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An Enantioselective Approach to Highly Substituted Tetrahydrocarbazoles through Hydrogen Bonding-Catalyzed Cascade Reactions

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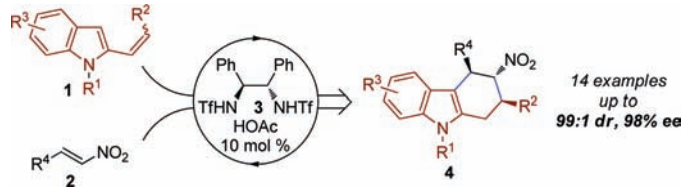
ABSTRACT



A hydrogen bonding-mediated double Michael addition−aromatization cascade of 2-propenylindoles and nitroolefins has been disclosed. The methodology allows an efficient synthesis of diverse and structurally complex tetrahydrocarbazoles in good to excellent enantioselectivities and diastereoselectivities.

Tetrahydrocarbazoles have become recognized as common structural components of a diverse array of naturally occurring alkaloids and pharmacological agents of various therapeutic actions.[1] The development of novel and highly efficient methods to construct this cyclic architecture is therefore of great importance from both industrial and academic points of view.[2] In this regard, the catalytic intramolecular alkylation of alkenyl indoles using transition metal complexes has emerged as a preeminent strategy for the tetrahydrocarbazole synthesis in the past few years.[2b−l] However, in contrast to many nonasymmetric procedures, catalytic enantioselective approaches to tetrahydrocarbazoles are rare; these include intramolecular hydroarylations of indole-substituted alkenes or allenes catalyzed by chiral scandium(III),[2e] platinum(II),[2d,g] and gold(I)[2h,i,l] complexes, respectively. To our knowledge, the analogous asymmetric intermolecular reaction, which directly results in the construction of the tetrahydrocarbazole skeleton with a wide range of functionalities, has not been realized yet.

Besides transition metal catalysis, asymmetric organocatalysis is now well established as a powerful tool for the preparation of optically active compounds from simple and

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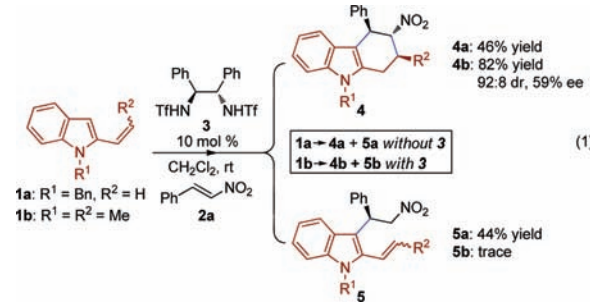
readily available starting materials.[3] In this context, it becomes clear that small organic molecules capable of activating substrates through hydrogen bondings possess tremendous potential in the development of novel asymmetric processes.[4] Although remarkable advances have been achieved, the vast majority of hydrogen bonding catalysis is based on either chiral phosphoric acids[5] or thioureas,[6] and strategies based on simple hydrogen bonding donors (e.g., bis-sulfonamide such as **3**) remain largely unexplored (especially their applications to cascade reactions[7]).[8] From a practical and atom-economic perspective, the exploration of the hydrogen bonding catalysis by means of simple and readily accessible small molecules is highly desirable.

As part of our ongoing project on the heterocycle-oriented methodology development,[9] we describe herein a novel double Michael addition−aromatization reaction cascade of 2-propenylindoles with nitroolefins catalyzed by a chiral bis-sulfonamide, which can efficiently generate three consecutive stereogenic centers in one operation. Importantly, this procedure allows a rapid access to diverse and structurally complex tetrahydrocarbazole derivatives in excellent enantioselectivities (up to 98% ee) and diastereoselectivities (up to 99:1 dr). This is a prominent example of asymmetric cascade reactions[10] catalyzed only by a simple chiral hydrogen bonding donor.



