TfOH-promoted synthesis of indoles and benzofurans involving cyclative transposition of vinyl ketone†

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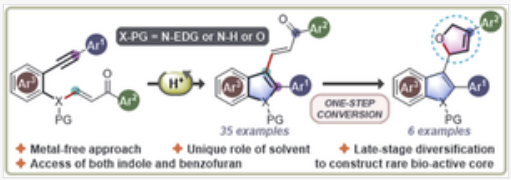


~~A metal-free approach to construct indole rings from vinylogous amides derived from *o*-alkynylanilines involving a cyclization, retro-aza-Michael reaction and amine trapping cascade is reported here~~A metal-free approach to construct indole rings from vinylogous amides derived from *o*-alkynylanilines involving a cyclization, retro-aza-Michael and amine trapping cascade is reported here. It has been extended to synthesize benzofuran derivatives..

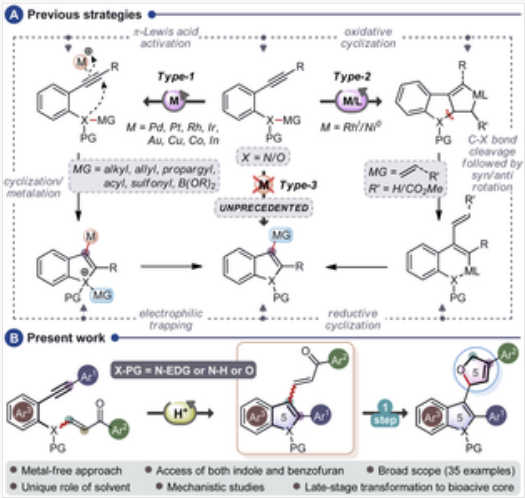
Abstract

A metal-free approach to construct indole rings from vinylogous amides derived from *o*-alkynylanilines involving a cyclization, retro-aza-Michael reaction and amine trapping cascade is reported here. This atom-economical transformation has been extended to synthesize benzofuran derivatives using analogous vinylogous esters derived from *o*-alkynylphenols. The excellent stereochemical outcome of the double bond geometry in the products makes it attractive.

Interest towards the construction of peripherally decorated indoles/benzofurans has been consistent over decades due to their growing utility in medicinal and material chemistry.[1] Among the substituted indoles, 2,3-disubstituted analogues are privileged motifs with a broad spectrum of pharmacological activities.[2] In the context of their synthesis, transition metal-catalyzed reactions come in handy as they bring wide opportunities, though at the expense of their high costs.

