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Asymmetric Diels–Alder Reaction of 2-Methyl-3-indolylmethanols via in Situ Generation of *o*-Quinodimethanes

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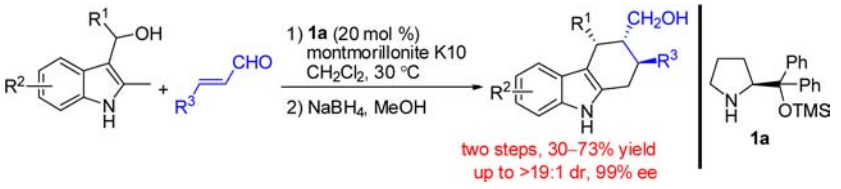
ABSTRACT



An asymmetric Diels–Alder reaction of 2-methyl-3-indolylmethanols and α,β-unsaturated aldehydes has been developed that relies on in situ generation of active indole-2,3-quinodimethane intermediates under mild acidic conditions and uses a secondary chiral amine as iminium activation catalyst. An array of highly enantioenriched tetrahydrocarbazoles have been efficiently produced in fair to good yields.

Chiral tetrahydrocarbazoles have been recognized as important structural motifs in a diversity of natural products and pharmacological compounds (Figure 1).[1] A number of asymmetric methodologies have been developed for the construction of this type of cyclic architectures.[2] Among them, the catalytic stereoselective Diels–Alder cycloadditions provide one of the most efficient and straightforward protocols, while previously positioned 2-vinylindoles or 3-vinylindoles were commonly used as the diene counterparts in combination with diverse dienophiles (Scheme 1).[3]

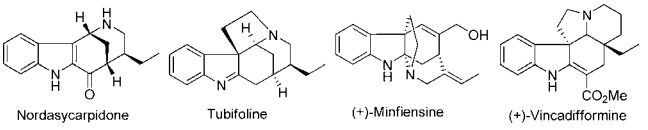


Figure 1. Selected examples of bioactive and natural products containing tetrahydrocarbazole motif.

On the other hand, the *o*-quinodimethanes (*o*QDMs), even though they have been widely employed to prepare

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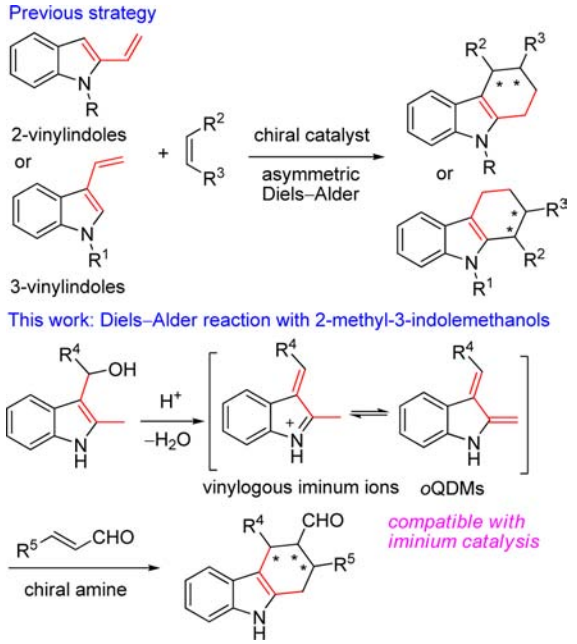
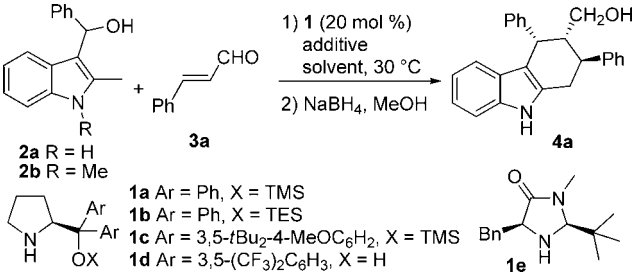
many complex compounds, have been much less used in catalytic asymmetric Diels–Alder reactions, probably because of the instability and high reactivity of such dienes and the deficiency of compatible catalytic systems.[4] In particular, a special type of *o*QDMs, indole-2,3-quinodimethanes, have also been well established as active intermediates in the construction of tetrahydrocarbazoles through Diels–Alder cycloadditions.[5] Nevertheless, only very recently did Melchiorre and co-workers successfully document the amine-catalyzed asymmetric Diels–Alder reaction of β-indolyl unsaturated aldehydes, from which indole-2,3-quinodimethanes were generated and acted as the active dienes.[6] On the other hand, 3-indolemethanol compounds has been disclosed as valuable alkylation reagents by formation of vinylogous iminium ions under diverse acidic conditions.[7] As part of our continuing interest in the direct transformations with indole substrates,[8] we envisaged that indole-2,3-quinodimethanes might be produced from 2-methyl-3-indolemethanols through tautomerization of the corresponding iminium ions, as outlined in Scheme 1. Thus, an asymmetric Diels–Alder reaction of these active species and α,β-unsaturated aldehydes could be carried out by the iminium activation of a chiral amine.[9]

