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HNTf$_2$-Catalyzed Formal [3 + 2] Cycloaddition of Vinyldiazoacetates to Indole-Substituted Diazo Compounds and Their Conversion to Carbazoles

Ming Bao, Diana Victoria Navarrete Carriola, Hadi Arman, and Michael P. Doyle*

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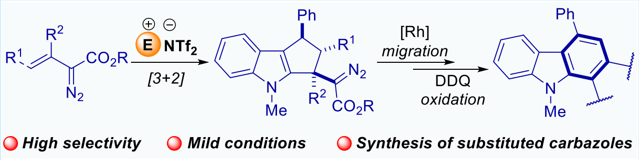
ABSTRACT: Triflimide catalysis of the [3 + 2]-cycloaddition of 3-indolymethanols with vinyldiazoacetates provides general access to β-tetrahydrocyclopenta[*b*]indol-substituted α-diazoesters. Initiated by addition of the *in situ* generated vinylogous iminium electrophile from 3-indolymethanol to the vinylogous position of the vinyldiazo compound and completed by intramolecular cyclization from the vinyldiazonium ion intermediate, this transformation occurs in good yields and excellent diastereoselectivity with a broad substrate scope under mild conditions. The resulting α-diazoesters undergo Rh$_2$(OAc)$_4$-catalyzed substrate-dependent 1,2-migration to form multisubstituted carbazoles in high yields.



Carbazole and its derivatives are important nitrogen-containing heterocyclic compounds that play significant roles in photorefractive materials, organic dyes, and bioactive molecules.[1] Over past decades, a variety of approaches for the construction of carbazole skeletons have been reported.[2] Among these methods, the conversion of indole and its derivatives to carbazoles is a particularly attractive and efficient strategy.[3] For example, carbazoles are constructed via intermolecular [2 + 4]- or [2 + 2 + 2]-cyclizations from indole and suitable reagents, mainly through transition metal catalysis, in which indole serves as a C2 synthon (Scheme 1a, path a).[4] Catalytic intermolecular [4 + 2]-cyclization of indole derivatives with olefins and alkynes as C2 reagents also provides a convenient method for the practical construction of substituted carbazoles (Scheme 1a, path b).[5] Indole derivatives can also act as C3 synthons to produce carbazole compounds through Lewis acid-catalyzed intermolecular [3 + 3]-cyclization with donor−acceptor cyclopropanes (Scheme 1a, path c).[6] In addition, intramolecular electrophilic cyclization has also emerged as a powerful tool for the synthesis of substituted carbazoles through the activation of alkynes using a transition metal catalyst[7] or iodocyclization[8] (Scheme 1a, path c). Despite these advances, which each have limitations,[2] the development of novel and practical synthetic methods to construct carbazoles with broad functional group compatibility is still needed to meet the demand for structural diversity in chemistry and biology.[1,2]

Vinyldiazo compounds are easily accessible versatile reagents that have provided an attractive platform for a variety of metal carbene transformations.[9] Their dipolar nature makes them susceptible to addition by different electrophilic reagents, affording vinyldiazonium ion intermediates, that undergo substitution or migration reactions.[10] Very recently, we reported HNTf$_2$-catalyzed formal [3 + 2]-cycloaddition of vinyldiazo compounds with quinone ketals via vinyldiazonium ion intermediates for the synthesis of β-benzohydrofuran-substituted α-diazo esters that formed benzofurans through Sc(OTf)$_3$-catalyzed C → C migration (Scheme 1b).[11] Inspired by these advances, we envisioned that a formal [3 + 2]-cycloaddition process of vinyldiazoacetates with 3-indolymethanol might be facilitated by HNTf$_2$ catalysis to synthesize structurally complex indole-substituted diazo compounds and, from them, carbazoles. Herein, we report that highly selective [3 + 2]-cycloaddition of vinyldiazo acetates with 3-indolymethanol provides a convenient methodology for the synthesis of β-tetrahydrocyclopenta[*b*]indol-substituted α-diazo esters that offer direct synthetic access to substituted carbazoles via subsequent metal carbene-based migration reactions. This method complements previous constructions of carbazoles from indoles but has greater structural versatility (Scheme 1c, path e).