We initially studied the reaction of 2-alkenyl indoles **1a**,**b** and *trans*-β-nitrostyrene **2a** in dichloromethane to examine the feasibility of the cascade protocol (eq 1). When the reaction was performed with **1a** and **2a** at room temperature, two products, a formal [4+2] adduct **4a** and Friedel−Crafts alkylation product **5a**, were obtained in 46% and 44% yield, respectively. Encouraged by this result, we examined the reaction in detail by varying R,[1] R[2], chiral hydrogen bonding catalysts, solvents, and temperature in an attempt to increase the yield of the tetrahydrocarbazole product.[11] After an extensive screen of the catalysts, bis-sulfonamide catalyst **3**, which was easily prepared from simple and commercially available chiral diamines,[12] was identified as the most promising catalyst. In particular, it was found that the reaction provided stereochemically enriched tetrahydrocarbazole **4b** in 82% isolated yield, 92:8 dr, and 59% ee with the corresponding alkylation product **5b** only in trace amount, when 1-methyl-2-propenylindole **1b** was employed as the substrate in the presence of 10 mol % of **3** at −40 °C (eq 1). Having further recognized water-saturated dichloromethane as the solvent of choice and −78 °C as the optimal reaction temperature for this transformation, we then examined a diverse range of additives in an effort to elevate the stereoselectivity of the process (Table 1). While variation of additives has a pronounced effect on the stereochemistry of the reaction (Table 1, entries 2 and 3 vs entries 9 and 10), moderate levels of enantioselectivity were observed for various Brønsted acids. Notably, the superior levels of asymmetric induction and efficiency exhibited by catalytical amounts of **3** and acetic acid in H_2O-saturated CH_2Cl_2 at −78 °C (Table 1, entry 7, 88:12 dr and 87% ee) prompted us to use these conditions for further exploration.

Experiments that probe the scope of both 2-propenylindoles (**1**) and nitroolefins (**2**) are summarized in Table 2. Under optimized conditions, a wide range of aromatic

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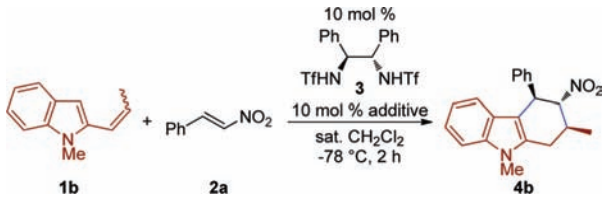
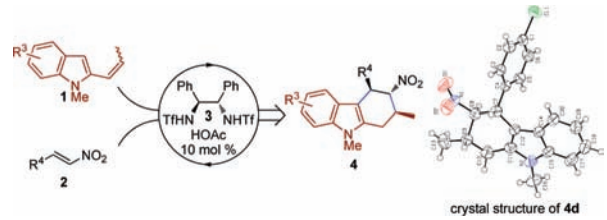
Table 1. Effect of Various Additives on the Stereoselectivity of the Cascade Reaction[a]



entry	additive	yield (%)[b]	dr[c]	ee (%)[c]
1		85	88:12	78
2	$HClO_4$	79	83:17	83
3	CF_3COOH	78	85:15	83
4	HCOOH	77	73:27	84
5	L-tartric acid	88	89:11	82
6	PhCOOH	82	85:15	86
7	HOAc	80	88:12	87
8	PhOH	82	70:30	84
9[d]	4 ÅMS	93	85:15	70
10[d]	$MgSO_4$	86	76:24	60

[a] The reaction was carried out with 1 equiv of **2a**, 1.6 equiv of **1b** (*Z*/*E*: 1/1), 10 mol % of **3**, and 10 mol % of additive in H_2O-saturated CH_2Cl_2 at −78 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Anhydrous CH_2Cl_2 was used in this case.

Table 2. Effect of Various Additives on the Stereoselectivity of the Cascade Reaction[a]



