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Brønsted Acid-Catalyzed Enantioselective Cycloisomerization of Arylalkynes

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Dedicated with gratitude and affection to Prof. Jean-Pierre Genêt

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Abstract: This communication reports the first example of an enantioselective carbocyclization of an alkyne-containing substrate catalyzed by chiral Brønsted acids. The use of the 2-hydroxynaphthyl substituent on the alkyne as a directing group constitutes the key parameter enabling both efficient regioselective protonation of the carbon-carbon triple bond and chiral induction. The key cationic intermediate can be depicted either as a cationic vinylidene *ortho*-quinone methide or a stabilized vinyl cation. Atropoisomeric phenanthrenes derivatives were produced in high yields and good enantioselectivities under mild, metal-free reaction conditions in the presence of chiral *N*-triflylphosphoramide catalysts. The carbenic nature of the cationic intermediate was also exploited to describe an example of alkyne/alkane cycloisomerization.

Activation of carbon-carbon unsaturations by carbophilic Lewis acid appeared during the last two decades as a new synthetic tool for hydrofunctionalization transformations.[1] The metallic catalysts employed exhibit a high affinity for carbon-carbon unsaturations, activating them towards outer sphere *anti* nucleophilic attack upon complexation. Although this carbophilic reactivity was observed for a set of late transition metals, the metals exhibiting the greatest reactivity feature gold, platinum and mercury,[2] characterized by their high cost and/or their relative low availability and/or their toxicity. Considering that the development of asymmetric transformations involving this type of activation would require additional chiral and often highly expensive ligands,[3] the search for new, alternative, catalytic and metal-free methodologies that could provide the same reactivity is of upmost interest.

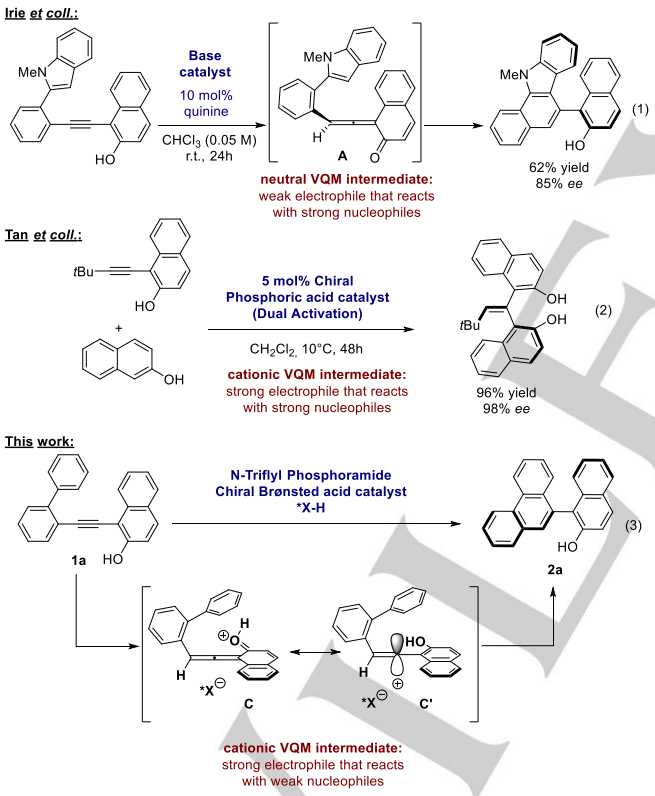
In this context, the analogy of reactivity between carbophilic transition metals and Brønsted acids (BA) has been well established,[4] and use of the latter for protonation of alkynes [5] and activation towards nucleophilic attack [6] is known for a long time and would represent an organocatalytic alternative for the development of asymmetric variants of reactions involving the electrophilic activation of alkynes. To date, most of the Brønsted acid-catalyzed cyclizations of substrates bearing an alkyne function have been reported to proceed through the intermediate generation of secondary/tertiary carbenium ions,[7] oxocarbenium ions[8] or ketiminium/ketenium ions,[9] but fewer examples deal with the direct protonation of an alkyne,[10] probably due to the long assumed instability of the corresponding vinyl cation intermediates.[5b],[11]

Since the seminal report of the use of phosphoric acids in asymmetric catalysis by Akiyama[12] and Terada[13] in 2004, the advent and development of chiral Brønsted acids has led to the emergence of a myriad of new enantioselective transformations that proceed via mechanisms involving either Brønsted acid catalysis[14] or hydrogen bond catalysis.[15] Notably, whereas reactions involving the activation of carbonyl, imines and Michael acceptors are very well described, enantioselective hydroelementations of non-activated carbon-carbon multiple bonds are less numerous, and invoke mechanisms based either on transient covalent bondings,[16] activation of nucleophilic partners[17] or more rarely direct protonations.[18] This situation is directly linked to the low stability of the corresponding carbocations that results in the formation of side-products and the lack of interaction between the conjugate base of the Brønsted acid and the carbocation that induces a weak chiral induction. So far, chiral Brønsted acids demonstrated their ability to promote the formation of stabilized allylic,[19] propargylic[20] or benzylic[21] carbocations, but generation of vinylic carbocations from alkynes and their use in asymmetric catalysis remains under-tackled.