When treated with a catalytic amount of triflimide at room temperature, quinone ketals undergo formal [3 + 2]-cycloaddition across the C═C of β-aryl-, β-alkyl-, and β-oximido-vinyldiazoacetates to form benzofuranyl-diazoacetates in moderate to good yields with high diastereocontrol (Scheme 1b).[11] Inspired by these results, 3-indolymethanol **2a** was

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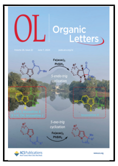

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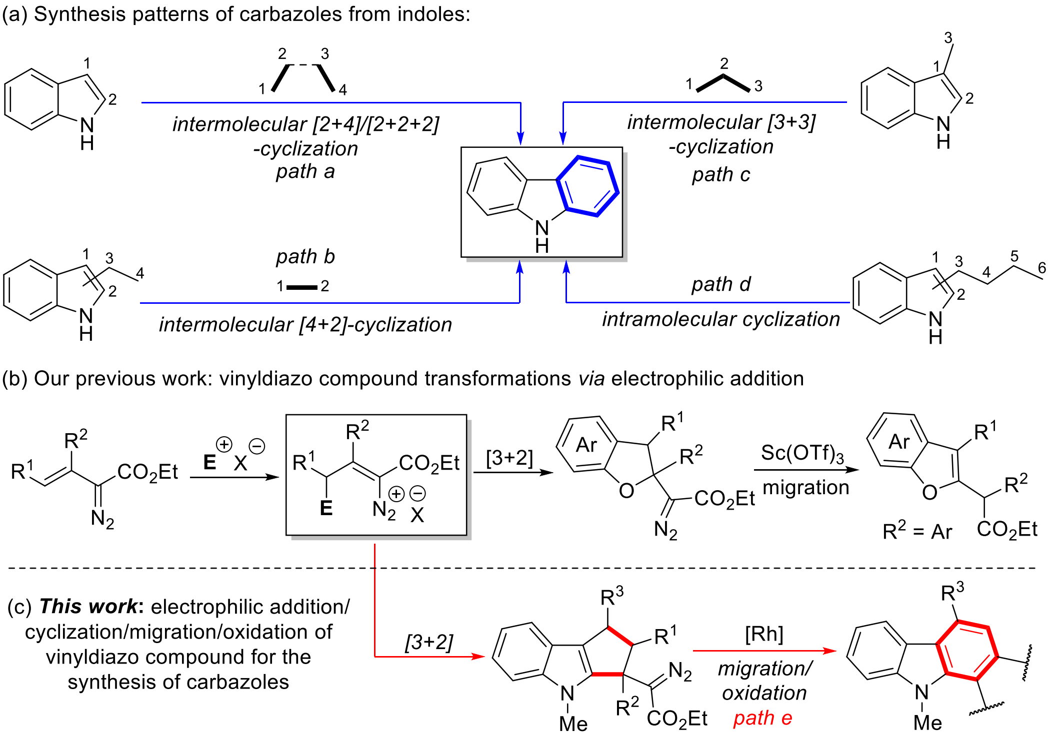
Scheme 1. Strategy for Constructing Carbazoles

