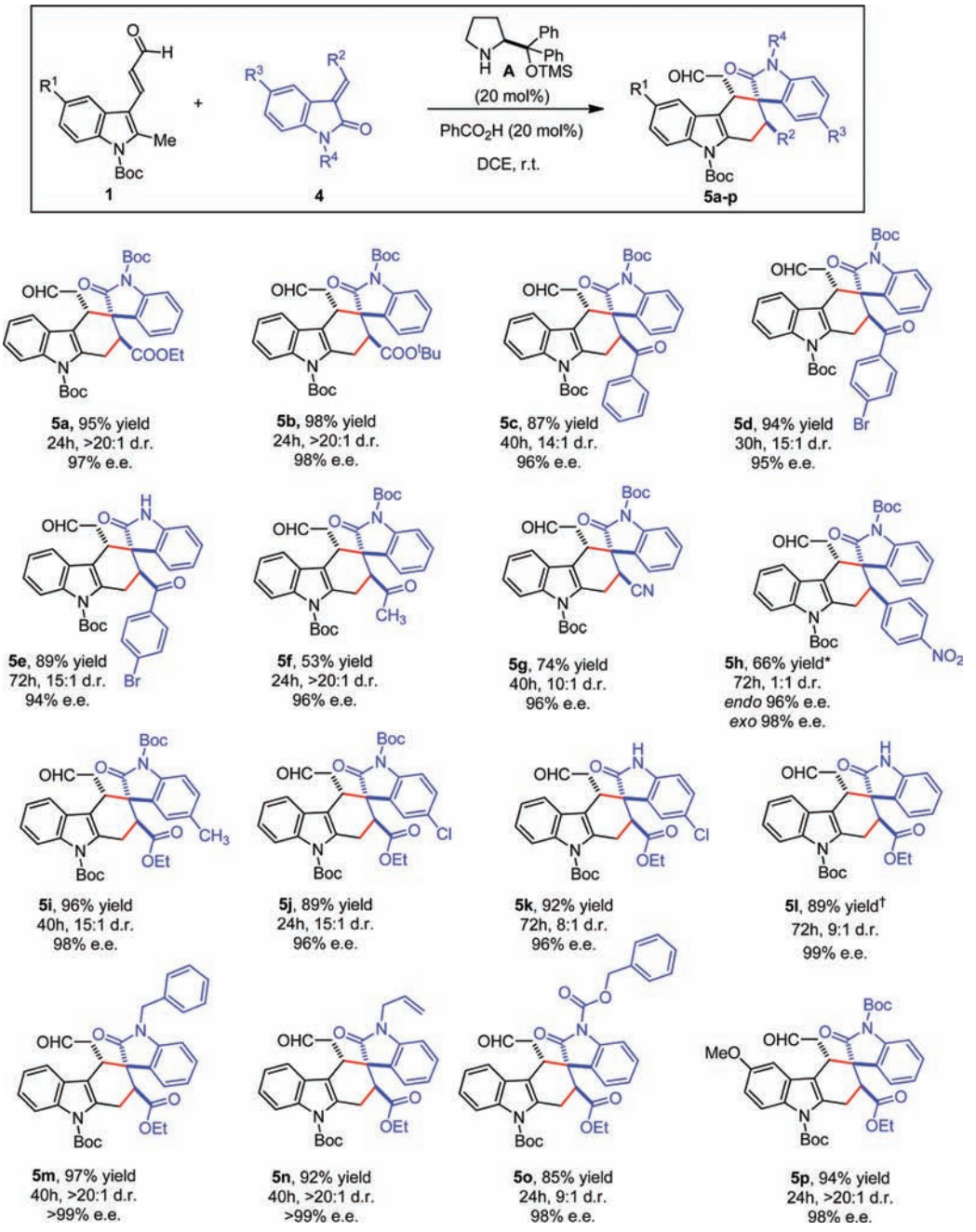

Figure 2. Methyleneindolinones as dienophiles in the Diels–Alder reaction: construction of tetrahydrocarbazole spirooxindoles. General reaction conditions: reactions performed on a 0.1 mmol scale using 20 mol % amine **A**, 20 mol % benzoic acid, 1.2 equiv of **1**, and $[4]_0$ = 0.5 M in DCE at room temperature (rt). Yields refer to the sum of the isolated diastereoisomers. The yields reflect the degree of reaction conversion. Selected reactions have been also performed using (*R*)-**A** as the catalyst to afford the opposite enantiomer of compounds **5**; see Table S9 in the Supporting Information for details. Compound **5h** was prepared at 40 °C in toluene using trimethylacetic acid (TMAA) as the acidic additive. The *endo* and *exo* pure isomers were individually isolated by additional chromatography purification in 32% and 28% yield, respectively. See the Supporting Information for further details. †Reaction leading to compound **5l** was conducted using TMAA as the acidic additive.

