Cycloaddition

International Edition: DOI: 10.1002/anie.201509693
German Edition: DOI: 10.1002/ange.201509693

Enantioselective Formal [4+2] Cycloadditions to 3-Nitroindoles by Trienamine Catalysis: Synthesis of Chiral Dihydrocarbazoles

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Abstract: *The first enantioselective formal [4+2] cycloadditions of 3-nitroindoles are presented. By using 3-nitroindoles in combination with an organocatalyst, chiral dihydrocarbazole scaffolds are formed in moderate to good yields (up to 87%) and enantioselectivities (up to 97% ee). The reaction was extended to include enantioselective [4+2] cycloadditions of 3-nitrobenzothiophene. The reaction proceeds through a [4+2] cycloaddition/elimination cascade under mild reaction conditions. Furthermore, a diastereoselective reduction of an enantioenriched cycloadduct is presented. The mechanism of the reaction is discussed based on experimental and computational studies.*

The ubiquity of the indole heterocycle in natural products and pharmaceuticals underscores the importance of this privileged motif.[1] Therefore, the preparation of substituted indole derivatives has received significant attention over the years.[2] The vast majority of these methods involve the well-known nucleophilic character of indole.[2] Exploiting the umpolung[3] reactivity of indole would provide complementary synthetic methods to access complex indole derivatives.[4] Recently, electrophilic indoles have been disclosed as promising electron-deficient alkenes in the asymmetric catalysis area.[5] In this context, we hypothesized that combining electrophilic indoles and trienamine catalysis[6] might provide access to new highly functionalized indole scaffolds which are difficult to obtain by conventional strategies.

The synthesis of a key heterocyclic moiety, such as carbazole, has been broadly studied.[7] However, the syntheses of the related tetrahydro-[8] and dihydrocarbazoles[9] have received less attention because of the limited synthetic procedures available, even though, the unique dihydrocarbazole scaffold constitutes a compound class (dihydrotubingensins A and B; Figure 1) which has been isolated from natural sources.[10] Consequently, asymmetric organocatalytic protocols providing access to these compounds are highly desirable for the development of reactions for skeletal diversity.[11]

Herein, we disclose a catalytic enantioselective formal [4+2] cycloaddition/elimination cascade of 2,4-dienals with 3-nitroindoles, thus providing chiral dihydrocarbazole scaffolds in good yields and high enantioselectivities. We demonstrate that the reaction concept can also be extended to 3-nitrobenzothiophene.

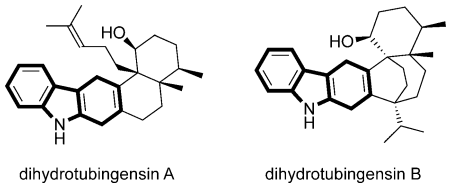
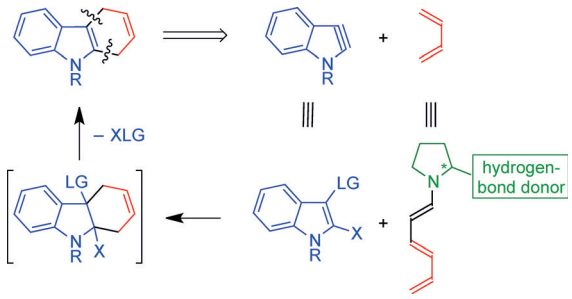


Figure 1. The 4,9-dihydro-1*H*-carbazole alkaloid scaffold in natural products.

Different approaches for the formation of chiral dihydrocarbazole scaffolds can be envisioned. The most direct approach would be the cycloaddition of a diene to 2,3-indolyne (Scheme 1, top). However, 2,3-indolynes and related heteroarynes have, according to the best of our knowledge, not been generated and applied in catalytic asymmetric reactions.[12]



Scheme 1. Synthetic strategy for the formation of dihydrocarbazoles. LG = leaving group.

