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Harnessing the Polarizability of Conjugated Alkynes toward [2 + 2] Cycloaddition, Alkenylation, and Ring Expansion of Indoles

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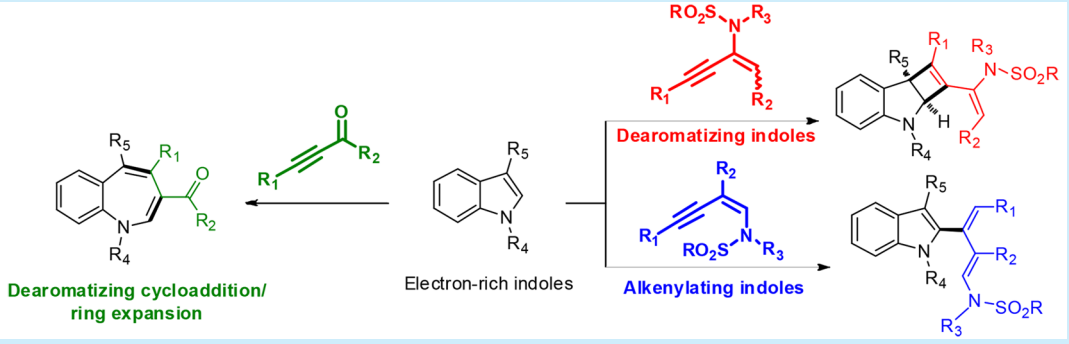
Supporting Information



ABSTRACT: Reported is the utilization of electronically biased conjugated alkynes in the development of highly diastereo- and regioselective dearomative [2 + 2] cycloadditions, alkenylations, and ring expansions of electron-rich indoles. Regioselective protonations of cross- and linear-conjugated alkynes were found to be crucial for accessing various cyclobutene-fused indoline and alkenylated indole derivatives. Furthermore, the facile ring expansion of [2 + 2] keto adducts, which were successfully synthesized from ynones, provided 1*H*-benzo[*b*]azepine scaffolds.

Owing to the degree of unsaturation associated with them, conjugated enynes have been utilized for the development of novel synthetic routes to valuable structurally diversified compounds.[1] An electronic switch around unsaturated C−C bonds is an essential event that underpins their site-selective reactivities either with metals or under metal-free conditions.[2] A pertinent strategy for selective reactions is to alter the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) through suitably tethered electron-donating/withdrawing substituents or the conjugation length.[3] Additionally, broken or continuous electron flow driven by cross and linear conjugation[4] may perturb the electron density around the reaction sites and result in site-selective interception by nucleophiles through an activator, such as a Brønsted or Lewis acid. It is, therefore, of interest to study such electronic events in order to obtain a powerful, yet undiscovered, switchable vector for divergent manipulations and more general control of regio- and stereoselectivity.

Despite the diversity of alkynes tailored toward [2 + 2] cycloadditions with alkenes (inter- or intramolecular), many of them operate through combinations of precious metal catalysts and supporting ligands.[5] Directed intermolecular cycloadditions using Au,[5a] Ni,[5e] and Co[5h] utilizing the distinct reactivity of conjugated enynes are some examples. When an acid is used, proper electronic balance between the two coupling partners is required,[6] a characteristic that has been exploited in numerous methods, with some exceptions.[7] However, to date, reactions between electron-rich alkynes and electron-rich alkenes have not been systematically studied, particularly for electron-rich indoles. For instance, while electron-rich ynamides are known to undergo Ficini-type [2 + 2] cycloadditions with electron-deficient alkenes,[6c,8] they undergo hydroarylation[9] with electron-rich indoles in the presence of a gold catalyst (top, Scheme 1A). Conversely, electron-deficient symmetric alkynes (e.g., dimethyl acetylenedicarboxylate) were known to react with electron-rich indoles in Lewis acid mediated[10a] and photochemical reactions[10b] in the early 1980s (bottom, Scheme 1A); however, complete control toward cycloaddition over alkenylation[11] has been elusive since then. Moreover, the cycloadducts are reversibly converted into 1*H*-benzazepines, ring-expanded products, due to heat and light.[10]

As part of our recent research on regio- and stereoselective C−H annulation using branched ynenamides[12] and selective synthesis of linear ynenamides,[13] we hypothesized that electronically perturbed cross- and linear-conjugated alkynes could be selectively activated by an acid to provide a practical solution to the above-mentioned problems, consequently leading to the development of divergent intermolecular coupling reactions with indoles. Gratifyingly, while cross-conjugated alkynes provided cyclobutene-fused indolines, linear-conjugated alkynes gave C2-alkenylated indoles, regio- and stereoselectively (top, Scheme 1B). Additionally, the recognition of potential ring expansion of cyclobutenes[14] led us to focus on the synthesis of

