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Organocatalytic asymmetric synthesis of dihydrocarbazoles via a formal [4+2] cycloaddition of in situ generated *o*-quinodimethanes with enals

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ABSTRACT

An organocatalytic asymmetric [4+2] eliminative cycloaddition reaction of 2-methyl-indolyl methylenemalononitriles with α,β-unsaturated aldehydes via in situ generated indole-*ortho*-quinodimethane intermediates has been developed. This approach provides straightforward access to 2,9-dihydro-1*H*-carbazole-3-carbaldehydes, as well as its analogous dihydrodibenzofuran and dihydrodibenzothiophene in good yields and with high enantioselectivities.

1. Introduction

Polycyclic carbazole units, particularly tetrahydro- and dihydrocarbazoles are ubiquitously found in many natural products and biologically active compounds (Fig. 1).[1] Therefore, numerous efforts have been dedicated to developing efficient methods to construct these privileged motifs.[2–4]

To the best of our knowledge, the most rapid and effective method to build six-membered ring is the catalytic Diels–Alder cycloadditions.[5] Recently various substrates such as 2-vinylindoles, 3-vinylindoles[6] and *o*-quinodimethanes (*o*QDMs)[7] have been designed as the diene component to react with dienophiles for the preparation of tetrahydrocarbazoles and dihydrocarbazoles. To date, the *o*QDMs have been extensively employed to construct many complex polycyclic aromatic compounds, but fewer literature precedents have been reported using *o*QDMs in enantioselective Diels–Alder reactions probably because of its high activity, instability and lack of compatible systems.[8] The indole-2,3-quinodimethanes, a special type of *o*QDMs, have been well established as diene intermediates in the construction of tetrahydrocarbazoles through the Diels–Alder cycloadditions.[9] With the pioneering work on using indole-*o*QDMs in secondary amine-catalyzed asymmetric Diels–Alder reactions by the groups of Melchiorre and Chen,[10] the indole-2,3-quinodimethanes have successfully served as active intermediates to construct chiral tetrahydrocarbazoles (Scheme 1).

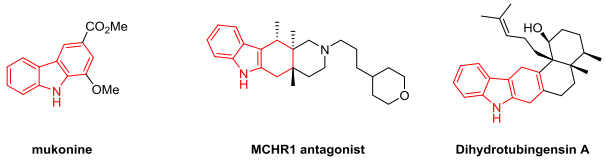

Fig. 1. Biologically active products containing carbazole skeletons.

In comparison to tetrahydrocarbazoles, the synthesis of dihydrocarbazoles, especially in enantioselective ways, have received less attention. In 2015, Zanardi et al. reported an elegant method to build linear and angular polycycles embedding a cyclohexadiene carbaldehyde frame via a [4+2] eliminative cycloaddition of extended monocyclic and polycyclic allylidene malononitriles with enals.[11] Inspired by this result and others, we envisaged that the 2-methyl-3-carbaldehyde malononitriles could be used as the precursor of *o*QDMs to react with enals to enantioselectively construct dihydrocarbazoles (Scheme 1).

2. Results and discussion

To test the hypothesis, we initially synthesized 2-((2-methyl-1-tosyl-1*H*-indol-3-yl)methylene)malononitrile **1a** and examined its

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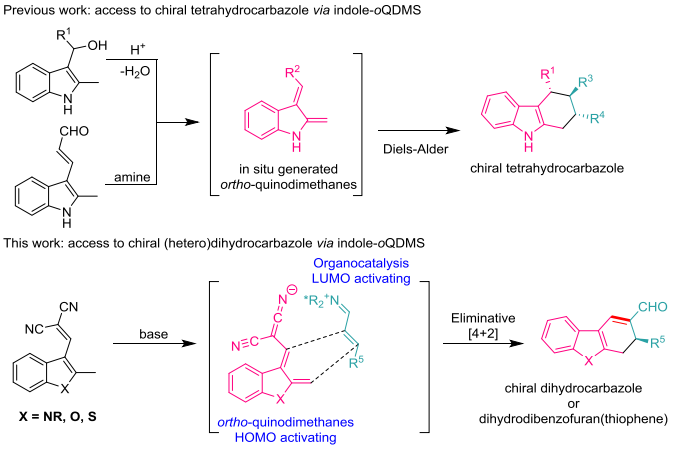
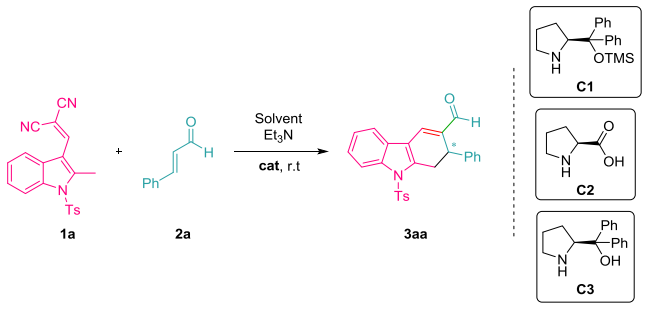


Scheme 1. Chiral secondary amine-catalyzed asymmetric [4+2] cycloaddition.

reactivity in [4+2] eliminative cycloaddition with commercially available *trans*-cinnamaldehyde **2a**. After screening of several chiral secondary amines (Table 1, entries 1–3), to our delight, the reaction occurred smoothly in the presence of TMS-protected prolinol catalyst **C1** at room temperature and cyclic product **3aa**, was obtained in 62% yield with 97% ee (Table 1, entry 1).

