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Cascade Reactions

Brønsted Acid-Catalyzed Cascade Reactions Involving 1,2-Indole Migration

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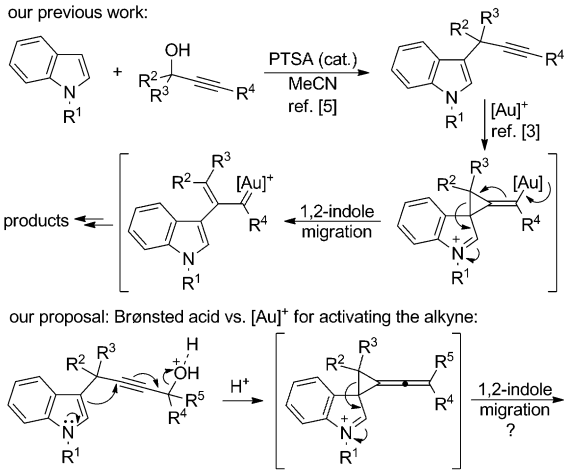
Dedicated to our inspiring mentor Professor José Barluenga on the occasion of his 75th birthday

Abstract: A cascade reaction of indoles with propargylic diols involving an unprecedented metal-free 1,2-indole migration onto an alkyne was carried out. DFT calculations support a mechanism consisting of a concerted nucleophilic attack of the indole nucleus with loss of water, followed by the 1,2-migration and subsequent Nazarov cyclization. This Brønsted acid-catalyzed protocol affords indole-functionalized benzofulvene derivatives in high yields.

Metal-catalyzed rearrangements have become the most powerful tool for the construction of cyclic scaffolds from simple materials, usually under mild reaction conditions.[1] For instance, propargylic esters are versatile precursors of a wide range of carbo- and heterocyclic compounds, through tandem processes initiated by 1,2-acyl migration reactions onto the alkyne activated by gold or platinum catalysts.[2] In this regard, we have reported that 3-propargylindoles evolve in the presence of catalytic amounts of cationic gold(I) complexes by previously unknown 1,2-indole migration (Scheme 1).[3] However, to the best of our knowledge, this type of rearrangement in propargylic derivatives, which implies the rupture and formation of carbon–carbon bonds, has not been reported under metal-free conditions.

In the past few years, our group has developed methodologies for the direct nucleophilic substitution reaction of π-activated alcohols under metal-free Brønsted acid-catalysis.[4] In this context, we have described a robust method for the reaction of indoles with propargylic alcohols that provides suitable access to a wide variety of 3-propargylindole derivatives (Scheme 1).[5] In addition, cascade rearrangements of propargylic alcohols, and their derivatives, have been demonstrated to be a useful synthetic tool[6] through their transformation into allenic carbocations[7] and subsequent intramolecular trapping with electron-rich arenes, alkenes, enols, and heteroatom nucleophiles.[8]



Scheme 1. Previous work and our proposal.

We have considered the possibility that a Brønsted acid could trigger an intramolecular nucleophilic attack of the indole onto a propargylic cation, generated from the corresponding alcohol, followed by the opening of the cyclopropyl ring, thus mimicking the behavior of cationic gold(I) catalysts (Scheme 1); it has been reported that some reactions can be catalyzed by π-acids as well as by protons.[9] We describe herein the first examples of metal-free promoted 1,2-indole migration onto alkynes. This Brønsted acid-catalyzed rearrangement is feasible in a cascade fashion, starting from simple indoles and propargylic diols, delivering a new and efficient synthetic access to 2-indol-3-ylbenzofulvenes with water as the only byproduct.

Our study began by assessing the viability of a cascade reaction in alkyne **1a**, bearing an indole at one propargylic position and an activated hydroxyl group at the other propargylic position, promoted by *p*-toluenesulfonic acid (PTSA) as a simple and easily available Brønsted acid catalyst. Gratifyingly, we found that under our standard conditions for Brønsted acid-catalyzed direct nucleophilic substitution reactions (MeCN, 5 mol% PTSA), a new product with a benzofulvene core **2a** was formed (Scheme 2). It is worth noting that benzofulvenes

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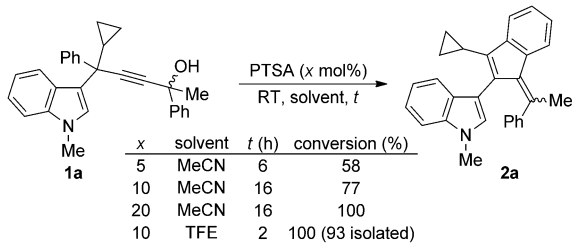


x	solvent	t (h)	conversion (%)
5	MeCN	6	58
10	MeCN	16	77
20	MeCN	16	100
10	TFE	2	100 (93 isolated)

Scheme 2. Preliminary results and proof of concept.

are interesting compounds with relevance in applied chemistry.[10] Although different synthetic strategies for accessing the benzofulvene core have been reported,[11] the development of straightforward and efficient methods for the synthesis of functionalized benzofulvenes is still highly desirable.