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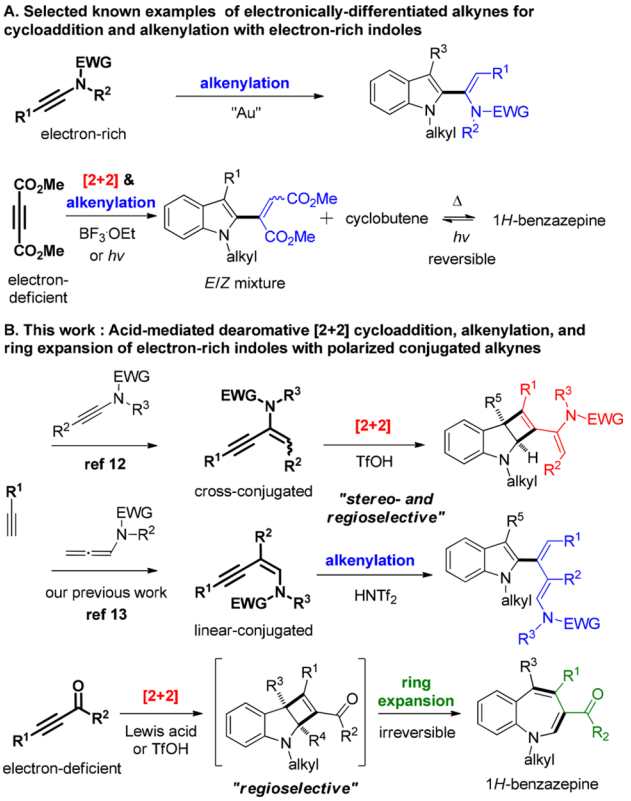
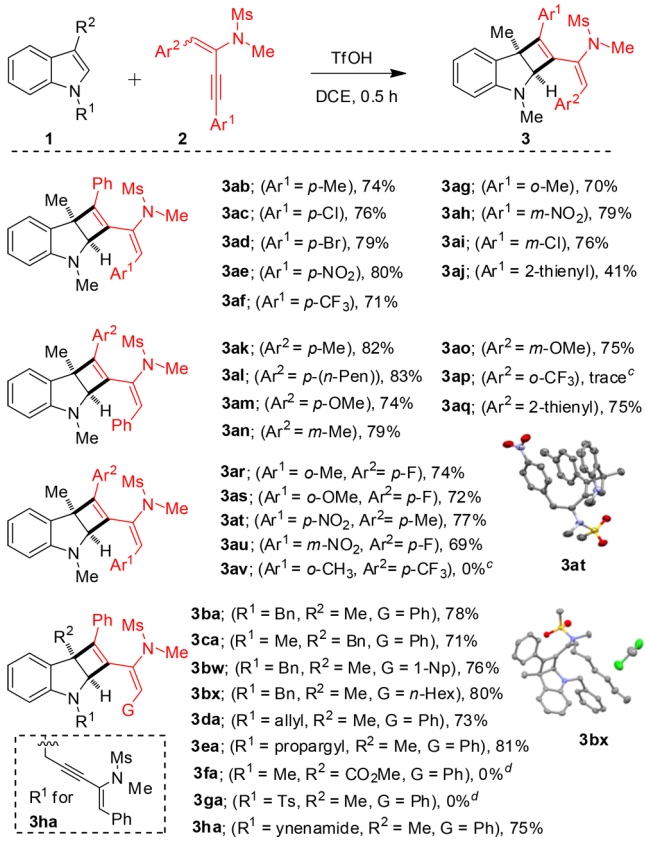
Scheme 1. Comparison between Previous Work and Our Work



Scheme 2. Scope of Branched Ynenamides 2 with Substituted Indoles 1[a,b]



[a]All reactions were carried out under the optimized conditions (0.15 mmol of **1** and 0.1 mmol of ynenamide **2** using 1.2 equiv of TfOH in 0.4 M DCE with MS 4 Å). [b]Isolated yield. [c]Reaction was conducted for 3 h. [d]Both starting materials were recovered.

fused N-heterocycles; serendipitously, we found reagent-free ring expansion conditions for the dearomative cycloadducts, obtained from conjugated ynones, to access pharmaceutically privileged 1*H*-benzazepine scaffolds (bottom, Scheme 1B).[15]