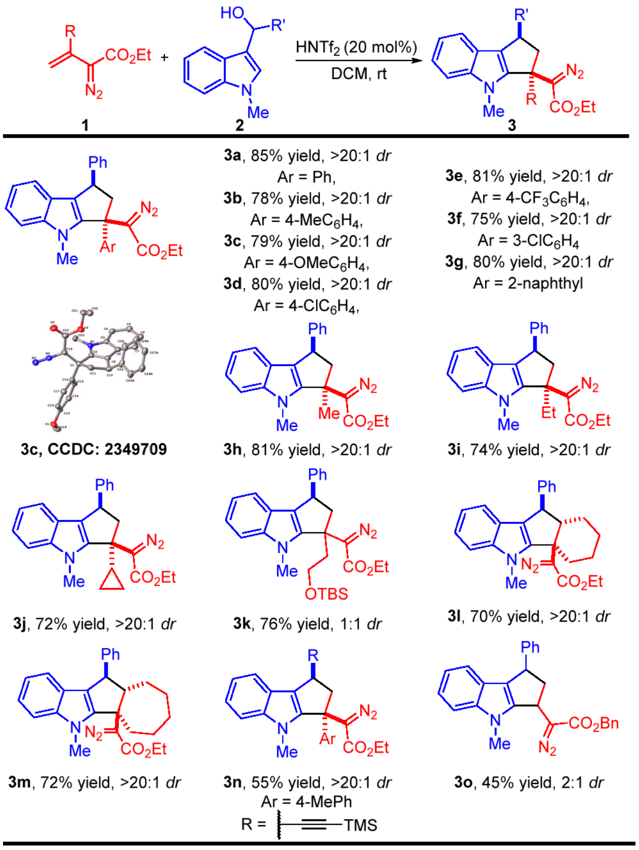


selected as the model substrate to investigate the viability of its reaction with vinyldiazoacetate **1a**[11a] through catalysis by triflimide. Interestingly, with optimization, the desired [3 + 2]-cycloaddition product **3a** was obtained in 85% isolated yield with greater than 20:1 diastereocontrol (see Table S1 in the SI). Examining the substrate scope of this formal [3 + 2] cycloaddition (Scheme 2), both electron-donating and electron-withdrawing substitutions on the aryl ring of vinyldiazo compound **1** were well-tolerated, delivering cycloaddition products **3a**−**3f** in 75−85% yields with high diastereocontrol (>20:1 dr). The 2-naphthyl-substituted vinyldiazo compound was also effective, providing product **3g** in 80% yield and >20:1 dr. Moreover, alkyl-substituted analogues of the vinyldiazo compound, including methyl, ethyl, and cyclopropyl, gave the corresponding products **3h**−**3j** in good yields and excellent diastereoselectivity, but product **3k** with R = CH_2CH_2OTBS was surprisingly obtained with low diastereocontrol (1:1 dr). This transformation could also be applied to cyclic analogues of vinyldiazo compounds (**3l** and **3m**) with good yields and >20:1 dr. Notably, the alkynyl-substituted 3-indolymethanol compound **2b** performed well under the optimal conditions, furnishing the corresponding product **3n** in 55% yield with >20:1 dr. The benzyl ester of 2-diazobut-3-enoate also underwent the reaction smoothly, leading to **3o** with >20:1 dr but in moderate yield. To demonstrate the scalability and the practicality of the current method, a 1.0 mmol scale reaction was carried out from which 348 mg of **3a** was isolated (0.8 mmol, 80% yield) with >20:1 dr (see the SI for details). The structure of product **3c** was confirmed by single-crystal X-ray diffraction analysis, and the other products were assigned by analogy.

To illustrate the utility of these processes, transformations of representative α-diazoacetate products with dirhodium tetraacetate were performed (Scheme 3). Because the carbon adjacent to the diazo functionality is quaternary with three possible pathways for carbon migration, we anticipated that all three migratory outcomes might be possible.[12] Not surprisingly, these catalytic reactions occurred under mild conditions, but subtle structural changes in the reactants resulted in changes in the pathway for 1,2-migration. For example, the phenyl and naphthyl analogues **3a** and **3g** underwent only $Rh_2(OAc)_4$-catalyzed ring expansion from the sp^2-hybridized carbon adjacent to the indole nitrogen to generate the ring-fused products in high yields, followed by oxidation to the corresponding carbazole derivatives by DDQ (**5a** and **5g** in 85% and 87% yields, respectively). In contrast, ethyl-substituted **3i** gave two migration products in which the $Rh_2(OAc)_4$-catalyzed ring expansion product **4i** from the sp^2-hybridized carbon adjacent to the indole nitrogen was dominant and **6i** from sp^3-carbon migration was the minor product; however, with $Rh_2(TPA)_4$ catalysis instead of $Rh_2(OAc)_4$, the dominant product was **6i** instead of **4i**. Surprisingly, the cyclopropyl vinyldiazoacetate-derived **3j** underwent $Rh_2(OAc)_4$-catalyzed ring expansion only from sp^3-carbon migration (85% yield), and the corresponding carbazole product **5j** was obtained in 85% yield via subsequent oxidation. With the fused ring α-diazoacetate product **3l**, the same rearrangement process occurred as for **3a**, delivering migration product **4l** in 82% yield and oxidation product **5l** in 89% yield. Their stereochemistry was confirmed by NMR experiments (see the SI for details).

Based on the experimental data and previous reports,[11,13] a probable mechanism for electrophile-induced transformations of vinyldiazo compounds is proposed in Scheme 4. Dehydration of 3-indolymethanol **2a** in the presence of $HNTf_2$ afforded the corresponding carbocation **A** shown with its indolyliminium ion pair resonance structure **A′**. Selective addition of this species to the vinylogous position of vinyldiazo compound **1a** gives the vinyl diazonium ion

Scheme 2. Catalytic [3 + 2]-Cycloaddition of Vinyldiazo Compounds with 3-Indolymethanol[a]



[a] Optimized reaction conditions: to vinyldiazo compound **1** (0.1 mmol), 3-indolymethanol **2** (0.15 mmol, 1.5 equiv), and 4 Å MS (100 mg) in anhydrous DCM (1.0 mL) was added a solution of $HNTf_2$ (3.0 mg, 20 mol %) in anhydrous DCM (1.0 mL) via a syringe pump over 2 h at room temperature. Isolated yields are given.

intermediate **B**/**B′**, followed by intramolecular cyclization to give the final product **3a** via **C**.