The effect of the solvent for this reaction was investigated subsequently. Interestingly, the results indicated that CH_3CN gave a moderate yield, excellent enantioselectivity and short reaction time (61% yield, 99% ee, 20 h), but ethyl acetate (EA) led to an excellent yield, poor enantioselectivity and prolonged reaction time (80% yield, 84% ee, 72 h) (Table 1, entries 4–11). This phenomenon led us to test the effect of mixed solvents. Next, we screened the volume ratio of the EA and CH_3CN, and the choice of 7:3 (EA/CH_3CN) afforded the best results giving **3aa** in 74% yield and 99% ee (Table 1, entry 14). After further screening studies (See the Supplementary data), the optimal reaction conditions were carried out in the presence of **1** and **2** (1:2 mol ratio), chiral secondary amine **C1** (20 mol %) and Et_3N (20 mol %) in EA/CH_3CN (7:3 volume ratio) at room temperature.

Table 1
Optimization of the reaction conditions



Entry	Catalyst	Solvent	*t*/h	Yield [%][a]	ee [%][b]
1	**C1**	CH_2Cl_2	24	62	97
2	**C2**	CH_2Cl_2	24	0	—
3	**C3**	CH_2Cl_2	24	<5	—
4	**C1**	THF	24	57	87
5	**C1**	CH_3CN	20	61	99
6	**C1**	Toluene	48	0	—
7	**C1**	CH_3OH	72	58	91
8	**C1**	CH_3CH_2OH	72	0	—
9	**C1**	DMF	24	60	89
10	**C1**	DMSO	24	42	88
11	**C1**	EA	72	80	84
12	**C1**	EA/CH_3CN=5:5	24	65	89
13	**C1**	EA/CH_3CN=6:4	24	70	98
14	**C1**	EA/CH_3CN=7:3	24	74	99
15	**C1**	EA/CH_3CN=8:2	24	73	98
16	**C1**	EA/CH_3CN=9:1	24	76	91

Conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), **cat** (20 mol %), Et_3N (20 mol %) and solvent (1.0 mL).
[a] Isolated yields.
[b] Determined by chiral HPLC analysis.

Under optimized reaction conditions, the scope of the methodology was investigated by examining various protecting groups on substituted indolyl-methylenemalononitriles with cinnamaldehyde firstly. The *N*-methyl protected **1e** and *N*-Bn protected **1f** showed no reactivity with cinnamaldehyde. On the other hand, if the electron-donating groups were replaced with electron-withdrawing groups such as Boc, Ac, Ns, the desired products were all obtained with moderate yields and excellent enantioselectivities (61–65% yields, >99% ee). These results suggested that only in the presence of electron-withdrawing protecting groups the reaction could proceed smoothly. Then different groups substituted on the indolemalononitrile and benzofuranmalononitrile **1i**, benzothiophenemalononitrile **1j** were also tolerated and all the products were obtained in good yields with excellent enantioselectivities (55–60% yields, 98–>99% ee) (Table 2).

Next we investigated the scope of enals. Either electron-withdrawing or -donating substitutions on α,β-unsaturated aldehydes including the *o*-, *m*-, and *p*-substituted aromatic aldehydes, heteroaromatic aldehydes such as furanyl and pyridyl derivatives were examined. All had subtle impact on reactions and diverse dihydrocarbazole skeletons were constructed in good yields and excellent enantioselectivities (51–63% yields, 94–>99% ee). Moreover, it is notable that aliphatic substituted α,β-unsaturated aldehydes were also subjected to the reaction conditions, to our surprise, the desired products **3ai**, **3ak** were still obtained with outstanding enantioselectivities although the yields fell dramatically in comparison to previous results (35–42% yields, 97–98% ee). The reason is possibly that aliphatic α,β-unsaturated aldehydes in this system exist as a mixture of enamine and imine, which can react with themselves leading to generation of some by-products (Table 2).

To further evaluate the synthetic utility of this process, the asymmetric [4+2] cycloaddition between 2-((2-methyl-1-tosyl-1*H*-indol-3-yl)methylene)malononitrile **1a** with cinnamaldehyde **2a** was carried out on a gram scale, and **3aa** was obtained in 67% yield with >99% ee (Table 1). In addition, the absolute configuration of **3aa** was determined as the (*R*)-configuration by X-ray crystallographic analysis as shown in Table 2.

Finally, the [4+2] eliminative cycloaddition product was submitted to further transformations. Chiral product **3aa** could be easily reduced to give unsaturated carbinol **4** in the presence of $NaBH_4$ without any loss of enantioselectivity. Compound **3aa** was also treated with glycine Schiff base to give [3+2] cycloaddition product tetrahydrocarbazole **5**. Such motif and its derivatives could be used as analgesic agents (Scheme 2).[12]

A plausible stepwise mechanism is proposed to rationalize the enantioselectivity of this [4+2] cycloaddition (Scheme 2). First the indole *o*-quinodimethane **I** is formed from **1a** in the presence of Et_3N and iminium **II** is formed through the reaction between **2a** and **C1**. Then **I** and **II** undergo a bis-vinylogous Michael addition to give intermediate **III**. Further intramolecular Michael occurs to give **IV**, followed by the hydrolysis to release **C1** and retro-Michael to afford final product **3aa** (Scheme 3).

3. Conclusion

In conclusion, we have developed an organocatalytic asymmetric [4+2] eliminative cycloaddition of extensive 2-methyl-3-carbaldehyde malononitriles with enals via in situ generated *ortho*-quinodimethanes as the key intermediates. This synthetic