To test the feasibility of the proposed reaction, we began our investigation by reacting **1a** with a 1:10 stereoisomeric mixture of **2a** (Table S1 and S2), from which the optimum conditions were found, and TfOH (1.2 equiv) was determined to be the best activator in 0.4 M DCE using 4 Å molecular sieves (entry 6, Table S1).[16] With these optimized conditions, first, the scope and generality of the intriguing [2 + 2] cycloaddition process were investigated, and the results for 25 different cross-conjugated ynenamides and six indole derivatives are displayed (Scheme 2). The cycloaddition of indole **1a** with ynenamide substrates bearing electronically different aryl groups on the enamide terminus furnished the corresponding [2 + 2] cycloadducts. Changing the substituents on the aryl ring at the yne terminus is also possible, but a CF_3 group at the *ortho* position reduced the reactivity and resulted in no observed cycloadduct **3ap**. Further study on the electronic effects of the aryl rings suggested that the substituents could be either electron-rich or poor in positions affecting the electron density around the phenyl nuclei. Cycloadduct **3at** was recrystallized, and its single-crystal X-ray structure was unequivocally assigned. Unfortunately, no traces of **3av** were observed, possibly owing to electronic and steric effects. Then, we examined the effect of changing the substituents on neighboring reaction sites of indole and found similar cycloadducts with comparable yields. An alkyl substituted *cis*-ynenamide reacted in a similar fashion to provide corresponding cycloadduct **3bx**, the structure of which was confirmed using single-crystal X-ray diffraction. However, indoles with electron-withdrawing substituents were not successful to provide cycloadducts (**3fa** and **3ga**). The reactivity of the other ynenamides, comprising sterically and electronically differentiable groups on the N-atom as well as 2,3-substituted indole, was tested (Table S3). It is of note that an unexpected [4 + 2] cycloaddition pathway was followed by 2,3-dimethyl indole with decent yield, which may be ascribed to the steric hindrance promoting the nucleophilic enamide addition to iminum.

When **3a** was replaced with linear ynenamide **4a** under the optimized conditions for [2 + 2] cycloaddition (entry 6, Table S1),[16] an appreciable amount of nondearomative alkenylation product **5a** was obtained (68%). The yield of **5a** was improved to 78% by using bistriflimide (entry 3, Table S5). It is worth mentioning here that the alkenylation process also proceeds through *cis*−*trans* isomerization of the enamide unit. Next, we turned our attention to generalizing the alkenylation reaction between various indole derivatives **1** and linear ynenamides **4** under the optimized conditions (Scheme 3). Substrates **4** bearing various electron-withdrawing and donating aromatic groups at the alkynyl terminus generated the desired coupling products, **5a**−**f**, in comparable yields and regioselectivities. An alkyl terminated ynenemide also did not deviate to afford the desired alkenylation product **5g**. Furthermore, the reaction exhibited excellent functional group compatibility with respect to functionalized indoles **1** bearing isopropyl, allyl, propargyl, and benzyl groups under our current reaction conditions, giving the desired products in good yields. Unfortunately, alkenylation

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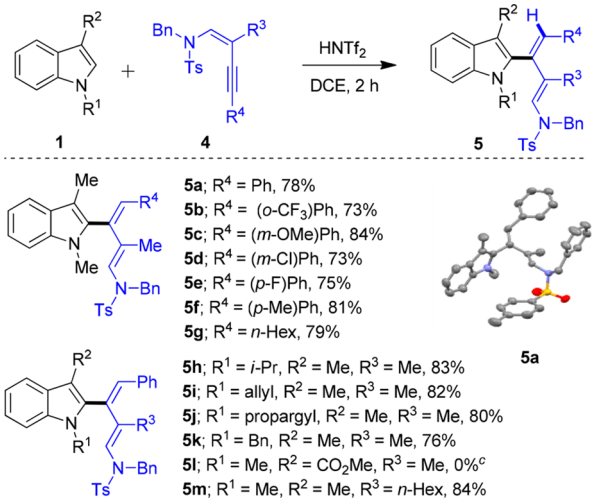
Scheme 3. Scope of Branched Ynenamides 4 with Substituted Indoles 1[a,b]



