Exploiting the Distal Reactivity of Indolyl Methylenemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles

Exploiting the Distal Reactivity of Indolyl-methylenemalononitriles: an Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles

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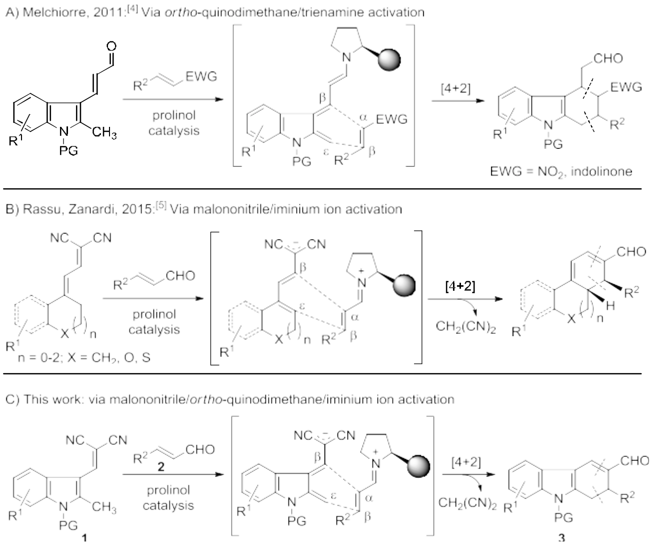
Abstract: An unprecedented modality for in situ generation of indole-*ortho*-quinodimethanes from 2-methylindole-based methylenemalononitriles by amine-mediated remote C(sp^3)-H deprotonation was developed. These intermediates were efficiently trapped by diverse enals to provide a rapid entry to 2,9-dihydro-1*H*-carbazole-3-carboxyaldehyde structures via formal asymmetric [4+2] eliminative cycloaddition governed by α,α-diphenylprolinol trimethylsilyl ether catalyst.

Polycyclic indole architectures including carbazole and hydrocarbazole skeletons represent privileged structural motifs found in a number of natural alkaloids many of which displaying interesting activities against a diverse set of biological targets.[1] Accordingly, the search for efficient methods for the assembly of these structures has drawn a great deal of attention by the synthetic organic chemistry community.[2,3]

In 2011, Melchiorre[4] devised a reliable synthetic platform to access tetrahydrocarbazoles by adopting a [4+2] strategy which relies on in situ generation of active indole *ortho*-quinodimethane intermediates in reactions with suitable dienophiles (e.g. nitrostyrene or indolinone derivatives) under trienamine catalysis (Scheme 1, section A). More recently, our research group[5] discovered a direct [4+2] eliminative cycloaddition modality to access carbocycles embedding fused cyclohexadiene frames focused on the use of remotely enolizable methylenemalononitriles as diene precursors in reactions with enals under iminium ion-driven organocatalysis (Scheme 1, section B).



Scheme 1. Diarylprolinol silyl ether-catalyzed asymmetric [4+2] cycloaddition strategies.

Capitalizing on these inspiring studies, we now wondered whether merging the distinctive issue of the malononitrile activation strategy,[5,6] with the indole *ortho*-quinodimethane modality[4,7] supported by the chiral iminium ion LUMO-lowering concept,[8] 2,9-dihydro-1*H*-carbazole structures could be accessed by reacting 2-methylindole-based methylenemalononitriles with enals, as shown in section C of Scheme 1. In this paper we describe the successful realization of this idea, focusing on the organocatalytic, asymmetric [4+2] eliminative cycloaddition between 2-methylindolyl methylenemalononitriles **1** and enals **2** mediated by the popular Hayashi-Jørgensen α,α-diphenylprolinol trimethylsilyl ether catalyst.[8,9] This chemistry offers a streamlined access to hitherto elusive 2,9-dihydro-1*H*-carbazole 3-carboxaldehydes **3** with excellent levels of enantioinduction.