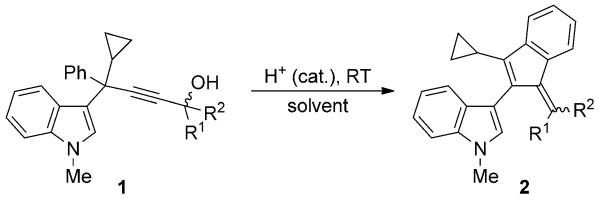
Full conversion was easily achieved in the model reaction by increasing the catalyst load and the reaction time. Moreover, by using trifluoroethanol (TFE) as solvent,[12] the reaction time was shortened and the final benzofulvene **2a** was isolated as a mixture of geometrical isomers in pure form and excellent yield by simple filtration. Interestingly, its structure, which was confirmed by X-ray diffraction of the *Z* isomer,[13] indicates that the intended metal free-promoted indole migration has occurred along with the formation of a new five-membered ring involving the phenyl group initially attached to the same progargylic carbon as the indole.

To examine the scope of this novel Brønsted acid-catalyzed cascade cyclization, we applied this reaction protocol to a set of 3-propargylindoles **1** having varied substitution at the alcohol position. The results have been summarized in Table 1. We found that the tandem 1,2-indole migration/cyclization is general for a wide variety of alkynols possessing tertiary hydroxyl groups (Table 1, entries 1–11) as well as secondary ones (Table 1, entries 12–16). For the latter, activating groups such as aryl, alkenyl, or cyclopropyl are required as R^1 substituents.[14] When the two groups, R^1 and R^2, are different, variable mixtures of geometrical isomers are obtained, typically favoring the *E*-isomer. To ensure homogeneity of the reaction, some experiments were conducted in MeCN instead of TFE. In addition, for less activated alkynols higher loads of catalyst and/or the stronger 2,4-dinitrobenzensulfonic acid (DNBSA) were used. In most cases, excellent yields for the benzofulvene derivatives **2** were obtained in short reaction times (1–6 h).[15]

We decided to use DFT to study the mechanism of this novel reaction, in order to understand the steps involved in such a dramatic one-pot transformation (see Scheme 3 and Figure 1). For the calculations, we have chosen a model system bearing methyl groups at all the propargylic positions apart from the required phenyl-substituted one. Starting from the protonated alkynol, $\mathbf{I_H}$, a cationic cascade is triggered. The departure of water as a leaving group occurs without barriers and proceeds in concert with the S_N2' nucleophilic attack of the indole C3′ position to the incipient carbocation in C2. The resultant product, 11.7 kcal mol^{-1} lower in energy than $\mathbf{I_H}$, is an ethenylidenecyclopropane intermediate ($\mathbf{II_H}$), with a C1–C3′ bond significantly larger (by 0.07 Å) than the newly formed C2–C3′ bond. This slightly lower bond order for C1–C3′ (0.76 vs. 0.78) facilitates the cleavage of the C1–C3′ bond through $\mathbf{TS_{II-III(H)}}$, resulting in a low energy step requiring only 3.7 kcal mol^{-1} to complete the 1,2-indole migration. This migration leads to vinylallenyl cation $\mathbf{III_H}$, which undergoes a relatively facile (8.5 kcal mol^{-1} barrier) conrotatory four-electron electrocyclization to the much more thermodynamically favored (by 18.0 kcal mol^{-1}) structure $\mathbf{IV_H}$, which results in the formation of the benzofulvene product after rearomatization. Though low, the barrier of this electrocyclic ring-closure is significantly higher than the barrier corresponding to the electrocyclization of the allylallene (4.6 kcal mol^{-1}) or pentadienyl cations (4.3 kcal mol^{-1}), due to the loss of aromaticity of the phenyl group along the reaction path. This latter proposed step has been reported in the catalysis of α-allenyl benzyl alcohols using Brønsted or Lewis acids.[16]

