Organic LETTERS

Letter

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Diastereoselective Synthesis of Functionalized Tetrahydrocarbazoles via a Domino-Ring Opening−Cyclization of Donor−Acceptor Cyclopropanes with Substituted 2-Vinylindoles

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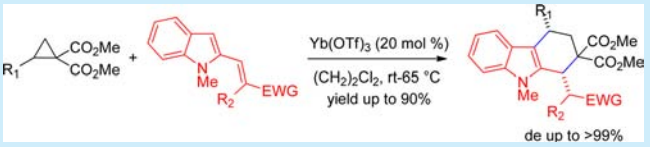
Supporting Information

ABSTRACT: A new domino synthetic approach for the synthesis of highly functionalized tetrahydrocarbazoles via DROC of various functionalized DA-cyclopropanes with 2-indolylnitroethylene and indole-substituted alkylidene malonate is described. The tetrahydrocarbazoles were obtained with excellent diastereoselectivity having *cis* alignment of the 1,4-appendages across the six-membered carbocyclic ring.



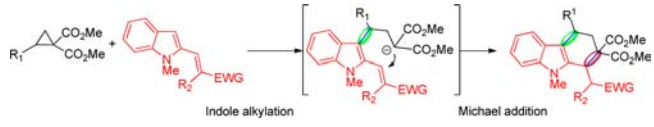
Tetrahydrocarbazole[1] is one of the most important classes of indole-based molecular frameworks. These heterocycles contain a saturated six-membered carbacycle fused to indole at the C-2 and C-3 positions. They are integral parts of several biologically active natural products[2] and other pharmaceutically relevant synthetic compounds.[3]

Over the years, several interesting synthetic routes have been devised for the synthesis of substituted tetrahydrocarbazoles and their analogues.[4,5] Some of the most important strategies include intramolecular allylic arylation,[4a,b] Friedel−Crafts-type cyclization reactions,[4c,d] and [4 + 2] cycloaddition of indole derivative bearing an unsaturated functionality at the C-2 or C-3 position with various kinds of dienophiles.[5] Kerr and co-workers reported an elegant [3 + 3] annulative strategy based upon the reaction of donor−acceptor (DA)-cyclopropanes with 2-alkynylindoles for the synthesis of substituted tetrahydrocarbazoles.[6] Development of a highly stereoselective route to substituted tetrahydrocarbazoles is still a challenging job and certainly would add value to the overall efforts toward tetrahydrocarbazole synthesis.

DA-cyclopropanes are versatile intermediates in synthetic organic chemistry[7,8] and have been utilized for the synthesis of a number of organic compounds including several bioactive natural products and drugs. Our recent ongoing research activity and success on DROC of DA-cyclopropanes for the construction of substituted carbocyclic rings[9] prompted us to investigate the synthesis of diastereomerically pure substituted tetrahydrocarbazoles.

We anticipated that the ring-opening of DA-cyclopropanes with indoles bearing an activated olefin would generate the corresponding substituted malonate anion which would further react with the tethered olefinic moiety via an intramolecular Michael reaction in a domino fashion leading to the diastereoselective formation of tetrahydrocarbazole scaffolds (Scheme 1). Herein, we report a new protocol for the synthesis of highly substituted tetrahydrocarbazoles via DROC of DA cyclopropanes with substituted 2-vinylindoles.

Scheme 1. Synthesis of Tetrahydrocarbazoles via DROC of 2-Activated Olefin-Tethered Indoles with DA-cyclopropanes



For this purpose, we have prepared indole substrates with activated olefinic moieties, **2a** and **2b**, following literature reports.[10] At the outset of our study, we performed the reaction of DA-cyclopropane **1a** with 2-indolylnitroethylene (**2a**) in the presence of a catalytic amount of $Yb(OTf)_3$ (20 mol %) as the Lewis acid (LA) catalyst in THF, and the product tetrahydrocarbazole **3a** was obtained in only 14% yield (Table 1, entry 1). In order to optimize the reaction conditions, we screened different solvents and Lewis catalysts. The optimal result came with 1.0 equiv of **1a** and **2a** in 1,2-dichloroethane in the presence of 20% LA, which afforded the tetrahydrocarbazole **3a** in high yield (69%) as a single diastereomer (Table 1, entry 2).

The structure of **3a** was determined by spectroscopic techniques and the relative stereochemistry was confirmed by X-ray crystallographic analysis where aryl and nitro methyl groups were found to possess *cis* appendages (Figure 1).