At the outset, the designed *N*-Boc-protected 2-methylindolyl-methylenemalononitrile **1a** was easily prepared from commercially available 2-methylindole-3-carboxaldehyde via *N*-protection followed by high-yielding Knoevenagel condensation with malononitrile (see Supporting Information for details). To test the feasibility of the transformation described in Scheme 1C, the reaction between **1a** and cinnamaldehyde **2a** was first

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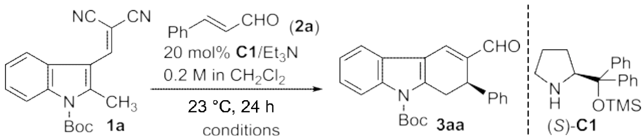
carried out in CH_2Cl_2 at room temperature in the presence of 20 mol% (*S*)-configured TMS-prolinol (*S*)-**C1** and 20 mol% Et_3N, using the previously established catalytic conditions.[5] We were pleased to find that, under these conditions, **1a** underwent the desired eliminative cycloaddition with enal **2a** giving dihydrocarbazole **3aa** with exceptional enantioselectivity (99% *ee*), albeit in only moderate yields (Table 1, entry 1). With this promising result in hand, we proceeded to optimize the reaction aiming at increasing the efficiency, while maintaining the almost perfect enantiocontrol of the lead conditions. Variation of solvents indicated that, except for toluene, other solvents such as THF, acetonitrile, and ethanol furnished very low yield, if any, of the desired product **3aa** (entries 2-5). No substantial improvement on yield was observed under higher or lower reaction concentration (entries 6 and 7), while the yield dropped to *ca* 20% when reducing the catalyst loading to 10 mol% (entry 8).

Table 1. Asymmetric eliminative [4+2] cycloaddition catalyzed by α,α-diphenylprolinol trimethylsilyl ether (*S*)-**C1**: effect of the reaction parameters.[a]