which is formed upon condensation with polyunsaturated enals, and the nucleophilic extended enamines (dienamine[27] and trienamine[28]intermediates). The resulting transmission of electronic effects through a conjugated π-system[29] was recently used to design catalytic asymmetric Diels–Alder transformations[27,28] exploiting vinylogous nucleophilicity in extended enamines.[30,31]

Adopting the conditions described in Table 1, entry 8, the generality of the method was demonstrated by evaluating a variety of indole moieties **1** and nitroalkenes **2**. As highlighted in Table 2, there appears to be significant tolerance toward structural and electronic variations of both precursors to enable access to a variety of complex tetrahydrocarbazoles (**3a**–**l**) having three stereocenters with very high diastereomeric ratio and optical purity. Different substituents on the indole core of enal **1** are well tolerated, since electronic modification of the aromatic ring can be accomplished without affecting the efficiency of the system.

Substitution at the 5-position efficiently provided diene precursors for the highly stereoselective Diels–Alder reaction with nitrostyrene (entries 1–3, Table 2). A substituent with a different electronic nature at the N-position did not alter the reactivity: N-methylindole-derived aldehyde, in which the electron-withdrawing Boc group was replaced by an electron-donating alkyl group, reacted smoothly with nitrostyrene, to afford the product **3d** in high optical purity (entry 4). However, the N-unprotected indole-derived enal remained unchanged under the reaction conditions (R=H, entry 5). This could be attributed to a tautomerization process[32] in which a more stable species is generated by proton transfer from the free N*H* moiety within the transiently generated *ortho*-quinodimethane to the vicinal methylene group, which results in a *trans* disposition of the electron-rich conjugated diene, disabling the system for Diels–Alder reactivity (where a *cis* disposition is required).

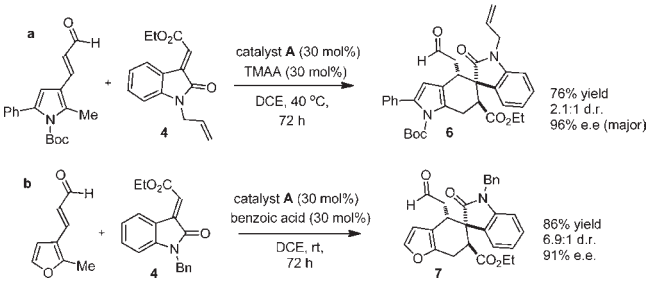

Figure 3. Extending the scope of the Diels–Alder reaction to pyrrole- and furan-based *ortho*-quinodimethanes. (a) Reaction performed on a 0.1 mmol scale using trimethylacetic acid (TMAA) as the additive, 1.2 equiv of the aldehyde precursor, and $[\mathbf{4}]_0 = 0.5$ M in DCE. (b) Reaction performed on a 0.1 mmol scale using benzoic acid as the additive, 1.2 equiv of the aldehyde precursor, and $[\mathbf{4}]_0 = 0.5$ M in DCE.

Concerning the scope of nitroolefinic derivatives, different substituents at the aromatic moiety are well-tolerated, regardless of their electronic properties. The corresponding adducts **3** were obtained in good to high yield and very high stereocontrol. Both electron-donating and electron-withdrawing functionalities at the *para* position were fully compatible with the method (entries 6 to 9), while substitution at the *ortho* position of the phenyl ring afforded product **3i** with high yield (96%) and stereocontrol (dr 11:1; 92% ee). The generality of the reaction was also verified by using nitroolefins with heteroaromatic β-substituents, including 2-[(*E*)-2-nitrovinyl]furan and 2-[(*E*)-2-nitrovinyl]thiophene (entries 11 and 12), and even with the less reactive aliphatic olefin (entry 13).