While significant advances have been made towards the synthesis of C2-substituted analogues *via* direct 5-*endo*-*dig* cyclization of *o*-alkynylanilines using π-philic metal catalysts,[3] the strategies to make C3-substituted indoles from *o*-alkynylanilines require certain tricks and are very limited.[4] A few groups have disclosed alkynophilic metals, *e.g.*, Pd, Pt, Rh, Ni, Ir, Au, Cu, Co, and In-catalyzed 5-*endo*-*dig* cyclization of 2-alkynylaniline/phenol derivatives to afford C3-functionalized indoles/benzofurans (Scheme 1A).[5] These transformations involve intramolecular migratory cycloisomerization *via* initial alkyne activation, and cyclization/C3-metalation followed by 1,3-migration sequences. This phenomenon was found for a variety of *N*- or *O*-substituents such as allyl,[5f] benzyl,[5c] propargyl,[5a] methyl,[5d] α-alkoxyalkyl,[5] acyl,[5c] sulfonyl,[5e] and $B(OR)_2$[5b,g] (Scheme 1A, Type-1). In this context, the Tanaka group disclosed the first report on a difficult vinyl migration to access 2-substituted 3-vinylbenzofurans from naphthol- or phenol-linked 1,6-enynes using the Rh(I)/*rac*-binap catalytic system.[6d] Tactically, the reaction proceeds through Rh-catalyzed oxidative cyclization between the alkyne and alkene moieties followed by C–O bond cleavage and finally reductive cyclative elimination (Scheme 1A, Type-2). Later, the Arisawa and Cho groups[6b,c] reported a similar strategy to synthesize 2-substituted benzofurans and indoles from vinylogous esters/carbamates derived from *o*-alkynylphenols/*o*-alkynylanilines using Ni(0) catalysts, involving transposition of the acrylate to the C3 position of the product. Despite the efficacy of these nickel-catalyzed protocols, drawbacks such as the formation of *E*/*Z* mixtures, limited compatibility of N substituents, *etc.* do exist. Therefore, there is a necessity to develop efficient protocols that avoid the usage of expensive metal catalysts/ligands. The common feature of the above Rh- and Ni-catalyzed reactions is the β-C–O/N bond cleavage after the first cyclization step and subsequent reductive cyclization through the heteroatom. We considered that such a C–N bond cleavage could be achieved *via* a simple retro-aza-Michael reaction[7] after the cyclization of the triple bond on the vinylogous amide derived from *o*-alkynylanilines. Retro oxa-Michael reaction has been reported to happen after the cyclopropanation of the aryloylsilane-derived carbene on the *o*-vinylogous carbonates under photochemical conditions.[7a] Also, a related retro-oxa-Michael reaction has been noticed after an intramolecular addition of a sulfur ylide to vinylogous carbonates.[Instruction: 7cd should be made superscript][7cd] Carbene and ylide, being strong nucleophiles, added smoothly onto the double bond of vinylogous carbonates. In the absence of such a strong nucleophilic center in the *o*-alkynylaniline derived enaminone, the activation of the poor Michael acceptor,[8] enaminone, for the addition of the less nucleophilic alkyne is vital. Thus, the use of a strong acid such as TfOH was considered for activating the enaminone based on our earlier successful experiences of using TfOH for efficient cyclization reactions.[9] Upon activation of enaminone[10] with TfOH, an iminium ion is expected to form which could be trapped by the alkyne.[11] Experiments were carried out to check the feasibility of achieving the proposed reaction using vinylogous amide derivative **1aa** and TfOH.

Scheme 1



Metal catalyzed ring-closure *vs.* our approach under metal-free conditions.

Optimization studies revealed that the target product was isolated in 91% yield with an exclusive *E* geometry of the olefin when the reaction was performed using 50 mol% of TfOH in HFIP at room temperature (for details, see the ESI[†]). The superiority of HFIP as the solvent is overwhelming as it is known to polarize the substrates and stabilize the polar intermediates.[12]

To understand the electronic and structural compatibilities of this transformation, a range of vinylogous amides derived from *o*-alkynylanilines having a variety of substitution patterns were treated under the optimized conditions. Gratifyingly, all of these substrates, irrespective of the electronic demands of their substituents, reacted well and afforded the expected products in high yields (Scheme 2). Substrates having electron donating (*e.g.*, *p*-Me, *p*-OMe) groups as R^1 and "H" as R^2 & R^3 efficiently provided compounds **4** and **5**. Electron-withdrawing substituents such as *p*-CO_2Me and *m*-F did not have any drastic effect on the reaction outcome and the products **6** and **7** were obtained in slightly lower yields of 82% and 87%, respectively. Then, the effect of R^2 was studied employing quite a few different substrates. Here also a slight decrease in the yield of the product was noticed when electron-withdrawing CF_3 and OCF_3 were present in the ortho and para positions, respectively. The yields were around 90% with electron-donating R^2 groups (**8–12**) and did not change much with di- or tri-substitution (**15** and **16**). A couple of reactions were studied by changing the R^3 group, which will have a direct influence on the electron density of the vinylogous amide. While an electron-donating methyl group increased the yield to give **17** in 94% yield, an electron-withdrawing cyano group reduced it to 80% (product **18**). Substrates having a random choice of R^1 and R^2 also underwent smooth reactions to yield their respective indole products. It is pertinent to note that substrates having a Br substituent, which is usually labile in the presence of a metal catalyst, could be handled very well. This method could be used to make indole-containing diarylideneacetone derivatives such as **22** in 86% yield. Photophysically interesting PAHs,[13] such as anthracenyl and pyrenyl group-conjugated highly fluorescent indole derivatives **23** and **24**, respectively, could be obtained in respectable yields. Heteroaryl groups could also be accommodated (**25–27**).