We envisioned that an electron-deficient indole[13] might be a suitable candidate for reacting under organocatalytic asymmetric conditions with an electron-rich diene functionality, which is generated in situ, by using the trienamine approach.[6] To be able to control the reaction course we assumed that installing a nitro functionality at the 3-position of the indole,[5] and use of a hydrogen-bonding organocatalyst[14] would direct the dienophile to approach the amino-activated diene functionality in a stereoselective manner (Scheme 1, bottom). The strategy was expected to induce LUMO lowering of the dienophile, thus making it more reactive with the in situ generated diene. We anticipated that the role of the catalyst would be threefold: activation of both

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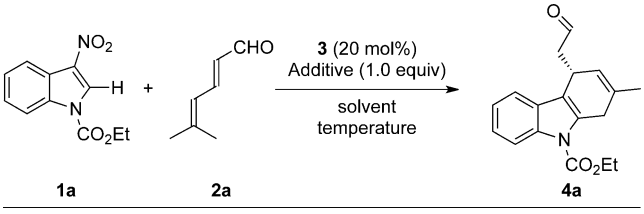
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509693.

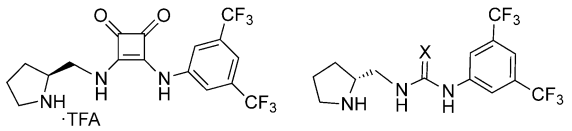
substrates, induction of stereoselectivity, and promotion of the elimination of the nitro group.

Towards our aim, the model reaction was envisioned to proceed by reaction of the 3-nitroindole **1a** with (*E*)-5-methylhexa-2,4-dienal (**2a**) in the presence of a hydrogen-bond directing organocatalyst (**3**), which should have the properties mentioned above (Table 1). Furthermore, a base additive would also be needed as the strategy is based on the elimination of HNO_2 from **1a**.[15] Table 1 presents some representative screening results. The reaction was dependent on the additive as greater than 95% conversion was obtained when a base was used, and no reaction took place when, for example, *N*,*N*-diethylacetamide (DEA) was present (entries 1 and 2). A basic additive such as DABCO was required for the reaction to take place, and in the presence of the squaramide-based catalyst **3a** high conversions were found in both toluene and CH_2Cl_2 (entries 2–4). The catalyst **3a** gave up to 79% *ee* of the cycloaddition product **4a** (entry 4), while the thiourea-based catalyst **3b** gave the same enantioselectivity and increased conversion to greater than 95% (entry 5). The corresponding urea-based catalyst **3c** showed promising results in various solvents and with various bases (entries 6–13). The best results were obtained in CH_2Cl_2 with DABCO as the base, with **4a** in 81% *ee* (entry 6). It was notable that the elimination of HNO_2 was normally slow at 0°C. However, by increasing the temperature to 40°C, after completion of the cycloaddition step, the elimination was accelerated without observing any deleterious effect on the enantioselectivity of **4a**. Moreover, the multiple roles of the additive DABCO were found to be essential in the reaction, thus preventing potential self-aggregation of **3c**, and increasing conversion and enantioselectivity (entries 6 and 12). We also tested other aminocatalysts for the model reaction and used, for example, the TMS-protected diarylprolinol catalysts, which gave lower conversions and enantioselectivities, required longer reaction times, and higher reaction temperatures, thus verifying the threefold role of **3** (see the Supporting Information).

To study the steric and electronic effects, the reaction of the 3-nitroindoles **1** with **2a** was investigated with various N-protecting groups in **1** (Scheme 2). From the results, it appears that the reaction is not dependent on the N-protecting group in **1**, as greater than 95% conversion was observed and the enantioselectivity was rather consistent (76–81% *ee*) for all four N-protecting groups studied.