In summary, we have developed a triflimide-catalyzed formal [3 + 2]-cycloaddition that provides general access for the synthesis of *β*-tetrahydrocyclopenta[*b*]indol-substituted *α*-diazo esters in good yields and excellent diastereocontrol. The *β*-tetrahydrocyclopenta[*b*]indol-substituted *α*-diazo esters undergo dinitrogen extrusion and 1,2-C → C migration to multisubstituted carbazole derivatives in high yields. The electrophilic addition reactions of the reactive indolyliminium ion pair occur at the vinylogous position of the vinyldiazo compound to afford vinyldiazonium ion intermediates, followed by intramolecular cyclization.

■ ASSOCIATED CONTENT

Data Availability Statement

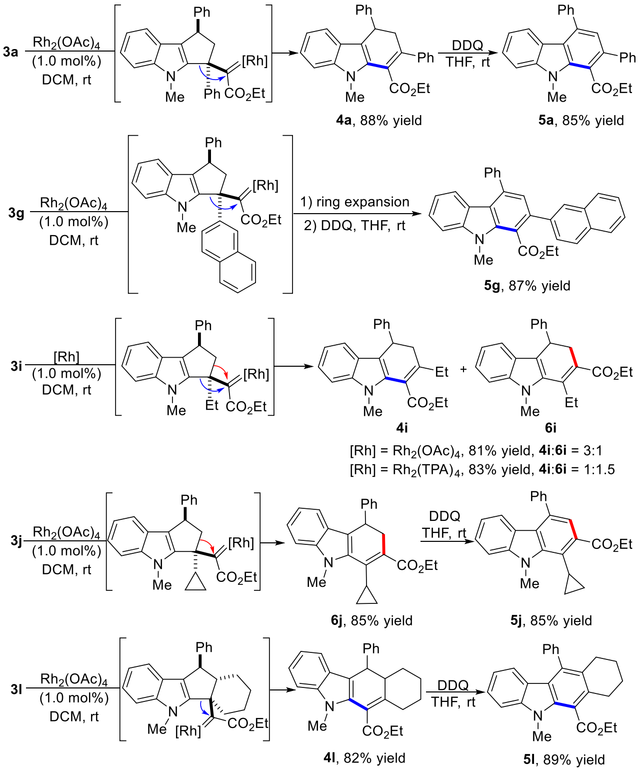
The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

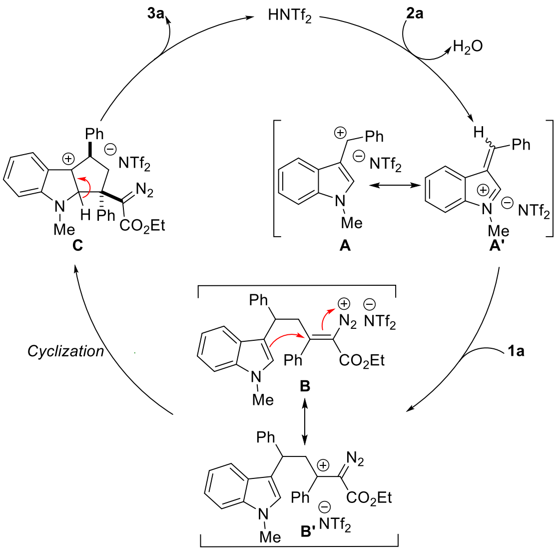
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01628.

Experimental procedures and spectroscopic data for all new compounds (PDF)

Scheme 3. Rhodium(II)-Catalyzed Transformations of *α*-Diazoacetates from [3 + 2]-Cycloaddition Reactions with 3-Indolymethanol



Scheme 4. Proposed Reaction Mechanism



Accession Codes

CCDC 2349709 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Michael P. Doyle − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States;* orcid.org/0000-0003-1386-3780;
Email: michael.doyle@utsa.edu

Authors

Ming Bao − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*

Diana Victoria Navarrete Carriola − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States; Laboratorio de Biotecnología Farmacéutica, Centro de Biotecnología Genómica, Instituto Politécnico Nacional, 88710 Reynosa, México*

Hadi Arman − *Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.4c01628

Notes

The authors declare no competing financial interest.

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