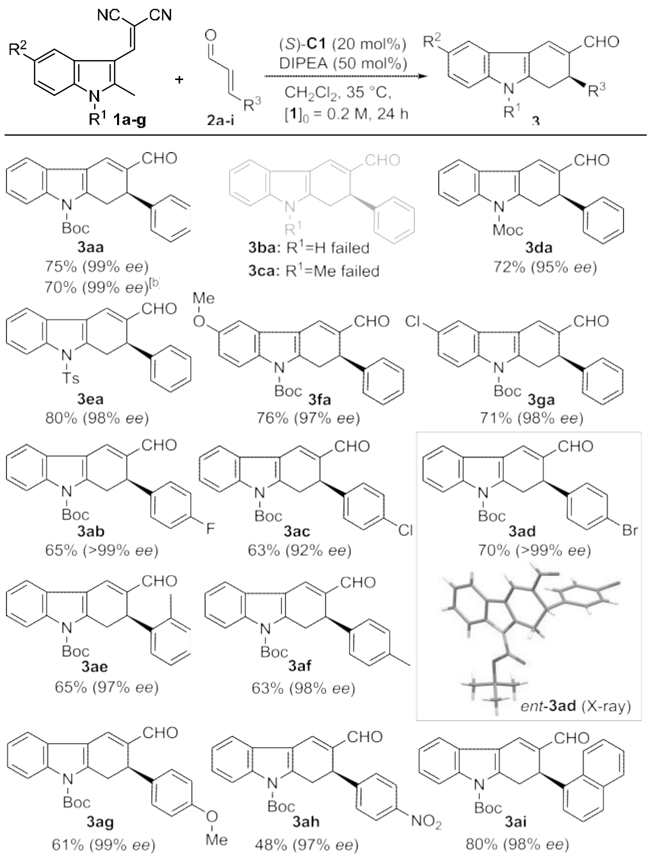


Entry	Variation from the conditions	Yield[b]	*ee*[c]
1	none	40(31)	99
2	toluene instead of CH_2Cl_2	39(29)	99
3	THF instead of CH_2Cl_2	<5	–
4	MeCN instead of CH_2Cl_2	<5	–
5	EtOH instead of CH_2Cl_2	0	–
6	0.05 M instead of 0.2 M	30(22)	99
7	0.4 M instead of 0.2 M	46(33)	99
8	10 mol% (*S*)-**C1**	29(20)	98
9	K_2CO_3 instead of Et_3N	0	–
10	Cs_2CO_3 instead of Et_3N	0	–
11	DIPEA instead of Et_3N	81(70)	99
12	DIPEA 50 mol% at 35 °C	88(75)	99
13	no catalyst	0	–
14	no base	0	–
15	*N*-Boc-2-methylindole-3-carboxaldehyde instead of **1a**	0	–
16	(*R*)-**C1** instead of (*S*)-**C1**	82(74)	99[d]

[a] Reactions performed on a 0.3-0.4 mmol scale (**1a**), using **2a** (1.2 equiv), in air. [b] Determined by ^1H NMR analysis of the crude reaction mixture. Values in parentheses represent isolated yields after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The opposite enantiomer of **3aa** formed. DIPEA= *N,N*-diisopropylethylamine.

A screening of base co-catalysts revealed that inorganic salts such as K_2CO_3 or Cs_2CO_3 are not beneficial for this annulative reaction (entries 9 and 10), whereas use of DIPEA instead of Et_3N gratifyingly improved the productivity of the process[10] consigning **3aa** in 81-88% yields (70-75% isolated), again with a superb level of enantiocontrol (99% *ee*, entries 11 and 12). Finally, it may mentioned that under the optimized conditions of entry 12, control experiments revealed how the exclusion of any of the reaction promoters, i.e., prolinol catalyst or amine co-catalyst, entirely suppressed the process (entries 13 and 14), and how the use of the parent *N*-Boc-protected 2-methylindole-3-carboxaldehyde in lieu of the malononitrile derivative **1a** was inapplicable in this cyclization process (entry 15). As such, optimum conditions were established as in entry 12 of Table 1 namely, use of 1.0 equiv **1a**, 1.2 equiv **2a**, 20 mol% (*S*)-**C1**, and 50 mol% DIPEA in 0.2 M CH_2Cl_2 at 35 °C.

Table 2. Enantioselective iminium ion-mediated [4+2] eliminative cycloaddition: indolylmalononitrile and enal scope.[a]



[a] All reactions were performed using **1** (0.39 mmol), **2** (0.47 mmol), prolinol (*S*)-**C1** (0.078 mmol), DIPEA (0.19 mmol) in 1.95 mL CH_2Cl_2 in air at 35 °C over 24 h. All the reactions were also performed using (*R*)-**C1** as the catalyst to afford the opposite enantiomers of **3**. Yields of the isolated products **3** are given. Enantiomeric excess (*ee*) values were determined via HPLC analysis on commercially available chiral stationary phase columns. [b] Performed on a 8× scale.

With these conditions in hand, we next examined the generality, scope and limitations of this [4+2] eliminative cycloaddition utilizing diversely substituted methylenemalononitriles **1** and enals **2** (Table 2). Gratifyingly, we found that the core structure of the formed formyl dihydrocarbazoles **3** could be readily decorated at different positions and the reactions proceeded smoothly with excellent levels of enantioinduction for a broad range of substrates. First, we elected to examine reactions of substituted indole substrates **1a-g**. In contrast to the excellent results with *N*-Boc protected malononitrile **1a** leading to **3aa**, unprotected indole **1b** proved totally unreactive, with no **3ba** detected after 24 h, possibly due to unproductive NH-induced tautomerization within the transient *o*-quinodimethane structure, as suggested by Melchiorre et al.[4] Also, a substituent with a different electronic nature at the *N*-position of the indole substrate severely altered the reactivity of the system, and *N*-methyl indole-derived malononitrile **1c**, in which an electron-withdrawing group was replaced by an electron-donating methyl, does not react with cinnamaldehyde, suggesting that the presence of a withdrawing group at indole nitrogen is needed for the reaction to occur.