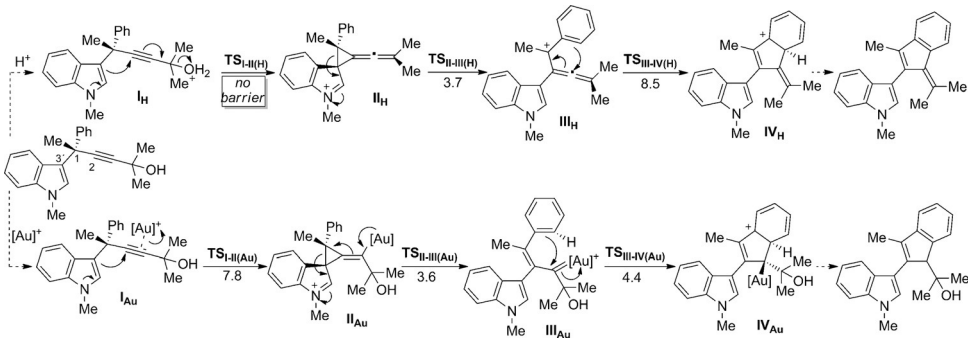
Using $[AuPH_3]^+$-coordinated **1** as a starting point, we calculated the equivalent gold-catalyzed mechanism (see the Supporting Information for details) to ex-

Table 1. Synthesis of 2-indol-3-ylbenzofulvenes **2**. Scope of the reaction.



Entry	1	R^1	R^2	H^+ (*x* [mol%])	Solvent	2	*Z*/*E*[a]	Yield [%][b]
1	**1a**	Ph	Me	PTSA (10)	TFE	**2a**	1.2/1	98
2	**1b**	Ph	*c*-C_3H_5	PTSA (10)	TFE	**2b**	1/3.5	96
3	**1c**	Ph	*i*Pr	PTSA (10)	TFE	**2c**	1/3.4	88
4	**1d**	4-$MeOC_6H_4$	Me	PTSA (10)	TFE	**2d**	1/2	95
5	**1e**	2-Th	Me	PTSA (10)	TFE	**2e**	1.3/1	93
6	**1f**	Ph	Ph	PTSA (10)	MeCN	**2f**	–	98
7	**1g**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PTSA (10)	MeCN	**2g**	–	88
8	**1h**	4-ClC_6H_4	4-ClC_6H_4	DNBSA (30)	MeCN	**2h**	–	93
9	**1i**	Me	Me	PTSA (30)	MeCN	**2i**	–	67
10	**1j**	Et	Et	PTSA (30)	MeCN	**2j**	–	69
11	**1k**	$-(CH_2)_4-$		PTSA (30)	MeCN	**2k**	–	93
12	**1l**	4-MeC_6H_4	H	DNBSA (20)	MeCN	**2l**	1/1	95
13	**1m**	4-BrC_6H_4	H	DNBSA (50)	TFE	**2m**	1/1.5	75
14	**1n**	2-Th	H	DNBSA (10)	TFE	**2n**	1/1.7	75
15	**1o**	CH=CH(4-$MeOC_6H_4$)	H	PTSA (10)	TFE	**2o**	1/2	85
16	**1p**	*c*-C_3H_5	H	DNBSA (20)	MeCN	**2p**	1/2.4	94

[a] *Z*/*E* ratio determined by ^{1}H NMR analysis. [b] Isolated yield after filtration or column chromatography.



Scheme 3. Detailed mechanism based on our computational exploration. The free energies values (relative to starting compound) are given in kcal mol^{-1}.

plore the potential of Brønsted acids as a replacement for cationic gold in synthesis. The Brønsted acid-catalyzed and the gold-catalyzed mechanisms display a similar sequence of steps and reaction profile, with the main difference being the lower barrier for the electrocyclization in the latter. The most remarkable feature, however, is the downhill path followed by the Brønsted acid-catalyzed system upon protonation of **1**, which is expected to be much more favorable than the alternative reaction with gold. Protonation of **1** provides a substrate already poised to react, resulting in a barrierless ***TS***$_{\mathbf{I\text{-}II(H)}}$. After this, the stability of the water leaving group results in a cationic cascade of reactions downhill from the reactant, whereas, for the gold-catalyzed manifold, only the final product is lower in energy than the activated substrate $\mathbf{I_{Au}}$ (see the Supporting Information).