To further explore the potential of our approach to rapidly build up complex frameworks from simple starting materials, we investigated the reactivity of in-situ-generated indole-2,3-quinodimethanes toward electron-deficient olefins bearing the oxindole moiety. The Diels–Alder reaction with methyleneindolinone derivatives **4** provided direct access to spirocyclic oxindole scaffolds, which feature in a large number of natural[33,34] and unnatural compounds[35–37] with important biological activities. Advances have been made recently in the stereocontrolled synthesis of

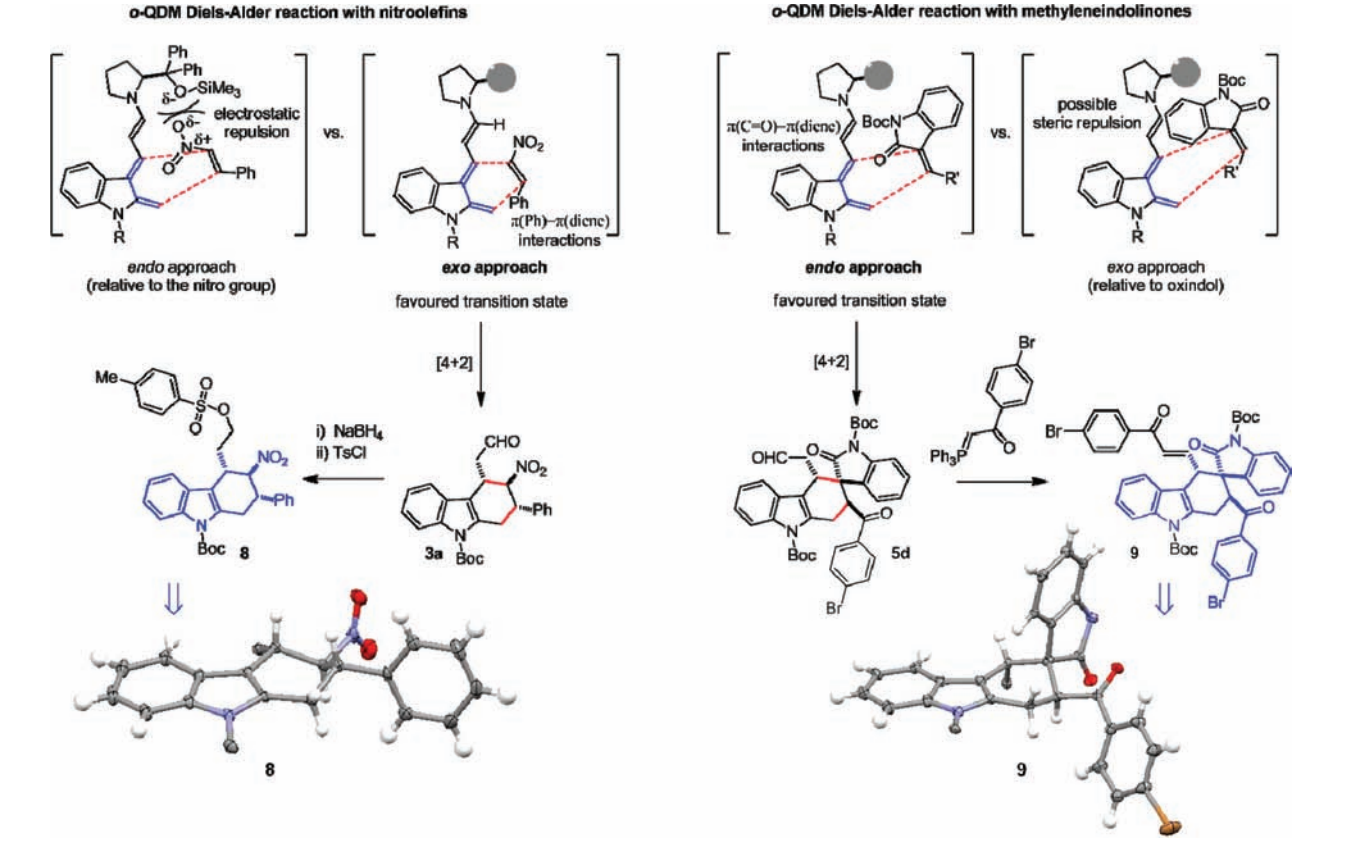

Figure 4. Rationalization of the stereochemical outcome of the Diels–Alder reaction with nitroolefins and methyleneindolinones. X-ray structures showing the spatial arrangement of the substituents in the newly formed cyclohexane ring (some parts of the molecule have been removed for clarity). ORTEP drawing at 50% probability. The complete information on the crystallographic structural determination can be found in the Supporting Information.[45]

spirooxindoles,[38] mainly based on catalytic asymmetric cycloaddition[39−41] and cascade strategies.[42,43] However, it remains highly relevant and far from easy to efficiently install the challenging spiro-quaternary stereocenter in a chemo-, regio-, and stereocontrolled manner. As shown in Figure 2, our Diels−Alder approach provides an easy and reliable entry to highly enantioenriched compounds **5**. These are complex molecular scaffolds, in which two biologically relevant and privileged molecular units[22,38] (a tetrahydrocarbazole and a spirooxindole) are merged. The chemistry reported in Figure 2 may thus be useful for synthesizing nature-inspired compound collections that may find application in other scientific domains such as medicinal chemistry and chemical biology research.[44]