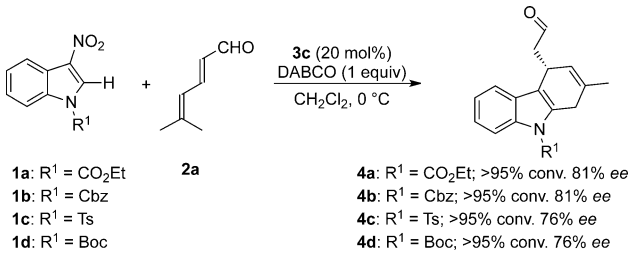
Table 1: Screening and optimization of reaction conditions for the formal [4+2] cycloaddition to 3-nitroindole **1a**.[a]





Entry	Catalyst	Additive	Solvent	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	**3a**	DEA[d]	toluene	RT	<1	–
2	**3a**	DABCO	toluene	RT	>95	−72
3[e]	**3a**	DABCO	toluene	0	68	−55
4	**3a**	DABCO	CH_2Cl_2	0	85	−79
5	**3b**	DABCO	CH_2Cl_2	0	>95	79
6	**3c**	DABCO	CH_2Cl_2	0	>95	81
7	**3c**	DABCO	$CHCl_3$	0	>95	79
8	**3c**	DABCO	$ClCH_2CH_2Cl$	0	>95	75
9	**3c**	DEA[d]	CH_2Cl_2	0	<1	–
10[e]	**3c**	DIPEA	CH_2Cl_2	0	37	–
11[e]	**3c**	Et_3N	CH_2Cl_2	0	>95	79
12	**3c**	DABCO[f]	CH_2Cl_2	0	85	69
13[g]	**3c**	DABCO	CH_2Cl_2	−10	>95	76

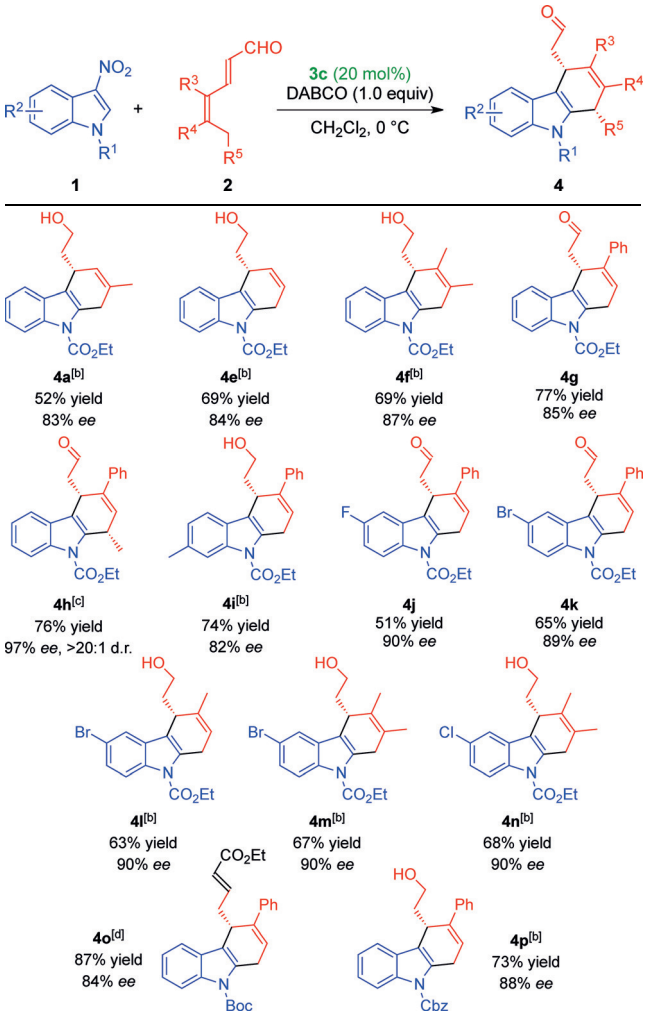
[a] All reactions were performed using **1a** (0.05 mmol), **2a** (0.1 mmol), 0.2 mL solvent, reaction time: 24 h. Then, the reaction mixture was heated up to 40°C to complete the elimination of HNO_2. [b] Conversion of limiting reagent was measured by ^{1}H NMR analysis of the crude reaction mixture after 24 h. [c] The *ee* value was determined by chiral-phase UPC^2 after reduction of **4a** into the corresponding alcohol. [d] DEA = *N*,*N*-diethylacetamide. [e] Reaction time: 72 h. [f] 20 mol% DABCO was used. [g] Reaction time: 48 h. DABCO = 1,4-diazobicyclo-[2.2.2]octane, TFA = trifluoroacetic acid.