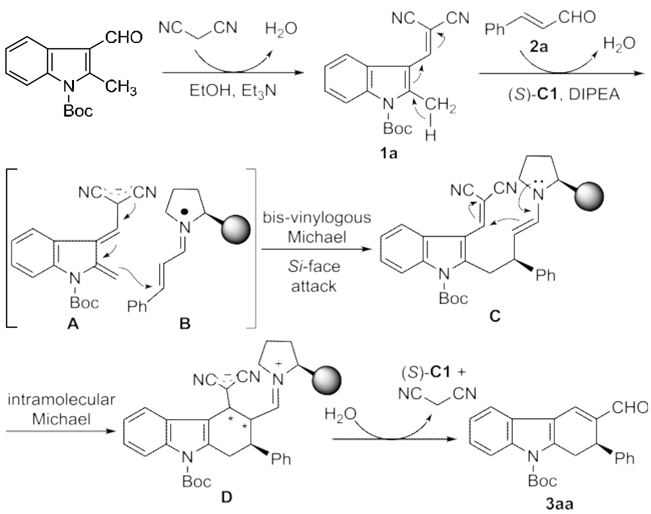
As for the *N*-Boc representative **1a** providing **3aa**, *N*-Moc- and *N*-Ts-substituted substrates **1d** and **1e** efficiently reacted with cinnamaldehyde providing dihydrocarbazoles **3da** and **3ea**, respectively, with high levels of enantioinduction. Different substituents on the indole core of **1** were also tolerated, since electronic modification of the aromatic ring could be accomplished without affecting the reactivity of the system. Thus, substitution at the indole C-5 position with methoxy- or chloro-groups provided useful pronucleophilic substrates **1f** and **1g** for the highly enantioselective coupling with cinnamaldehyde, giving **3fa** and **3ga**, respectively, with very good enantioselectivity.

Concerning the scope of the olefinic aldehyde derivatives **2**, varied substituents at the aromatic moiety were tolerated, regardless of their position and electronic properties. The *para*-substituted fluoro, chloro, and bromo aldehydes **2b-d** were all combined with **1a** without incident, providing the halo-substituted dihydrocarbazoles **3ab**, **3ac**, and **3ad**, respectively, in fairly good yields and with 92 - >99% *ee*s. The functional group tolerance of this reaction was further demonstrated by the use of *ortho*- and *para*-methyl-substituted cinnamaldehydes **2e** and **2f** to give highly enantioenriched carbazole products in good yields (**3ae** and **3af**). The reaction was also compatible with methoxy- and nitro-derivatives **2g** and **2h**, rendering the expected products **3ag** and **3ah**, respectively, again with excellent enantioselectivity albeit with lower efficiency in the case of **3ah**. In addition, the indole substrate **1a** was partnered with naphthyl aldehyde **2i** to give the carbazole product **3ai** in very good yield and enantioselectivity. Regrettably, aliphatic enals showed only very poor reactivity with this protocol; we made efforts to perform such reactions by elongating the reaction time or elevating the catalyst loading, but some unidentified by-products were only observed, which were deduced to be decomposed from the indole substrates.

To showcase the practicality of the process, we performed a gram-scale reaction using **1a** and enal **2a**. Pleasingly, the conditions did not impact the outcome of the reaction and **3aa** was obtained with comparable efficiency and enantioselectivity.