Scheme 2

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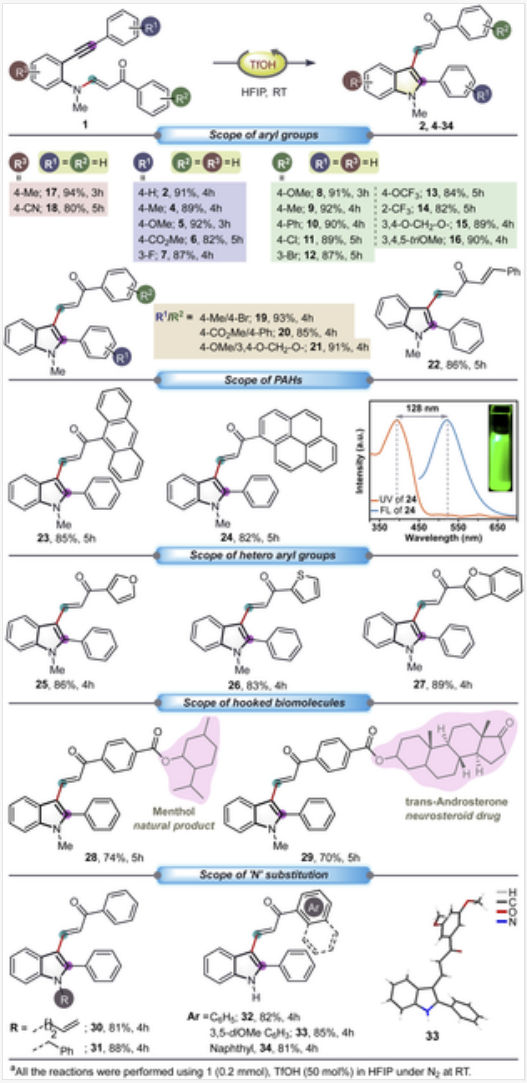

Substrate scope[a].

Replacement Image: Scheme2.cdx

Replacement Instruction: Position of substituent details of compounds 17 and 18 has been to the right side (appropriate place)

Hybrid natural products/bioactive compounds have shown tremendous potential in drug discovery.[14] In this respect, the synthesis of natural product-conjugated indole derivatives such as **28** and **29** highlights the power of this protocol (Scheme 2). Next, we evaluated the compatibility of the substituent on the nitrogen of the vinylogous amide (Scheme 2). Pleasingly, apart from a methyl group, 3-butenyl and benzyl groups were also compatible (**30–31**). Very importantly, this indole synthesis could be achieved with great efficiencies on vinylogous amide derivatives having a free N–H group (**32–34**). Remarkably, the nitrogen did not cyclize on the alkyne directly to afford a different indole derivative. Therefore, this method is unique and advantageous ~~for~~ than known metal-catalyzed indole formation accompanied by N to C3 migration as this reaction requires mandatory protection of the nitrogen. It should also be noted that the olefin geometry in the products **32–34** is *trans*. This reveals that only the product with the *trans* olefin geometry is obtained from both the N-protected and unprotected substrates having *trans*- and *cis*-enaminone, respectively.

In pursuit of the expansion of the scope of this methodology, the cyclization of vinylogous esters derived from *o*-alkynyl phenols was also studied (Scheme 3). The corresponding 3-alkenyl benzofurans (**36–38**) were obtained in promising yields (87–90%). Interestingly, the double bond geometry is mostly *cis* in products **36** and **38**. The *cis*/*trans* ratio in product **37** was found to be 9 : 1. Unlike the nitrogen analogues, where the exclusive *trans* geometry of olefin was noticed in the products derived from both *trans* and *cis*-enaminones, the *trans* vinylogous ester resulted in the *cis* olefin geometry in its product. A plausible reason for this is provided during the discussion of the mechanism ~~Scheme 3~~Scheme 4.