To generalize this approach, a number of DA-cyclopropanes with a variety of aryl substituents were studied for the DROC with 2-indolylnitroethylene **2a**, and the results are shown in Table 2. In the case of the reaction of **2a** with 2-phenylcyclopropanedicarboxylate **1b**, the corresponding tetrahydrocarbazole **3b** was obtained as a single diastereomer in comparable yield. 4-Methylphenylcyclopropanedicarboxylate **1c** behaved similar to **2a** and generated tetrahydrocarbazole **3c**. Fluorinated tetrahydrocarbazole **3d** was also synthesized in high yield when **1d** was reacted with **2a** (Table 2, entry 4).

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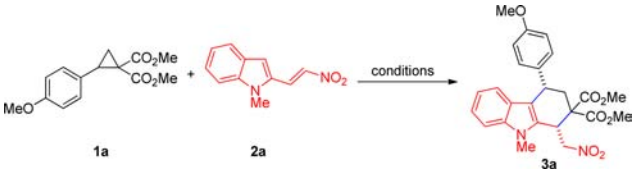
Table 1. Optimization Study



entry	conditions[a]	time	yield[b] (%)
1	$Yb(OTf)_3$ (20 mol %), THF, rt to 60 °C	12 h	14
2	**$Yb(OTf)_3$ (20 mol %), DCE, rt to 65 °C**	**30 min**	**69**
3	$Yb(OTf)_3$ (1.0 equiv), DCE, rt to 65 °C	20 min	69
4	$Yb(OTf)_3$ (20 mol %), DCE, rt	2 days	67
5	$Yb(OTf)_3$ (20 mol %), DCM, rt	1 day	58
6	$Sc(OTf)_3$ (20 mol %), DCE, rt to 65 °C	45 min	62
7	$Zn(OTf)_2$ (20 mol %), DCE, rt to 65 °C	4 h	55
8	$Cu(OTf)_2$ (20 mol %), DCE, rt to 65 °C	5 min	10
9	$AlCl_3$ (20 mol %), DCE, rt to 65 °C	20 min	25
10	$FeCl_3$ (20 mol %), DCE, rt to 65 °C	3 h	30
11	$Yb(OTf)_3$ (20 mol %), toluene, rt to 65 °C	50 min	44

[a]In all cases, 1.0 equiv of **1a** was reacted with 1.0 equiv of **2a**. [b]The product was obtained as a single diastereomer.

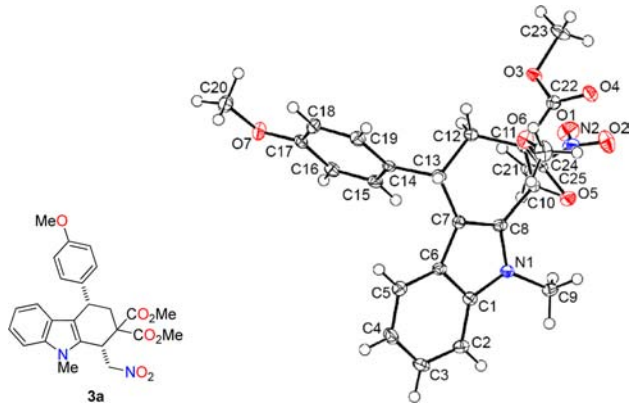


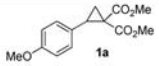
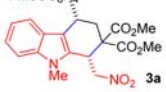
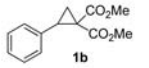
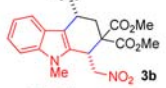
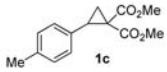
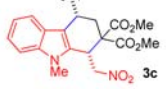
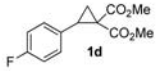
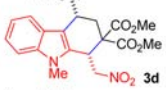
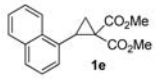
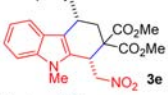
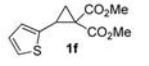
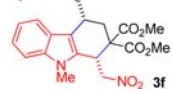
Figure 1. X-ray crystal structure of **3a** with 50% thermal ellipsoids.

Similarly, naphthyl and thiophene-yl tetrahydrocarbazoles (**3e** and **3f**, respectively) were generated in high yields via DROC of the corresponding DA-cyclopropanes **1e** and **1f**, respectively, with **2a** (Table 2, entries 5 and 6, respectively).

Next, to extend the scope of our methodology, reactions of several functionalized DA-cyclopropanes **1a**−**c**,**f**−**l** were carried out with indole substituted alkylidene malonate **2b** under the same optimized reaction conditions, and the results are summarized in Table 3.