Scheme 1. Constructions of Chiral Tetrahydrocarbazoles via Diels–Alder Cycloadditions of Diverse Indole Compounds



Initially, (2-methyl-1*H*-indol-3-yl)(phenyl)methanol (**2a**) and *trans*-cinnamaldehyde (**3a**) were selected as the model substrates in dichloromethane, using α,α-diphenylprolinol *O*-TMS ether[10] (**1a**) as the catalyst in the presence of excess acetic acid. We indeed observed the expected cycloadduct in high diastereoselectivity, along with the dimerization byproduct of indole compound. Pleasingly, the enantioselectivity of the major *endo*-diastereomer was quite promising after conversion to the corresponding

Table 1. Screening Studies[a]



entry	cat.	solvent	additive	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	CH_2Cl_2	AcOH	62	10:1	93
2	**1b**	CH_2Cl_2	AcOH	56	9:1	94
3	**1c**	CH_2Cl_2	AcOH	53	7:1	90
4	**1d**	CH_2Cl_2	TFA	trace		
5	**1d**	CH_2Cl_2	AcOH	trace		
6	**1e**	CH_2Cl_2	TFA	trace		
7	**1a**	toluene	AcOH	57	9:1	90
8	**1a**	THF	AcOH	43	12:1	96
9	**1a**	$CHCl_3$	AcOH	58	8:1	92
10	**1a**	CH_2Cl_2	$PhCO_2H$	37	9:1	93
11	**1a**	CH_2Cl_2	silica gel[e]	48	10:1	97
12	**1a**	CH_2Cl_2	M-K10[f]	65	10:1	96
13	**1a**	CH_2Cl_2	M-K10[g]	71	10:1	96

[a] Unless otherwise noted, the reaction was carried out with **2a** (0.12 mmol), **3a** (0.1 mmol), acid (0.12 mmol), and catalyst **1** (0.02 mmol) in solvent (1.0 mL) at 30 °C for 72 h. [b] Isolated yield of the major *endo*-isomer **4a** for two steps. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis. [e] 60 mg. [f] Montmorillonite K10 (60 mg). [g] Montmorillonite K10 (30 mg).

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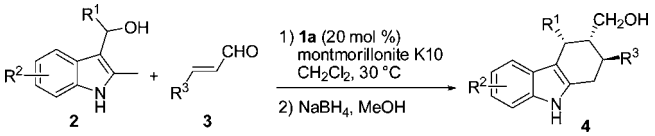
Table 2. Substrate Scope and Limitations[a]



entry	R^1	R^2	R^3	4	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	H	Ph	**4a**	71	10:1	96
2	4-BrC_6H_4	H	Ph	**4b**	58	10:1	98
3	2-ClC_6H_4	H	Ph	**4c**	60	9:1	97
4	3-MeC_6H_4	H	Ph	**4d**	63	6:1	99
5	4-MeC_6H_4	H	Ph	**4e**	61	8:1	99
6	1-naphthyl	H	Ph	**4f**	68	>19:1	93
7	2-thienyl	H	Ph	**4g**	43	2.5:1	99
8[e]	cyclopropyl	H	Ph	**4h**	65	>19:1	98
9	Ph	5-Br	Ph	**4i**	56	6:1	90
10	Ph	5-Me	Ph	**4j**	53	7:1	96
11	Ph	7-Me	Ph	**4k**	53	10:1	99
12	Ph	H	4-ClC_6H_4	**4l**	73	12:1	99
13	Ph	H	4-FC_6H_4	**4m**	47	>19:1	90
14	Ph	H	4-$CF_3C_6H_4$	**4n**	56	10:1	96
15	Ph	H	4-EtOOCC_6H_4	**4o**	52	>19:1	97
16	Ph	H	4-MeC_6H_4	**4p**	63	7:1	99
17	Ph	H	2-furyl	**4q**	57	16:1	99
18[e]	cyclopropyl	H	4-$NO_2C_6H_4$	**4r**	63	>19:1	99
19[e]	cyclopropyl	H	4-MeC_6H_4	**4s**	53	7:1	93
20	Ph	H	phenylethynyl	**4t**	30	9:1	95