Scheme 3

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Substrate scope[a].

Replacement Image: Scheme 3.cdx

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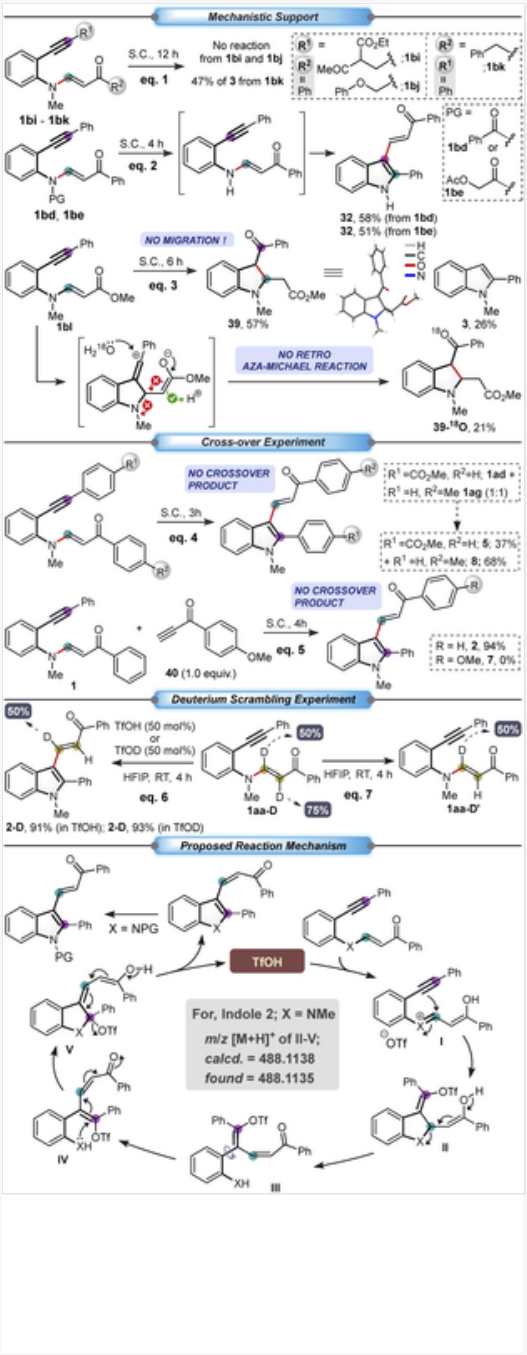
While the reactions of substrates **1bi** and **1bj** having alkyl groups on the alkyne were recovered unreacted, **1bk** having alkenone resulted in 47% of 2-phenyl-*N*-methylindole **3** with the extrusion of the enone portion (Scheme 4). Interestingly, the reactions of substrates having electron-withdrawing groups such as benzoyl and acetoxyacetyl on the nitrogen (**1bd** and **1be**) delivered N–H containing 2-alkenylindole derivative **32** accompanied by the cleavage of the amide bond. Perhaps, TfOH might have promoted the deprotection as it is known to deprotect *N*-arylsulfonamides.[15] The vinylogous carbamate derived from 2-phenylaniline, as reported earlier,[11a] did not undergo retro aza-Michael reaction after the initial nucleophilic addition of the triple bond on the iminium ion. Substituted indoline **39** was obtained in 57% yield along with 26% of 2-phenyl-*N*-methylindole **3**. A competition experiment using equimolar quantities of **1ad** and **1ag** did not result in any cross-over products. Also, the cyclization of **1aa**, when conducted along with an equimolar quantity of 1-(4-methoxyphenyl)prop-2-yn-1-one **40**, resulted in the product **2**. Non participation of **40** in the above reaction and the result of the cross-over reaction reveals the intramolecular nature of the reaction. A set of deuterium-scrambling experiments were conducted on substrate **1aa-D** having 75% and 50% D content, respectively, at the α- and β-positions of the enaminone moiety. Reaction of **1aa-D** separately with TfOH and TfOD resulted in **2-D** with 50% and 0% deuterium content, respectively, at the β- and α-positions of the enone moiety. In another experiment, it was indicated that there is a strong polarization of the enaminone leading to the exchange of deuterium with hydrogen in HFIP.