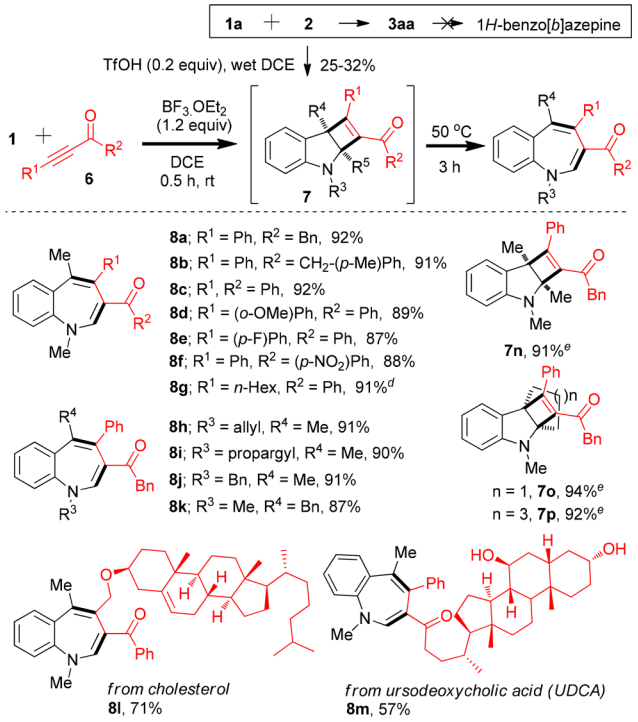
[a]All reactions were carried out under the optimized conditions (0.15 mmol of **1** and 0.1 mmol of ynenamide **4** using 1.2 equiv of $HNTf_2$ in 0.4 M DCE). [b]Isolated yield. [c]Reaction was conducted for 12 h.

was limited for an indole with an electron-withdrawing substituent (**1l**) at the 3-position. An ynenamide derived from a substituted allenamide was also suitable for this transformation, selectively providing **5m**.

Realizing that there is ring strain associated with a cyclobutene ring, we attempted the ring expansion of cyclobutene-fused indole **3aa**, as a showcase of its synthetic applicability. An earlier report on thermal and Ag-catalyzed ring expansion was unsuitable[17a,b] for our substrate, **3aa** (box, in Scheme 4). Inspired by the recent report by Hsung et al. on the carbonyl-group-assisted ring opening of fused cyclobutenamides[14a] and thermal ring opening of cyclobutene-fused indolines,[10] we reasoned that the hydrolyzed product could undergo the same to afford highly substituted benzazepines. To our delight, the ring expansion of **7a** occurred without any catalyst or reagent. Because the yields from ynenamides were disappointing (25–32%, Table S6; top, Scheme 4), we envisaged an alternative synthetic route to 7 using ynone **6**. A short optimization study revealed that the Lewis acid $BF_3{\cdot}OEt_2$ gave the best results, providing isolable [2 + 2] cycloadduct **7a** in 92% yield.[16] Furthermore, owing to internal Lewis acids, mild heating of the reaction mixtures accelerated the ring expansion, giving highly functionalized benzazepines in quantitative yields, thus providing a transition-metal-free approach, complementing the previous metal-catalyzed precedents.[15] The scope of the reaction was excellent for both enolizable and nonenolizable ynones, for yne-terminus alkyl moieties, and for neighboring sensitive and hindered functionalities on the indole ring (Scheme 4). Remarkably, installation of benzazepine moieties into natural products such as cholesterol and ursodeoxycholic acid derivatives was also possible (**8l** and **8m**), highlighting the synthetic utility of the present transformation. However, attempts to synthesize fully substituted and bridge-head benzazepines were unfruitful; instead, the corresponding cycloadducts (**7n–p**) were obtained in high yields (91%–94%).

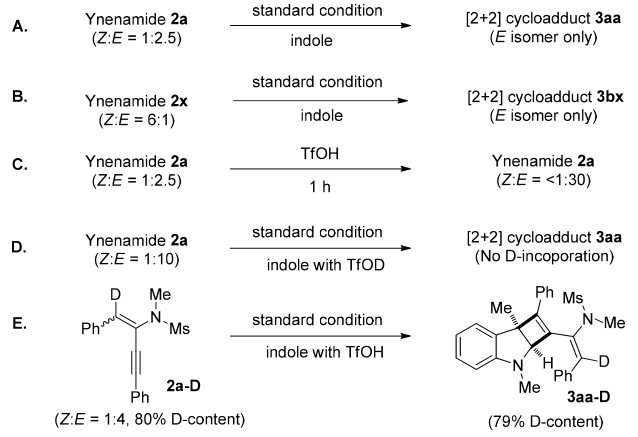
To determine a mechanism for the [2 + 2] cycloaddition, we gathered some experimental results obtained during optimization and scope examination. A single *E* isomer was detected in the *Z*/*E* mixture (1:2.5) (Scheme 5A) as well as major *cis*-

Scheme 4. Scope of Ynones 6 for One-Pot [2 + 2] Cycloaddition and Ring Expansion[a,b,c]



[a]All reactions were carried out with 0.15 mmol of **1** and 0.1 mmol of ynone **6** using 1.2 equiv of $BF_3{\cdot}OEt_2$ in 0.4 M DCE for 0.5 h at rt followed by 3 h at 50 °C. [b]Isolated yields obtained under one-pot conditions from **6**. [c]Quantitative conversion of **7** to **8**, as indicated by ^{1}H NMR. [d]Ring expansion was performed by heating at 100 °C for 2 h. [e]Only cycloadducts **7n–p** were isolated.