entry	R^3	R^4	yield (%)[b]	dr[c]	ee (%)[c]
1	5-H	C_6H_5	**4b**: 80	88:12	87
2	5-H	4-FC_6H_4	**4c**: 86	92:8	88
3	5-H	4-ClC_6H_4	**4d**:[d] 75	95:5	89
4	5-H	3-BrC_6H_4	**4e**: 63	99:1	90
5	5-H	2-ClC_6H_4	**4f**: 63	80:20	98
6	5-H	3,4-$F_2C_6H_3$	**4g**: 68	99:1	90
7	5-H	4-MeC_6H_4	**4h**: 70	95:5	90
8	5-H	2-furanyl	**4i**: 69	83:17	82
9	5-H	2-thienyl	**4j**: 68	96:4	82
10	5-CH_3	4-$MeOC_6H_4$	**4k**: 70	84:16	86
11	5-CH_3	2-furanyl	***4l***: 75	89:11	88
12	5-Cl	4-FC_6H_4	**4m**: 55	99:1	88
13	5-Cl	4-ClC_6H_4	**4n**: 42	99:1	92
14	6-Cl, 7-CH_3	C_6H_5	**4o**: 49	99:1	90

[a] The reaction was carried out with 1.6 equiv of **1** (*Z*/*E*: 1/1 to 2/1), 1 equiv of **2**, 10 mol % **3**/HOAc in H_2O-saturated CH_2Cl_2 at −78 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **4d** was determined by X-ray crystal-structure analysis. The absolute configurations of the other products were assigned by analogy.

nitroolefins underwent reactions with 2-propenylindole **1b** in high yields and stereoselectivities (Table 2, entries 1−9). The reaction sequence displays substantial generality with respect to the electronic and steric contribution of the substituent on the benzene ring of the nitroolefin component (Table 2, entries 1−7). Note that *o*-, *m*-, and *p*-halogen-substituted *β*-nitrostyrenes were successfully employed in this hydrogen bonding-mediated transformation to generate the corresponding tetrahydrocarbazoles with high to excellent enantioselectivities (up to 98% ee) and diastereoselectivities (up to 99:1 dr) (Table 2, entries 2−5). Incorporation of two substituents at the meta- and para-positions of the nitrostyrene could be accomplished with little influence on the reaction efficiency (Table 2, entry 6, 68% yield, 99:1 dr, 90% ee). As highlighted in entries 8 and 9, the nitroolefin bearing a heteroaromatic substituent also proved to be a suitable reaction partner (68% yield, 83:17 dr, 82% ee).

As revealed in entries 1 and 10 to 14 of Table 2, this hydrogen bonding-catalyzed cascade reaction is also general with respect to indole architecture. Significant structural variation in the indole ring can be well tolerated. The electronic nature of the indole ring does not affect the selectivity much (Table 2, entries 10 vs 1 and entries 12 vs 1). Perhaps more significant, we have successfully utilized electron-deficient 2-propenylindoles in the context of a 5-chloro-substituted 2-vinylindole (Table 2, entries 12 and 13). Such halogenated tetrahydocarbazoles can be further manipulated through transition metal-catalyzed couplings.[13] Furthermore, disubstituted vinyl indole derivatives (Table 2, entry 14) can readily participate in this reaction and afford a polysubstituted enantioenriched tetrahydrocarbazole in excellent stereoselectivities (99:1 dr, 90% ee). In the case of aliphatic nitroalkenes, the reaction also proceeded smoothly, albeit with diminished stereoselectivity.[11] The absolute configuration was unambiguously determined to be (2*S*,3*R*,4*R*) by X-ray crystallographic analysis of **4d**,[14] and the stereochemistry of other products could be tentatively assigned by assuming an analogous enantioinduction (Scheme 1).

To identify the possible reaction mechanism between Diels−Alder pathway and double Michael addition−aromatization sequence, we carried out the cyclization reaction between **1b** and **2a** on gram scale (Scheme 2).[11] It was found that the *Z*-isomer of vinylindole was consumed much faster than the *E*-isomer, which proved that a stepwise process was more possible. Moreover, the exclusive formation of **5a** and the fact that the Diels−Alder adduct[10i] was not observed make the cascade cycle more favorable (eq 1 and Scheme 1).