Scheme 4



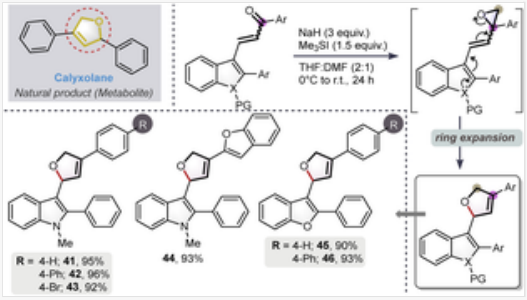
Control experiments. S. C. means standard reaction condition.

A plausible mechanism is drawn to explain the mode of cyclization (Scheme 4). Protonation of the *trans* vinylogous amide/ester moiety generates electrophilic iminium/oxocarbenium ion species **I**. Nucleophilic addition of alkyne on the iminium/oxocarbenium ion would generate the vinyl triflate **II**. ~~Nucleophilic addition o~~[Instruction: repeating sentence has been deleted]~~f alkyne on the iminium/oxocarbenium ion would generate the vinyl triflate **II**.~~ Retro aza/oxa-Michael reaction would open the formed ring to give **III** keeping the *cis* configuration of the enone double bond. The C–C bond connecting the aryl and vinyl triflate moieties rotates to place the double bond to effect an intramolecular aza/oxa-Michael addition on the dienone. Thus, the formed intermediate **V** would eliminate OTf^- leading to the indole/benzofuran derivatives. The *cis* geometry of the eneone double bond might isomerize to the more stable *trans* form in the indoles under the acidic reaction conditions. Such isomerisations are reported to happen under certain reaction conditions.[6b] The high electronegativity of oxygen and the consequent less electron density at the C3 of benzofuran does not promote such *cis* to *trans* isomerism in the benzofuran products. HRMS analysis of the reaction mixture after 30 min of reaction of **1aa** showed a peak at *m*/*z* 488.1135, which may be assigned to the $[M + H]^+$ of triflate incorporated intermediates **II–V** (X = NMe).

In pursuit of late-stage transformation, 2,4-disubstituted-2,5-dihydrofuran derivatives were accomplished upon treating the synthesized 3-alkenyl-indoles/benzofurans with ~~trimethylsulfonium ylide~~dimethylsulfonium methylide (Scheme 5). The aryl substituted dihydrofuran scaffold is found in many natural products such as pteleifolins C, calyxolane, *etc.* and

commonly used in anti-pyretic, anti-inflammatory and analgesic ~~drugs~~agents.[16] Pleasingly, we were able to synthesize diverse indole and benzofuran linked 2,5-dihydrofuran derivatives **41–46** in excellent yields (90–96%).

Scheme 5



Late-stage diversification.

In conclusion, a straightforward triflic acid-promoted cyclative transposition of vinyl ketones to access 3-alkenylindole/benzofuran analogues with excellent stereochemical outcome was uncovered. The effect of triflic acid and HFIP is truly noteworthy to accomplish the transformation with excellent productivity and selectivity.

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Conflicts of interest

There are no conflicts to declare.

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Footnotes

[†] Electronic supplementary information (ESI)[Instruction: During the submission of the revision, the changes in made in the ESI-1 were highlighted. Please remove those highlighting at the time of its publication.] available: Detailed experimental procedures, spectroscopic/crystallographic data, and copies of NMR spectra. CCDC 2166456–2166460. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2cc03730k

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