When the reaction of **1a** was performed with **2b**, the product tetrahydrocarbazole tetraester **3g** was obtained in excellent yield as a single diastereomer (Table 3, entry 1). Similarly, DA-cyclopropanes **1b** and **1c** reacted with **2b** to provide the corresponding products **3h** and **3i**, respectively. Heteroaryl tetrahydrocarbazole tetraesters **3j** and **3k** could also be generated when thiophene-2-yl and 2-furyl cyclopropane dicarboxylates **1f** and **1g** were reacted with **2b**. DA-cyclopropanes having electron-donating substituents on the aromatic rings also afforded the corresponding tetrahydrocarbazoles (**3l**,**m**) in excellent yields (Table 3, entries 6 and 7, respectively). Halo-substituted DA-cyclopropanes **1j**,**k** served as excellent substrates for this reaction and produced the corresponding products **3n**,**o** in good yields. The Michael acceptor **2b** gave the corresponding tetraester products **3g**−**p** in excellent yields.

Table 2. Reaction of DA-cyclopropanes with 2-Indolylnitroethylene 2a[a,b]

entry	1	3	time (min)	yield (%)
1			30	69
2			40	69
3			35	65
4			45	66
5			90	64
6			30	65

[a]Yields of isolated products. [b]The compounds were obtained as single diastereomers.

The relative stereochemistry of **3p** was also found to be *cis* as determined by single-crystal X-ray diffraction data (Figure 2).

The scope of our strategy was further extended employing styrylcyclopropanedicarboxylate **1m** as the DA-cyclopropane. When **1m** was reacted with **2a** and **2b**, the corresponding tetrahydrocarbazoles **3q** and **3r**, respectively, were obtained in high yields (Scheme 2, eqs 1 and 2). Although the carbazole **3q** was obtained as a single diastereomer, **3r** was produced as a mixture of diastereomers (dr 4:1).

In the case of the reaction of **1m** with **2a**, a trace amount of the uncyclized product **4** was also isolated. This clearly indicated that the two steps, ring opening and intramolecular Michael addition, take place sequentially in a domino fashion.

Interestingly, when 4-methoxystyrylcyclopropanedicarboxylate **1m** was reacted with **2b**, cyclopentene dicarboxylate **5** was obtained in 90% yield as the sole product; this was generated via intramolecular rearrangement of **1m** upon interaction with the LA catalyst (Scheme 3). It is worth mentioning that construction of substituted cyclopentenes has always been an important goal in organic synthesis.[11]

The mechanism of the reaction is depicted in Scheme 4. The Lewis acid activates the cyclopropane ring generating a complex **D**, which upon attack of the indole nucleophile generates intermediate **E**. The ring-opened intermediate **E** undergoes attack of its malonate anion moiety to the tethered activated olefin in Michael fashion to produce the tetrahydrocarbazoles. The intermediate **E** can adopt two different cyclohexene like half-chair conformations **F** and **G**. In the conformer **F**, the Michael acceptor adopts a pseudoaxial position and faces a gauche interaction with one of the ester moieties, whereas the Michael acceptor adopts a pseudoequatorial position in the conformer **G** and suffers from a severe gauche interaction with both the ester groups. The more stable conformer **F** is preferred over **G**

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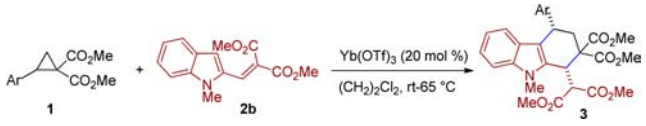
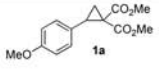
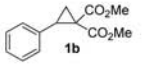
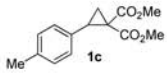
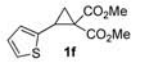
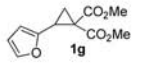
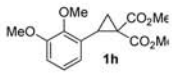
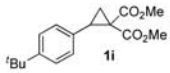
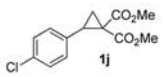
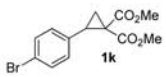
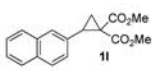
Table 3. Reaction of DA-cyclopropanes with Indole-Substituted Alkylidene Malonate 2b[a,b]



entry	1	3	time (min)	yield (%)
1	 1a	 4-MeOC$_6$H$_4$ 3g	40	88
2	 1b	 C$_6$H$_5$ 3h	60	85
3	 1c	 4-MeC$_6$H$_4$ 3i	45	86
4	 1f	 thiophene-2-yl 3j	50	75
5	 1g	 2-furyl 3k	60	87[c]
6	 1h	 2,3-(MeO)$_2$C$_6$H$_3$ 3l	40	80
7	 1i	 4-^{t}BuC$_6$H$_4$ 3m	45	83
8	 1j	 4-ClC$_6$H$_4$ 3n	70	78
9	 1k	 4-BrC$_6$H$_4$ 3o	75	90
10	 1l	 2-naphthyl 3p	90	85