The complete progress toward the optimized conditions for the Diels−Alder reaction of indole derivatives **1** with methyleneindolinones **4** is detailed in Tables S6, S7, and S9 in the Supporting Information. Dichloroethane (DCE) emerged as the most appropriate solvent for this transformation. As depicted in Figure 2, the reaction proceeds at room temperature in the presence of the catalytic salt **A**·benzoic acid (20 mol %), affording a wide variety of complex tetrahydrocarbazole spirooxindoles **5a**−**p** with almost perfect stereocontrol.

The general applicability of a chemical strategy is a crucial parameter for evaluating its usefulness for future endeavors to synthesize complex chiral molecules. To expand the scope of our Diels−Alder approach, we explored the possibility of using the chiral amine catalyst **A** to induce the generation of different heteroaromatic-based *o*QDMs from simple starting aldehydes, while directing the pericyclic reactions with methyleneindolinones **4** toward a highly stereoselective pathway. The results summarized in Figure 3 illustrate the potential of the chemistry for the stereoselective preparation of chiral spirocyclic oxindoles bearing a pyrrole (product **6**) or a furan moiety (**7**).

DISCUSSION

Crystals from compounds **8** and **9**, directly derived from cycloadducts **3a** and **5d**, respectively, were suitable for X-ray analysis. This established the stereochemical outcome of the reaction as well as the absolute configuration.[45] The high stereocontrol of these transformations can be rationalized as follows (Figure 4): Diels−Alder additions are governed by steric effects and electronic interactions between the interacting diene and dienophile π-electronic systems.[46] In both systems (reaction with nitroolefins **2** and with oxindole-derived dienophiles **4**), the chiral catalyst selectively provides face shielding of the generated *ortho*-quinodimethane intermediate inducing the π-facial-selectivity and securing high enantiomeric excess, while the regioselectivity is dictated by an optimum HOMO(*o*QDM)-LUMO(electron-deficient olefin) orbital overlap.[47] The reaction with nitroolefins proceeds with *exo* selectivity relative to the nitro group (alignment of the two reacting components in the transition state, interpreted by the Alder rules). This is the opposite selectivity pattern to the *endo* approach (relative to the oxindole moiety) observed for the methyleneindolinones dienophiles **4**. A common property of the Diels−Alder cycloaddition, whether thermal or catalyzed, is its *endo* diastereoselectivity. In contrast, examples of the Diels−Alder reaction displaying *exo* selectivity occur less frequently, at least in an intermolecular context. The uncommon stereochemical outcome of the reaction with nitroolefins was first noticed in the cycloaddition with Danishefsky's diene and explained by unfavorable electrostatic repulsion between the nitro group and the silyloxy group of the diene.[48] In addition, our results conform to the *exo* selectivity observed in Diels−Alder reactions of nitroolefins[28c] with enamines generated from aldehydes and chiral secondary amines.[49,50]

CONCLUSION

Asymmetric aminocatalysis has allowed us to develop the hitherto elusive catalytic asymmetric Diels−Alder reaction of in situ generated *ortho*-quinodimethane intermediates. The indole-2,3-quinodimethane strategy, originally conceived for the straightforward synthesis of indole alkaloids more than 30 years ago, can now be made catalytic with the chiral amine **A**. This strategy can then be used to synthesize a structurally diverse range of complex nitrogen and spirooxindole-containing tetrahydrocarbazoles with high chemical yield and excellent stereoselectivity. Demonstration that this new strategy can be easily extended to access complex pyrrole- and furan-based heterocyclic compounds while using mild and simple reaction conditions may provide for the rapid application of this chemistry in synthetic and medicinal arenas.

ASSOCIATED CONTENT

Supporting Information. Complete ref 37, experimental procedures, optimization studies, compound characterization, HPLC traces, and NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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