At this point, and taking advantage from our developed methodology for the direct propargylation of indoles under Brønsted acid catalysis,[5] we envisaged that this new process could be performed in a straightforward manner from simple indoles **3** and but-2-yne-1,4-diols **4** with the loss of water as the only byproduct (Scheme 4). The required acetylenic 1,4-diols **4** are easily prepared, though few, albeit highly interesting, synthetic applications have been described for them in recent years,[17] including a remarkable acid-catalyzed domino reaction of highly activated tetraarylbut-2-yne-1,4-diols with 1-naphthol.[18]

So, we evaluated the feasibility of our proposed intermolecular approach by employing 1*H*-indole **3a** and symmetric

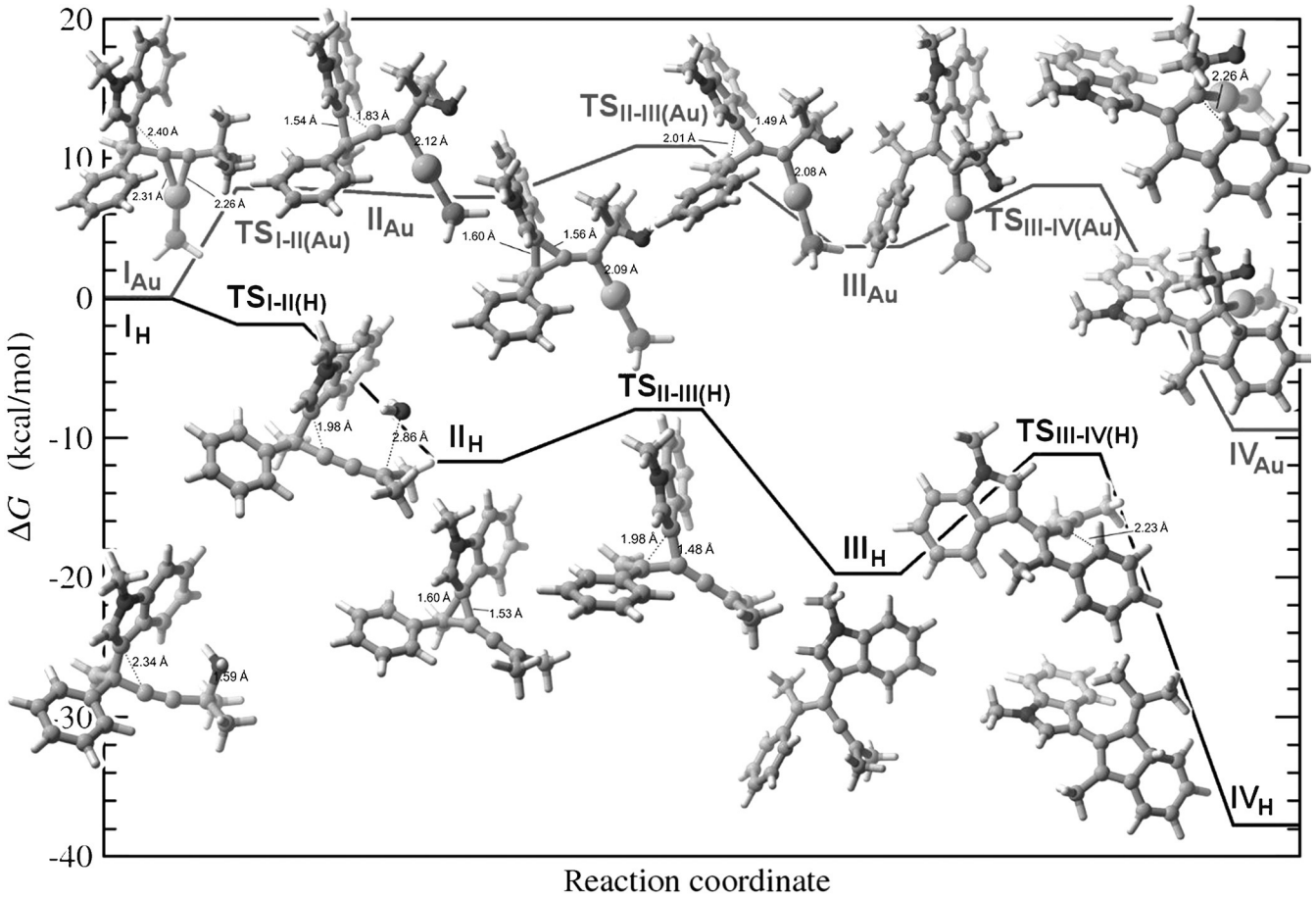
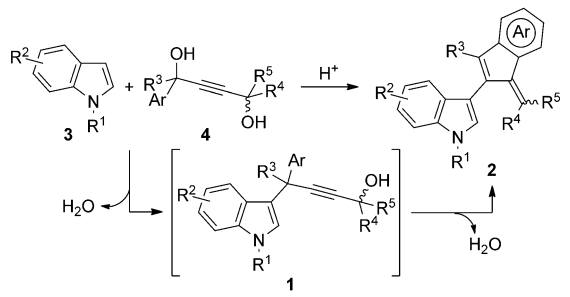