Scheme 2. Variation of the N-protecting group in the 3-nitroindoles **1**. Conversion of the limiting reagent was measured by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by chiral-phase UPC^2 after reduction of **4** into the alcohol. Boc = *tert*-butoxycarbonyl, Cbz = carboxybenzyl, Ts = 4-toluenesulfonyl.

Next, a variety of 3-nitro-1*H*-indole-1-carboxylates (**1**) and 2,4-dienals (**2**) were tested to study the scope of the reaction (Table 2). It was observed that better yields and enantioselectivities were obtained when 2,4-dienals other than **2a** were used for the reaction with **1a** (products **4e**–**h**). Notably, 4-phenylhepta-2,4-dienal gave excellent enantioselectivity (97% *ee*) and a nearly pure diastereoisomer (**4h**). Installing a methyl substituent at the 6-position of **1a** had a small effect on the outcome of the reaction (**4i**). Substrates with an electron-withdrawing substituent at the 5-position showed consistent reactivity and stereoselectivity when reacting with different 2,4-dienals and provided 89–90% *ee* (**4j**–**n**). During the process of expanding the substrate scope, we observed that 4-phenylhepta-2,4-dienal gave a better yield and enantioselectivity than **2a**, which we used for optimizing the reaction conditions. Therefore, we tested the reaction between 3-nitroindoles, bearing N-Boc and N-Cbz protecting groups, and 4-phenylhepta-2,4-dienal. As it appears from Table 2, the N-Boc- and N-Cbz-protected 3-nitroindole gave nearly the same enantioselectivity.

Table 2: Scope of the formal [4+2] cycloaddition of the 3-nitroindoles **1**.[a]



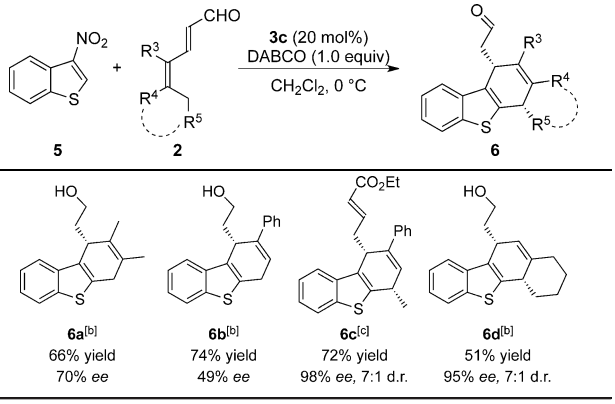
[a] All reactions were performed using **1** (0.1 mmol), **2** (0.2 mmol), **3c** (0.02 mmol), DABCO (0.1 mmol) in 0.4 mL CH_2Cl_2. All *ee* values were determined by chiral-phase UPC[2]. Absolute configuration was determined by X-ray crystallography analysis of **4k** and the remaining structures were assigned by analogy. See the Supporting Information. [b] Product isolation and determination of the *ee* value were carried out by converting the cycloadduct into the alcohol. [c] The *ee* value was determined by converting **4h** into the alcohol. The d.r. was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Product isolation and determination of the *ee* value were carried out by converting the cycloadduct into the Wittig adduct **4o**.

To evaluate the practicality of the present synthetic methodology we performed reactions on scales ranging from 0.1 to 1.0 mmol. These experiments gave the following results for **4h** (d.r. >20:1): 0.1 mmol: 76% yield, 97% *ee*; 0.5 mmol: 84% yield, 97% *ee* and 1.0 mmol: 85% yield, 97% *ee*. These scale-up experiments thus demonstrate the reliability of the method.