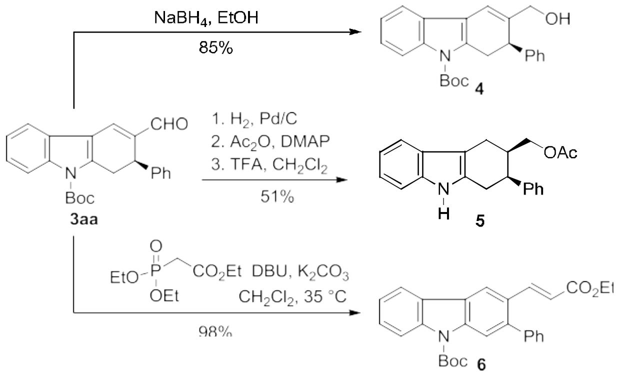
The (2*S*) absolute configuration of *ent*-**3ad** derived from *p*-bromocinnamaldehyde **2d** using catalyst (*R*)-**C1** was unambiguously established by X-ray crystallographic analysis[11] and, as a consequence, the opposite 2*R*-configuration was assigned to all compounds **3** listed in Table 2.

To account for the stereochemical outcome of the reaction, we propose a transition state where the *Si*-face of the iminium ion derived from covalent association of enal **2** to the prolinol catalyst (*S*)-**C1** is engaged with the nucleophilic methylene carbon of the indole *o*-quinodimethane intermediate as shown in Scheme 2. In particular, it is reasonable to assume that initial formation of the indole *o*-quinodimethane **A** and iminium ion **B** from respectively malononitrile **1a** and aldehyde **2a** takes place under the assistance of the binary prolinol/DIPEA catalytic system. The chiral environment in the resulting donor/acceptor complex **A-B** makes the subsequent bis-vinylogous Michael attack[12] to proceed stereoselectively to form the chiral enamine **C**. Next, this intermediate undergoes an intramolecular Michael ring closure to substituted tetrahydrocarbazole **D** which, upon hydrolysis and release of both the catalyst and the malononitrile handle[5,13], finally furnishes the (*R*)-configured dihydrocarbazole **3aa**.



Scheme 2. Possible mechanism of the formal catalytic asymmetric [4+2] cycloaddition of methylenemalononitrile **1a** with enal **2a** assisted by catalyst (*S*)-**C1**.

One feature of this vinylogous cycloaddition/elimination is that it provides direct access to chiral substituted 2,9-dihydro-1*H*-carbazoles **3** while installing the α,β-unsaturated aldehyde system. This moiety could be exploited to vary the structure of the molecule by simple transformations.



Scheme 3. Elaboration of dihydrocarbazole **3aa**.

To illustrate this synthetic potential, **3aa** was first subjected to selective $NaBH_4$ reduction of the aldehyde group, giving rise to unsaturated carbinol **4** in very good yield. Next, hydrogenation using 10% Pd on carbon in methanol ensured reduction of both the α,β-double bond and the aldehyde carbonyl of **3aa**, rendering enantiopure tetrahydrocarbazole **5**, which was isolated in 51% overall yield after acetylation and *N*-deprotection.[14] Finally, a HWE olefination with triethyl phosphonoacetate was performed, and this resulted in almost quantitative formation of *E*-configured carbazole **6**, with complete aromatization of the tricyclic skeleton.

In summary, a mild and highly enantioselective organocatalytic [4+2] eliminative cycloaddition of 2-methylindolyl methylenemalononitriles with enals has been developed as the first direct and asymmetric entry to hitherto elusive 2,9-dihydro-1*H*-carbazoles. Good levels of reaction efficiency and excellent enantioselectivity were achieved across a diverse range of indole and enal substrates using the chiral α,α-diphenylprolinol TMS-ether catalyst in combination with a tertiary amine (DIPEA). The ability of the malononitrile handle to enable the remote enolization of the 2-methylindole component to form an active indole *ortho*-quinodimethane intermediate is emphasized, and further studies to apply this nucleophilic activation mode in the vinylogous reactivity scenario is ongoing in our laboratories and will be disclosed in due course.

Keywords: • asymmetric synthesis • cycloaddition • heterocycles • organocatalysis • vinylogy

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