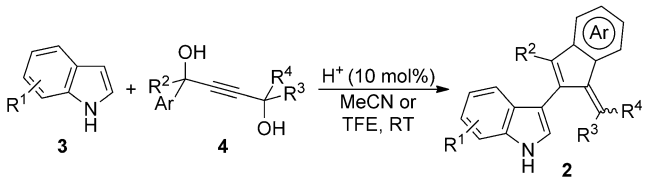
Figure 1. Schematic M06/def2-SVP (PCM, CH_2Cl_2) free energy profile for a model **1**–**2** transformation under Brønsted acid (black) and gold catalysis (red).



Scheme 4. Proposed direct synthesis of benzofulvenes **2** from indoles **3** and acetylenic 1,4-diols **4**.

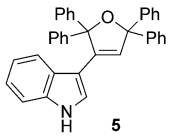
acetylenic 1,4-diol **4a** as substrate under PTSA-catalysis in TFE. Gratifyingly, a high yield of the benzofulvene derivative **2aa** was obtained (Table 2, entry 1.) We further tested this sequence with a variety of functionalized indoles **3** and symmetric diols **4a,b**. With diol **4a** mixtures of geometrical isomers of the corresponding benzofulvenes **2** were obtained in short reaction times,[15] with a small decrease in the yield observed when 5-bromoindole **3c** was used (Table 2, entries 1–3). Starting from highly activated tetraphenylbut-2-yne-1,4-diol (**4b**), we observed that its reaction with indole **3a** under PTSA-catalysis in MeCN gave rise to the expected benzofulvene **2ab** in moderate yield, along with furan derivative **5** that was isolated in 25% yield (Table 2, entry 4). Its formation shows that in this case an alternative mechanism should be at least partially operative. Based on a recent report about the reaction of 1-naphthol with diol **4b**,[18] we propose a competitive $S_{N'}$ attack of the indole to **4b** leading to an allenyl alcohol that subsequently undergoes furan formation[19] instead of a Nazarov electrocyclization.[20] The formation of the 2,5-dihydrofuran derivative **5** was suppressed by using DNBSA as catalyst, wherein **2ab** was isolated in 90% yield (Table 2, entry 5). Under these conditions, benzofulvene derivatives **2db**, **2eb**, and **2fb** were also obtained in excellent yields (Table 2, entries 6–8), even when using less nucleophilic indoles **3e**,**f**.[15]

Table 2. Synthesis of 2-indol-3-ylbenzofulvenes **2** from indoles **3** and acetylenic 1,4-diols **4**.



Entry	3	R^1	4	Ar	R^2	R^3	R^4	Met.[a]	2[b]	Yield [%][c]
1	**3a**	H	**4a**	Ph	Me	Ph	Me	A	**2aa**	87
2	**3b**	2-Me	**4a**	Ph	Me	Ph	Me	A	**2ba**	75
3	**3c**	5-Br	**4a**	Ph	Me	Ph	Me	A	**2ca**	66
4	**3a**	H	**4b**	Ph	Ph	Ph	Ph	A[d]	**2ab**	53[e]
5	**3a**	H	**4b**	Ph	Ph	Ph	Ph	B	**2ab**	90
6	**3d**	1-Me	**4b**	Ph	Ph	Ph	Ph	B	**2db**	85
7	**3e**	5-CO_2Me	**4b**	Ph	Ph	Ph	Ph	B	**2eb**	86
8	**3f**	6-NO_2	**4b**	Ph	Ph	Ph	Ph	B	**2fb**	75
9	**3a**	H	**4c**	Ph	*c*-C_3H_5	Ph	Me	A	**2ac**	90
10	**3a**	H	**4d**	4-$MeOC_6H_4$	Et	Ph	Me	A	**2ad**	95
11	**3a**	H	**4e**	Ph	Me	4-ClC_6H_4	Me	A	**2ae**	65[f]
12	**3a**	H	**4f**	Ph	*c*-C_3H_5	Ph	H	B[g]	**2af**	44
13	**3a**	H	**4g**	4-$MeOC_6H_4$	Et	Ph	H	B[g]	**2ag**	42
14	**3a**	H	**4h**	Ph	*c*-C_3H_5	Me	Me	B[g]	**2ah**	63
15	**3a**	H	**4i**	Ph	*c*-C_3H_5	–$(CH_2)_4$–		B[g]	**2ai**	70
16	**3a**	H	**4j**	Ph	Me	–$(CH_2)_5$–		B[g]	**2aj**	58

