Asymmetric Catalysis

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Organocatalytic Asymmetric Diels–Alder Reactions of 3-Vinylindoles**

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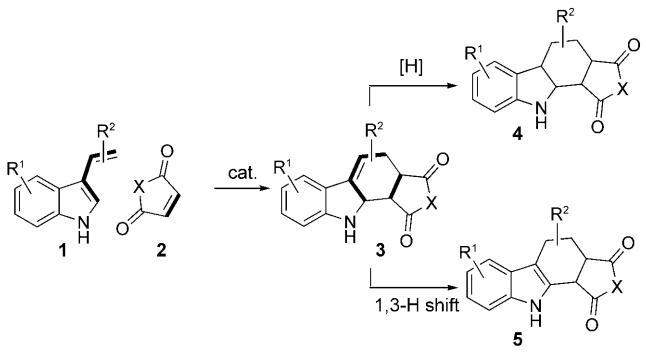
Diels–Alder type reactions are amongst the most useful transformations in organic chemistry for the construction of cyclohexene structures, often containing multiple stereocenters. Catalytic asymmetric variants of these [4+2] cycloadditions have been reported for different diene–dienophile combinations,[1] showing in several instances outstanding synthetic utility. Herein, we present the development of an unprecedented catalytic asymmetric Diels–Alder reaction of 3-vinylindoles **1** with different representative dienophiles **2** (Scheme 1). Our studies were motivated by the stunning

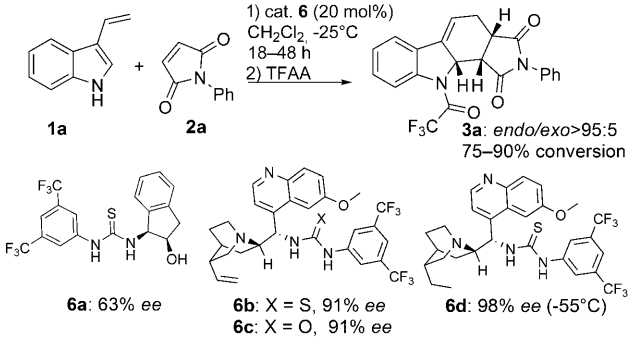


Scheme 1. Diels–Alder reaction of 3-vinylindoles **1**.

directness and versatility of this approach for the [*b*]anellation (at the C2–C3 bond) of the indole nucleus, giving partially saturated, optically active carbazoles **3**. Standard manipulations of these cycloadducts give access to tricyclic indolines **4** and tetrahydrocarbazoles **5** (Scheme 1), which are common scaffolds in a variety of natural and/or biologically active alkaloids.[2] It has long been recognized that 3-vinylindoles can participate in frontier-molecular-orbital-controlled Diels–Alder reactions with the HOMO of their electron-rich diene systems.[3] Control of the relative stereochemistry in the thus-formed hydrogenated carbazoles is often excellent, owing to the concerted mechanism and to secondary molecular orbital interactions, favoring an *endo* approach. However, no catalytic asymmetric variants of these useful transformations have been reported to date.[4]

To find a suitable catalytic system, we envisioned a scenario where a bifunctional acid–base organic catalyst coordinates through hydrogen-bond interactions to both the diene **1** and the dienophile **2**,[5] resulting in a highly organized transition state, potentially giving rise to the cycloadduct with good levels of stereoselectivity. The mild acidic nature of many commonly employed organic catalysts, often based on urea or thiourea motifs, should be compatible even with the acid-sensitive 3-vinylindoles. The asymmetric Friedel–Crafts reactions of 1-H-indole derivatives,[6] wherein the catalysts operate through a hydrogen-bonding network involving the indole N–H, as well as the cycloaddition reaction of 3-hydroxy-2-pyrones,[7] wherein the double activation of a diene and a dienophile by an organic catalyst was realized with great success, were both of great encouragement and inspiration.