To our surprise, the reaction proceeded successfully with 3-nitrobenzothiophene (**5**) as the dienophile[16] under mild reaction conditions, which are in striking contrast to the only previous reaction conditions for the [4+2] cycloaddition to 3-nitrobenzothiophene, where up to 180 °C were required.[16a] For the reaction of **5** with four different types of 2,4-dienals in the presence of **3c** and DABCO, the results presented in Table 3 show similar results to those obtained for the reactions employing **1a** as the substrate. The highest enantioselectivities were found for the products **6c** and **6d**, with 98% and 95% *ee*, respectively.

The utility of the enantioenriched cycloadducts **4** is outlined in Scheme 3. The diastereoselective reduction of

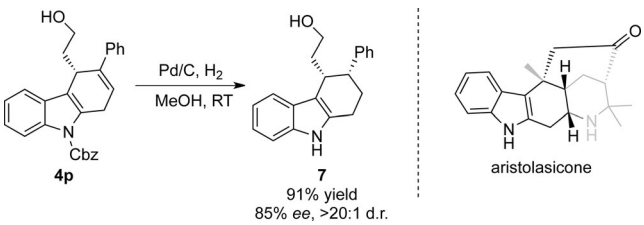
Table 3: Scope of the formal [4+2] cycloaddition of **5**.[a]



[a] All reactions were performed using **5** (0.1 mmol), **2** (0.2 mmol), **3c** (0.02 mmol), DABCO (0.1 mmol) in 0.4 mL CH_2Cl_2. All *ee* values were determined by chiral-phase UPC[2]. The absolute configuration was assumed to be identical to the cycloadducts obtained for **1** as the substrate. See the Supporting Information. [b] Product isolation and determination of the *ee* value were carried out by converting the cycloadduct into the alcohol. [c] Product isolation and determination of the *ee* value were carried out by converting the cycloadduct into the Wittig adduct **6c**. The d.r. value was determined by ^{1}H NMR analysis of the crude reaction mixture.

the olefin and cleavage of the Cbz-group in **4p** were performed in a single step, thus affording the cycloadduct **7** in high yield and excellent stereocontrol. Notably, the cycloadduct **7** is similar to the core structure of the natural compound aristolasicone, which has only been synthesized in racemic form.[17]

Experimental observations and computational investigations have provided some insight into the mechanism for the cycloaddition of 3-nitroindoles and 3-nitrobenzothiophene. During the optimization of the reaction conditions (Table 1), we observed an intermediate as a diastereoisomeric mixture (Scheme 1, lower left). For the reactions described in Tables 2 and 3, and Scheme 2, this intermediate was also observed by NMR spectroscopy for several of the reactions, while for the **5** the intermediate was observed for **6a**,**b**,**d** in about a 1:1 d.r.



Scheme 3. Diastereoselective reduction and cleavage of the Cbz group in the enantioenriched cycloadduct **4p**.

The role of **3c** acting also as a hydrogen-bonding donor is supported experimentally, as the installation of competing hydrogen-bonding functionalities, such as nitro and cyano groups at the 5-position of 3-nitroindole resulted in no reaction, even at 40 °C.

DFT calculations[18] (see the Supporting Information) were performed to account for the role of the catalyst for the activation of the dienophile (**5** was used to reduce the number of conformers). The electronic interaction leading to the reaction is that between the LUMO of **5** and the HOMO of the trienamine, represented as an *s-cis*-diene (Figure 2, top left).[19] Calculations have shown that the terminal carbon atom in the *s-cis*-diene moiety has the largest HOMO amplitude and might point towards an asynchronous or stepwise mechanism.[20] By activating **5** by hydrogen bonding to **3c** the LUMO is calculated to be lowered by 0.84 eV compared to that of the uncatalyzed system. We used the transition state for the addition of butadiene as a model for the *s-cis*-diene moiety of the trienamine (Figure 2, top right). The role of the hydrogen-bonding activation of **5** by **3c** is supported by the calculations as the activation energy is reduced from 79 to 37 kJ mol^{-1}. Furthermore, the calculations gave C1-C2 and C3-C4 bond lengths as 1.93 Å and 3.21 Å, respectively, in the transition state in the presence of **3c** (**TS I**, Scheme 2, bottom left). The same bond lengths in the absence of **3c** are 1.96 Å and 2.61 Å, respectively. These calculations indicate that the reaction without catalyst proceeds in a single step, while the catalyzed reaction occurs in two steps.[20]