Therefore, a plausible catalytic cycle involving double Michael addition−aromatization cascade is outlined in Scheme 1. We presumed that the exposure of nitroolefin **2** to chiral hydrogen bonding donor **3** would generate an

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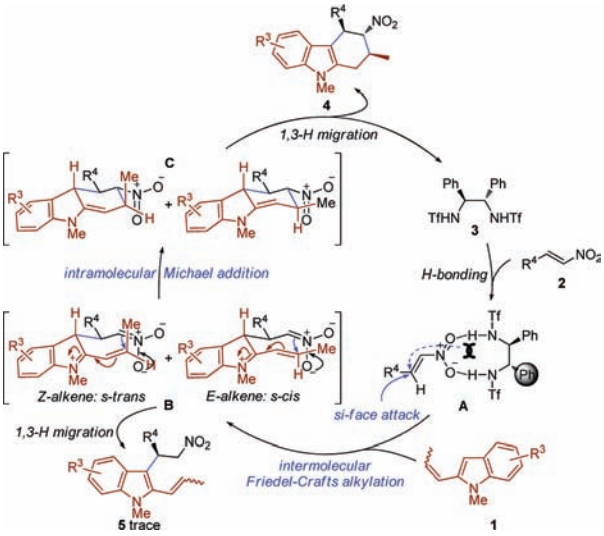
(14) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 734894. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.ca-m.ac.uk/daa_ request/cif.

electrophilic complex **A**[8a,d] that could then enantioselectively intercept a nucleophilic 2-propenylindole **1** through a Friedel−Crafts-type Michael addition. A new active intermediate **B** that contains both iminium and nitronate components[9b] will be produced to accomplish the intramolecular Michael addition to form **C**. Subsequently, a rapid

Scheme 1. Proposed Reaction Pathway for the Cascade Sequence

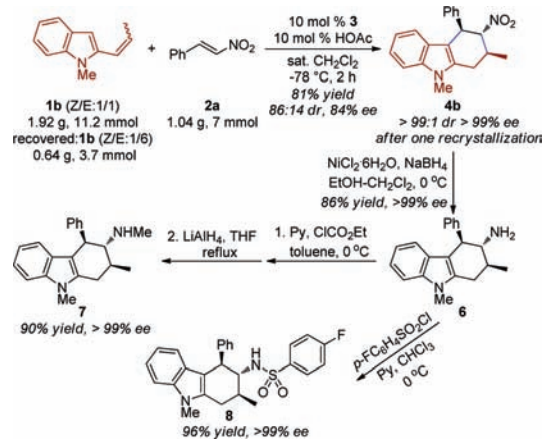


[1,3]-*H* migration would regenerate the aromaticity of indole ring, and therefore afford the corresponding tetrahydrocarbazole **4**. The Friedel−Crafts alkylation product **5** would arise from the rearomatization of **B**.

A demonstration of the synthetic potential of the present methodology is presented in the synthesis of Frovatriptan[15] and Ramatroban[16] analogues. As outlined in Scheme 2, treatment of **1b** (1.92 g, 11.2 mmol) with **2a** (1.04 g, 7 mmol) provides tetrahydrocarbazole **4b** in one step, 81% yield, 86:14 dr, and 84% ee. A single recrystallization provided almost optically pure **4b** in 47% yield. Elaborations of **4b** to Frovatriptan and Ramatroban analogues were accomplished by using three-step and two-step procedures, respectively. Significantly, this operationally trivial procedure shows that complex drug candidates can be easily accessed by this hydrogen bonding catalytic methodology.

In conclusion, we have developed a hydrogen bonding-mediated double Michael addition−aromatization cascade of 2-propenylindoles and nitroolefins. This strategy allows rapid and efficient access to diverse and structurally complex tetrahydrocarbazoles from simple starting materials and readily available chiral diamine-derived catalyst. Further investigations aimed at expanding the substrate scope and characterizing the medical properties of the products are currently underway.

Scheme 2. Derivatization of the Cascade Adduct **4b**



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Supporting Information Available: Experimental procedures and compound characterization data including X-ray crystal data (CIF) for **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Frovatriptan is a triptan drug developed by Vernalis for the treatment of migraine headaches, in particular those associated with menstruation. See: Easthope, S. E.; Goa, K. L. *CNS Drugs* **2001**, *15*, 969.

(16) Ramatroban is a drug used to treat coronary artery disease and asthma, which is developed in association with Bayer. See: Ishizuka, T.; Matsui, T.; Okamoto, Y.; Ohta, A.; Shichijo, M. *Cardiovasc. Drug Rev.* **2004**, *22*, 71.