[a]Yields of isolated products. [b]Unless otherwise noted, all the compounds were obtained as single diastereomers. [c]Obtained as a 7:2 diastereomeric mixture.

providing tetrahydrocarbazoles with a *cis* orientation of the 1,4-substituents on the cyclohexyl ring.

In conclusion, we have developed an efficient protocol for the synthesis of highly functionalized tetrahydrocarbazoles with

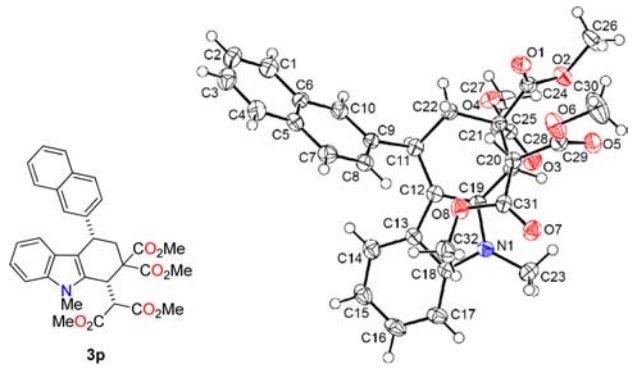
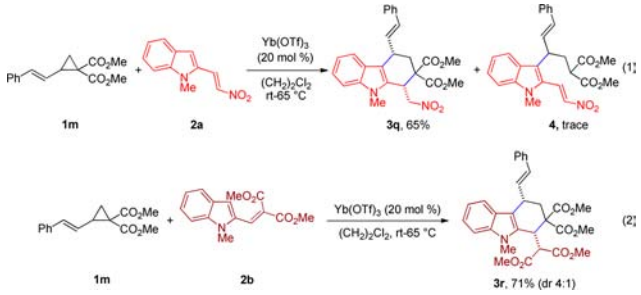
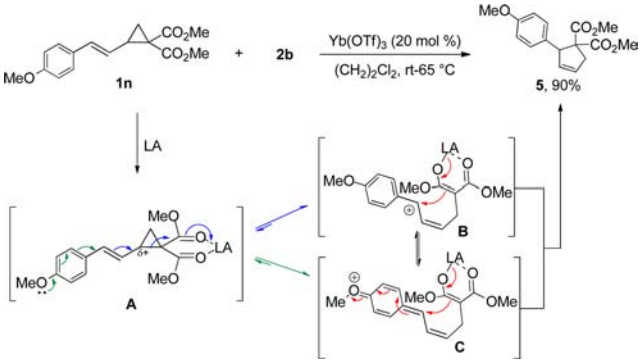


Figure 2. X-ray crystal structure of **3p** with 50% thermal ellipsoids.

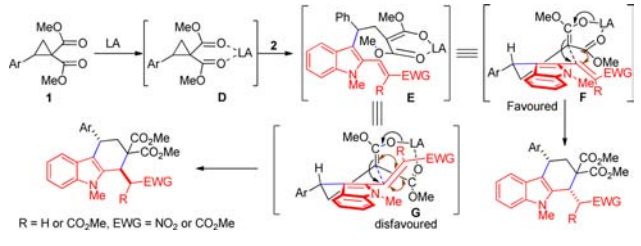
Scheme 2. Synthesis of Styryl-Substituted Tetrahydrocarbazoles 3q and 3r



Scheme 3. Synthesis of Cyclopentene Dicarboxylate via Intramolecular Rearrangement of 4-Methoxystyrylcyclopropanedicarboxylate



Scheme 4. Mechanism of the Reaction and Origin of Diastereoselectivity



excellent diastereoselectivity (de up to 99%) via domino ring-opening cyclization (DROC) of DA-cyclopropanes with 2-indolylnitroethylene **2a** and indole-substituted alkylidene malonate **2b**. The reaction proceeds via a half chairlike transition state where the activated olefin adopts a more stable pseudoaxial

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transition state for generation of a six-membered carbocyclic ring with 1,4-*cis* appendages.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data and X-ray crystallographic analysis of **3a** and **3p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. R. N. Mukherjee on the occasion of his 61st birthday.

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