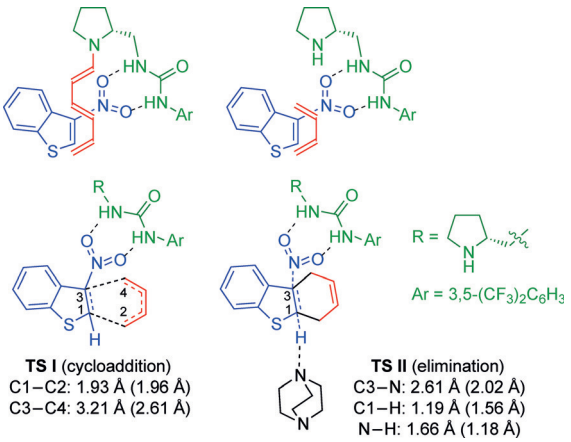


Figure 2. Selected results from the computational studies of the transition states for the simplified model for the formal cycloaddition of **5**. Values within brackets are those for the uncatalyzed reactions.

The role of DABCO as a base for the elimination step has also been investigated (Figure 2, bottom right). In the presence of **3c**, the bond length of the breaking C3–N bond is calculated to be 2.61 Å in the transition state (**TS II**), and is in sharp contrast to the value of 2.02 Å for the uncatalyzed reaction. The C1–H 1.19 Å (1.56 Å) and N–H 1.66 Å (1.18 Å) bond lengths show similar changes in the presence and absence of **3c** (values in brackets are for the uncatalyzed reaction). The catalyst lowers the activation energy from 98 kJ mol^{-1} to 36 kJ mol^{-1}. These results support the multiple roles of the hydrogen-bonding catalyst **3c**: it activates both substrates in the addition step and promotes the elimination of the nitro group in the second step, thus reforming the double bond.

In conclusion, the first enantioselective formal [4+2] cycloaddition to 3-nitroindoles is reported to proceed by using organocatalysis. The combination of 3-nitroindoles and 2,4-dienals in the presence of an organocatalyst leads to the formation of chiral dihydrocarbazole scaffolds in moderate to good yields (up to 87 %) and enantioselectivities (up to 97 % *ee*) under mild reaction conditions. This novel approach is applicable to the enantioselective cycloaddition reactions for 3-nitrobenzothiophene, thereby providing the cycloaddition products in up to 98 % *ee*. Synthetic manipulation of the chiral cycloadducts by a diastereoselective reduction of the olefin in the product is also presented. Mechanistic studies based on experimental observations and computational studies point towards an asynchronous/stepwise addition followed by an elimination in which the hydrogen-bonding catalyst plays a pivotal role. The present development provides an alternative reaction concept for cycloaddition reactions of 2,3-indolynes and 2,3-benzothiophynes, as the generation of these heteroarynes have not yet been possible.

Acknowledgements

This work was financially supported by Aarhus University and the Carlsberg Foundation. Y.L. acknowledges the Chinese Scholarship Council for a Ph.d. fellowship. F.T. acknowledges the European Commission for a Marie Curie Intra European Fellowship for Career Development (PIEF-GA-2013-622413) within the 7th European Community Framework Programme. Magnus E. Jensen is gratefully acknowledged for performing X-ray analysis. Thanks are expressed to a reviewer for suggesting that we perform computational studies.

Keywords: asymmetric catalysis · cycloaddition · heterocycles · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 1020–1024
Angew. Chem. **2016**, *128*, 1032–1036

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Received: October 16, 2015
Revised: November 16, 2015
Published online: December 4, 2015