[a] Unless otherwise noted, reaction was carried out with 3-indolemethanol **2** (0.12 mmol), enal **3** (0.1 mmol), catalyst **1a** (0.02 mmol), and Montmorillonite K10 (30 mg) in CH_2Cl_2 (1.0 mL) at 30 °C for 72 h. [b] Isolated yields of the major *endo*-isomers for two steps [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis. [e] For 8 h.

alcohol **4a** (Table 1, entry 1). Similar results were obtained when more bulky amine **1b** or **1c** was applied (entries 2 and 3). However, prolinol[11] (**1d**) and MacMillan's catalyst[9a−c] **1e** did not provide the desired product in combination with either AcOH or trifluoroacetic acid (entries 4−6). A survey of other reaction media revealed that the overall results could not be improved (entries 7−9). In order to reduce side reactions from labile indole substrate **2a**, more additives were investigated. While no reaction occurred in the absence of any acid, benzoic acid gave the desired product in a low yield (entry 10). Interestingly, using amine **1a** and simple silica gel could promote the reaction with higher enantioselectivity, though the yield was still fair (entry 11). To our delight, a cleaner reaction was observed when montmorillonite K10 was used, leading to better results in terms of yield, diastereoselectivity and enantioselectivity (entries 10 and 11). We also tested indole **2b** with an *N*-methyl group, which exhibited much lower reactivity and could not afford the desired cycloadduct.

With the established conditions in hand, we then explored the scope and limitations of both types of substrates. The reactions were catalyzed by amine **1a** (20 mol %) in the presence of montmorillonite K10 at 30 °C. The results are summarized in Table 2. For a diversity of 2-methyl-1*H*-indol-3-yl-arylmethanols with either electron-withdrawing or -donating substitutions, good to excellent diastereoselectivity along with outstanding enantioselectivity has been generally obtained in the reactions with cinnamaldehyde **3a** (Table 2, entries 1−6). Nevertheless, a 2-thienyl-substituted 3-indolemethanol gave a much lower dr value in the cycloaddition, while the ee value was still remarkable (entry 7). Notably, a 3-indolemethanol with a cyclopropyl group even showed higher reactivity, leading to the corresponding cycloadduct **4h** in excellent diastereo- and enantioselectivity (entry 8). Unfortunately, 3-indolemethanols bearing either other linear or branched alkyl groups were unstable under the current catalytic system and failed to produce the desired cycloadducts. In addition, similar good results were attained for 3-indolemethanols with various substituents on the indole ring (entries 9−11). Nevertheless, 3-indolemethanols with other 2-alkyl groups, such as benzyl or *n*-butyl ones, produced a complex mixture because of poor diastereoselectivity in the cycloaddition step. On the other hand, an array of α,β-unsaturated aldehydes with diverse aryl or heteroaryl substitutions were explored. The diastereo- and enantioselectivity were generally high, and the isolated yields were fair to moderate (entries 12−19). A β-phenylethynyl-substituted enal substrate showed lower reactivity, and a low yield was obtained (entry 20). We also tried to apply α,β-unsaturated aldehydes with β-alkyl substitutions. However, the major products came from

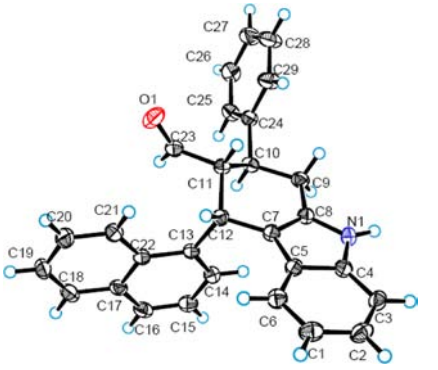


Figure 2. X-ray crystallographic structure of enantiopure aldehyde precursor of product **4f**.

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γ- or α-alkylation of the enal substrates via a dienamine catalytic pathway.[8a]

Crystals suitable for X-ray crystallographic analysis have been obtained from the corresponding aldehyde precursor of product **4f**. Thus, its absolute and relative configuration could be ambiguously determined, showing the normal *endo*-selectivity (Figure 2).

In conclusion, we have developed an asymmetric Diels–Alder reaction of 2-methyl-3-indolemethanols and α,β-unsaturated aldehydes that relies on in situ generation of active indole-2,3-quinodimethane intermediates under mild acidic conditions and uses a secondary chiral amine as iminium activation catalyst. A spectrum of chiral tetrahydrocarbazoles have been efficiently produced from easily available starting materials in fair to moderate yields, along with high to excellent diastereo- and enantioselectivity. We believe that the protocol presented in this work would provide more opportunities in asymmetric syntheses with in situ generated, highly reactive indole-2,3-quinodimethanes.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products; X-ray data of the enantiopure aldehyde precursor of product **4f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.