We initially investigated the catalytic reaction between 3-vinylindole **1a** and *N*-phenylmaleimide **2a** (Scheme 2). Carrying out the reaction at −25 °C in dichloromethane, screening of bifunctional organic catalysts[8] suggested **6a**, derived from (1*S*,2*R*)-1-aminoindanol, and **6b** and **c**, both derived from quinine,[9] as the most promising structures. Having identified dichloromethane as the solvent of choice for this transformation,[8] optimum selectivity (98% *ee*) was reached using catalyst **6d**, derived from hydroquinine, at −55 °C (Scheme 2). Derivatization with trifluoroacetic anhydride (TFAA) after the reaction gave additional stability to the cycloadduct, thus facilitating its isolation by chromatography on silica gel and subsequent HPLC analysis. As expected, exclusively the *endo* cycloadduct **3a** was obtained in all experiments, and isomerization of the double bond, restoring



Scheme 2. Selected results from catalyst-optimization screening reactions. TFAA = trifluoroacetic anhydride

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the aromatic indole nucleus, did not occur under these mild conditions.[10]

1-Tosyl-, 1-*tert*-butoxycarbonyl- (1-Boc) and 1-methyl-3-vinylindoles related to **1a** were also tested in the reaction with maleimide **2a**, using catalyst **6b**. The 1-tosyl and the 1-Boc derivatives afforded the corresponding products, albeit in racemic form, at +4 °C and −25 °C, respectively, whereas 1-methyl-3-vinylindole did not lead to substantial formation of the expected cycloadduct.[11] These results were tentatively taken to suggest the requirement of an interaction between the basic moiety of the catalyst and the N–H group of the diene, alongside activation of the dienophile by the thiourea moiety (Figure 1).

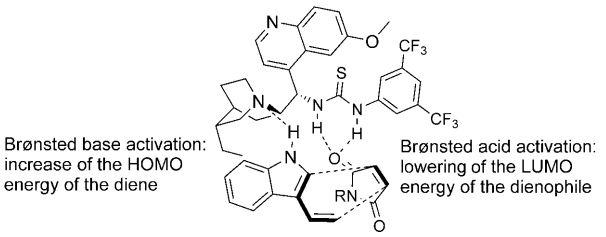
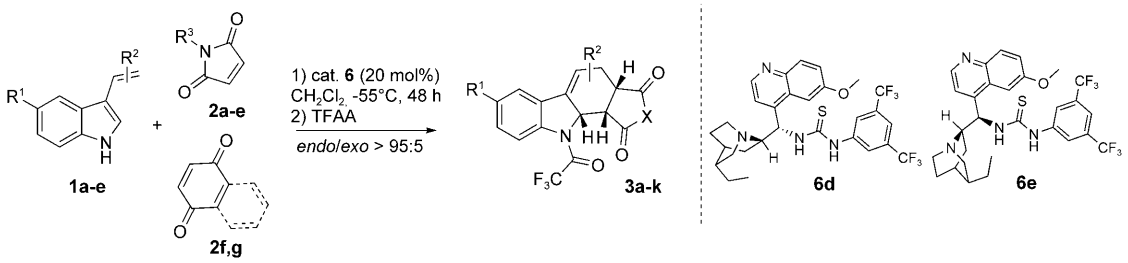


Figure 1. Proposed working model of the reaction transition state.

We then investigated the generality of this transformation (Table 1), varying first the structure of the 3-vinylindole **1** (Table 1, entries 1–5). An electron-withdrawing or donating group at the 5-position of the indole nucleus was well tolerated (Table 1, entries 2 and 3), as was a methyl substituent at the exocyclic double bond (Table 1, entries 4 and 5). In the latter case, although a 1:1 *E*/*Z* mixture of diene **1e** was employed, exclusively the *E* isomer underwent the cyclo-

Table 1: Scope of the reaction.[a]