Scheme 5. Observations for Mechanistic Insights for [2 + 2] Cycloaddition



isomeric ynenamide **2x** (Scheme 5B), which attest the dual role of the Brønsted acid in alkyne activation and enamide isomerization to the more stable *E* isomer. Meanwhile, a control experiment without indole suggested that the isomerization[18] occurs prior to cycloaddition (Scheme 5C). The lack of D-incorporation of **2a** (Scheme 5D) and nonerosion of D-content of **2a-D** (Scheme 5E) rule out enamide protonation.

On the basis of the above studies, a possible mechanism for the [2 + 2] cycloaddition is proposed in Scheme 6A. Following isomerization, chemoselective protonation of the alkyne (path

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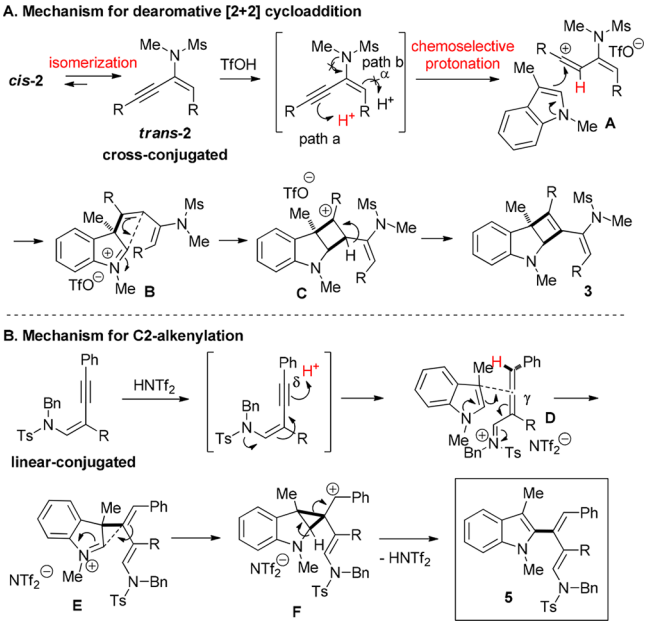
Scheme 6. Proposed Mechanisms



a) over the enamide (path b) gives vinyl cation intermediate **A**. Regioselective Friedel−Crafts alkenylation of an indole by **A** produces **B**. Subsequent ring closure of the alkene at the indole iminium ion gives **3** via addition−elimination (**C**). The proposed mechanism for alkenylation (Scheme 6B) involves the selective protonation of the -yne unit at the δ-position to produce isomerized intermediate **D**, which is likely formed through a continuous electron flow sequence. Nucleophilic attack of the indole on the more electrophilic γ-carbon of **D** affords cyclopropyl carbocation **F** via bond rearrangement of the ipso-carbon as shown in **E**. Finally, rearomatization through simultaneous loss of a proton and cyclopropane ring opening affords alkenylation product **5** from **F**.

In conclusion, we have developed robust acid-mediated protocols for the dearomative cycloaddition and alkenylation of electron-rich indoles with electronically biased ynenamides for the first time. An irreversible and chemoselective protonation of the conjugated ynenamide allowed us to achieve divergent site-selective functionalizations regio- and stereoselectively. More importantly, the reagent-free ring expansion of the corresponding isolable hydrolyzed cycloadducts extended our interests to the investigation of the reactivity of conjugated ynones, enabling expedient access to ubiquitous 1*H*-benzo[*b*]azepines. This work also contributes new knowledge on the behavior of a new class of alkynes tailored for indole chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02230.

Screening of reaction conditions, experimental procedures, X-ray diffraction data, and ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

Accession Codes

CCDC 1863503, 1863504, and 1856321 contain 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.

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Notes

The authors declare no competing financial interest.

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(16) The details of optimization study are described in the Supporting Information

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(18) No D-incorporation was observed with TfOD, and *E*/*Z* isomerization was also found with a catalytic amount of TfOH.

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