[a] Method A: PTSA, TFE; Method B: DNBSA, MeCN. [b] When $R^3 \neq R^4$, the resultant *Z*/*E* ratio was approximately 1/1, as determined by ^{1}H NMR analysis, except for **2ba** with a *Z*/*E* ratio of approximately 1/2.4. [c] Isolated yield after filtration or column chromatography. [d] Carried out in MeCN. [e] 22% of furan derivative **5** (see below) was also isolated. [f] Two benzofulvene derivatives **2ae** and **2'ae** were obtained in a ca. 1.2:1 ratio. The major one corresponds to Ar = Ph and the minor one to Ar = ClC_6H_4. Using MeCN as solvent, an approximately 2.8:1 mixture of **2ae** and **2'ae** was obtained. [g] Carried out with one (entries 12 and 13) or two (entries 14–16) subsequent additions of PTSA (10 mol%).



The diversity and applicability of this acid-catalyzed cascade cyclization for the synthesis of 2-indol-3-yl-benzofulvenes **2** starting from non-symmetric acetylenic 1,4-diols **4c–j** were also surveyed (Table 2, entries 9–16). We reasoned that the different degree of activation of both hydroxyl groups could bias the cascade sequence to selectively give rise to one benzofulvene derivative **2**. Ditertiary diols **4c–e** containing one aromatic and one alkyl group at each of the propargylic positions are the more challenging substrates. At these sites, selective reactions took place, provided that one of the hydroxyl groups was more activated than the other one, which was the case for **4c** (cyclopropyl vs. methyl) and **4d** (4-methoxyphenyl vs. phenyl) (Table 2, entries 9 and 10). However, for **4e** (4-chlorophenyl vs. phenyl) a mixture of two benzofulvene derivatives **2ae** and **2'ae** was obtained, derived from the initial attack of the indole at the two different hydroxyl groups (Table 2, entry 11). Not unexpectedly at this point, diols **4f–j**, which possess different activated alcohols (tertiary vs. secondary, or tertiary benzylic vs. tertiary) selectively gave rise to the corresponding benzofulvenes **2** in moderate to good yields (Table 2, entries 12–16). The lower yields obtained with diols **4f,g** are probably due to the lower reactivity of the secondary hydroxyl group that also leads to the need of a higher catalyst load (entries 12 and 13). Interestingly, with these non-symmetric diols **4c–j**, this cascade reaction formally involves the regioselective $S_{N'}$ addition of the indole to the less activated alkynol, leading to a tertiary allenyl alcohol that undergoes a Nazarov cyclization.

In conclusion, simple Brønsted acids have been demonstrated as useful catalysts for emulating the previously reported gold-catalyzed 1,2-indole migration of 3-propargylindoles, being the first examples of a metal-free promoted migration of a carbon-centered moiety in such propargylic substrates. In addi-

tion, DFT calculations reveal that the exothermicity of the water elimination step and the moderate energy requirements of the Nazarov-like electrocyclization are key to the occurrence of this reaction cascade under Brønsted acid catalysis. Although the mechanism is very similar to that experienced by the substrate under gold activation, replacement of gold by a Brønsted acid leads to a more favorable catalytic process. From a synthetic point of view, this methodology, one that implies the rupture and formation of carbon-carbon bonds, represents a significant addition to the armory of transformations catalyzed by Brønsted acids and provides an operationally simple and efficient manner to construct highly interesting indole-functionalized benzofulvene derivatives under metal-free conditions from easily accessible starting materials.

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Keywords: benzofulvenes · Brønsted acid · catalysis · indole migration · Nazarov cyclization

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