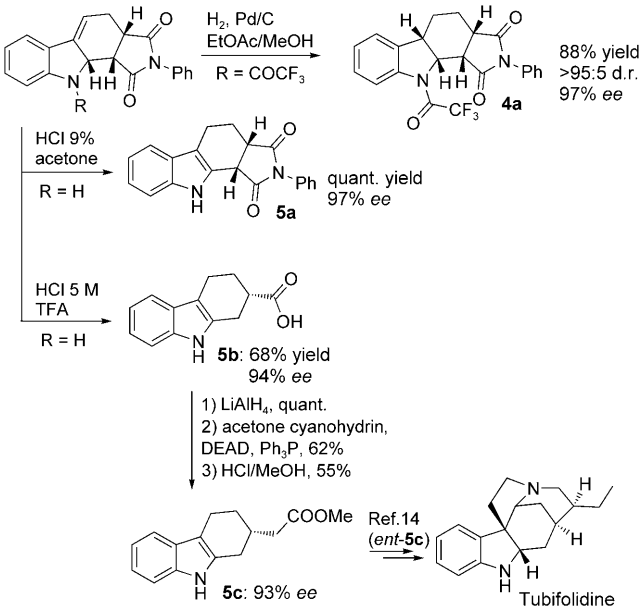


Entry	Diene **1**	Dienophile **2**	Cycloadduct **3**	Yield[b] [%]	*ee*[c] [%]
1	**1a**: R^1 = H	**2a**	**3a**: R^1 = H[d]	91 (86)	98 (95)
2[e]	**1b**: R^1 = Br		**3b**: R^1 = Br	86	90
3[e]	**1c**: R^1 = MeO		**3c**: R^1 = MeO	77	96
4	**1d**	**2a**	**3d**	79 (89)	96 (86)
5[e]	**1e**: *E*/*Z* = 50:50	**2a**	**3e**[d,f]	58	92
6	**1a**	**2b**: R^3 = Me	**3f**: R^3 = Me	89	98
7		**2c**: R^3 = Bn	**3g**: R^3 = Bn	89	96
8		**2d**: R^3 = *t*Bu	**3h**: R^3 = *t*Bu	81	88
9		**2e**: R^3 = H	**3i**: R^3 = H	72	52
10	**1a**	**2f**	**3j**	83 (71)	>99 (98)
11	**1a**	**2g**	**3k**	77	96

[a] Conditions: **2** (0.15 mmol), **6d** (0.030 mmol), **1** (0.18 mmol), CH_2Cl_2 (1.5 mL), −55 °C, 48 h. Results in parentheses refer to the opposite enantiomer, obtained using **6e** as the catalyst. [b] Yield of product isolated by chromatography on silica gel. [c] Determined by chiral stationary-phase HPLC. [d] Relative configuration determined by ^{1}H NMR spectroscopy (see the Supporting Information). [e] 2 equiv diene **1** used. [f] d.r. > 95:5. [g] Reaction carried out at −30 °C for 72 h.

addition reaction, giving the product **3e** as a single diastereoisomer. As stirring **1e** (*E*/*Z* mixture) in the presence of catalyst **6d** in CD_2Cl_2 at −30 °C overnight did not lead to any *E*/*Z* isomerization, two equivalents of this diene were used.[12] With 3-vinylindole **1a**, variation in the dienophile counterpart was then investigated (Table 1, entries 6–11). Maleimides **2b–d**, bearing substituents of different sizes at nitrogen, including a hindered *tert*-butyl group, were used in the Diels–Alder reaction, affording the cycloadducts **3f–h** with excellent results (Table 1, entries 6–8). We instead attributed the rather low enantioselectivity in the reaction with **2e** (Table 1, entry 9) to a possible interference by the imide hydrogen with the H-bond interactions between the catalyst and the substrates. Quinones, another popular class of dienophiles for Diels–Alder cycloadditions, could also be employed, as the cycloadducts **3j** and **3k**, derived from benzoquinone **2f** and naphthoquinone **2g**, were both obtained in good yields and excellent enantioselectivities (Table 1, entries 10 and 11). The quasi-enantiomeric catalyst **6e**, derived from hydroquinidine, gave access to the enantiomeric products *ent*-**3** with comparable results (Table 1, values in parentheses).

The reduction of the cycloadduct **3a** to the indoline **4a** was straightforward, as was the synthesis of the tetrahydrocarbazole **5a** through a 1,3-H shift, by treatment of the cycloadduct (before TFAA derivatization)[10] with dilute aqueous HCl (Scheme 3). Use of harsher conditions gave, besides the 1,3-H shift, hydrolysis of the imide and regiospecific decarboxylation[3i] at the 1-position (Scheme 3). Reduction of the carboxylic acid of **5b**, followed by homologation with a Mitsunobu reaction,[13] and methanolysis of the cyano group, afforded **5c**, the enantiomer of a synthetic intermediate used in the asymmetric synthesis of tubifolidine,[14] a *Strychnos* alkaloid, highlighting the synthetic potential of this catalytic transformation and allowing the assignment of the absolute configuration of the products.



Scheme 3. Elaborations of the cycloadducts. TFA = trifluoroacetic acid; DEAD = diethyl azodicarboxylate.

In conclusion, the use of a bifunctional acid–base organocatalyst allowed the development of the hitherto elusive catalytic asymmetric Diels–Alder reaction of 3-vinylindoles, offering a direct approach to optically active tetrahydrocarbazole derivatives. The possibility of activating 3-vinylindoles by interaction of a base with the N−H moiety might also serve as a useful platform for the realization of catalytic asymmetric Diels–Alder reactions using other classes of 1-amino-substituted dienes.[15]

Supporting information (including further optimization results, experimental details, and copies of the ^1H and ^{13}C NMR spectra) for this article is available on the WWW under http://www.angewandte.org or from the author.

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