To achieve such enantioselective transformations with alkynes, three problems must be overcome: (*i*) the lack of reactivity of alkynes towards BA that requires harsh conditions and/or the use of strong superacids to be protonated;[22] (*ii*) the lack of polarization of unactivated alkynes delivering a mixture of regioisomeric vinyl cations upon protonation;[23] (*iii*) the lack of interaction between the carbocation and the chiral anion, resulting in poor enantioinductions.[16] In particular, 1-naphthol substituted alkynyls were selected as promising substrates for this type of reaction. Indeed, whereas these versatile synthons are known to react in base-catalyzed inverse electron-demand [4+2] cycloadditions [24] and intramolecular hydroarylation of alkynes[25] *via* a neutral, axially chiral vinylidene *ortho*-quinone methide intermediate (VQM) (Scheme 1, eq. 1, intermediate **A**),[26] the group of Tan recently reported that chiral phosphoric acids could catalyze the intermolecular addition of naphthols to 1-alkynylnaphthols.[27] According to DFT calculations, the asymmetric induction results in this case from the formation of a

cationic chiral VQM intermediate via an enantioselective 1,5-proton shift, and involves the bifunctional activation of both electrophile and nucleophile reaction partners (Scheme 1, eq. 2). We thus considered that the reaction of 1-alkynylnaphthols with chiral Brønsted superacids would deliver a cationic intermediate that can be either depicted as a protonated VQM **C** or as a vinyl cation **C'** stabilized by conjugation (Scheme 1, eq. 3) exhibiting an enhanced electrophilicity that would allow the intramolecular attack of weak nucleophiles such as non-activated aromatic systems, delivering chiral atropisomeric products even in the absence of concomitant nucleophilic interaction with the catalyst by hydrogen bonding.

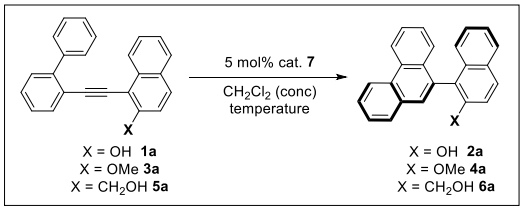
Following our recent investigations showing that the cycloisomerization of 2-alkynylbiaryls leading to phenanthrenes can be accomplished in the presence of catalytic amounts of BA,[28] we decided to study the enantioselective carbocyclization of such substrates bearing 2-naphthol as potential directing group in presence of chiral Brønsted superacids. Indeed, the reaction would lead under very mild and metal-free conditions to the corresponding atropisomeric[29] phenanthrenyl-2-naphthols after intramolecular attack by weak aryl nucleophiles.

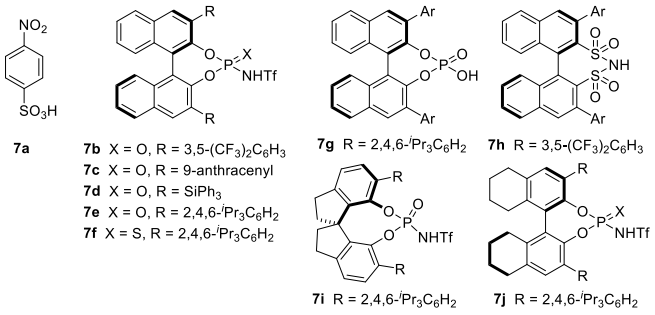


Scheme 1. Reactivity of neutral *vs* cationic VQM intermediates towards nucleophilic attack of aromatic systems

In the initial model experiments, substrate **1a** was cyclized in presence of 5 mol% of a selection of catalysts. In the presence of quinine as control experiment, no conversion of the substrate was monitored (Table 1, entry 1). As anticipated, this result showed that neutral VQM intermediates are not reactive enough towards weak nucleophiles such as a phenyl group.[30] On the contrary, employing achiral CF_3SO_3H or **7a**, the formation of phenanthrene **2a** was observed in excellent yields (Table 1, entries 2-3). As previously noted,[28] the chemo- and regioselectivity of the transformation was excellent and the formation of benzofuran resulting from the O-attack of the naphthol hydroxyl on the alkyne was not observed. The reactivity observed with catalyst **7a** was rather exciting, as its acidity was in the pKa range of known chiral Brønsted superacids[31] such as *N*-triflylphosphoramide ($pKa_{(MeCN)}$ ~ 6).[32] To test this hypothesis, the cycloisomerization of naphthol **1a** was engaged in the presence of various chiral Brønsted acids. Using 5 mol% of catalyst **7b** in CH_2Cl_2 at room temperature, the formation of **2a** was observed in 97% yield with an encouraging 62.5:37.5 e.r (Table 1, entry 4). Modifying the 3,3-disubstitution pattern of the 2,2-binaphtol moiety of the catalyst resulted in diminished activities and enantioselectivities for **7c** and **7d**, whereas a significant improvement of selectivity was observed with **7e**. Indeed, despite delivering **2a** in a low yield of 18%, a promising e.r of 82.5:17.5 was measured (Table 1, entries 5-7). Despite a lower postulated pKa, catalyst **7f**[33] exhibited no activity under our standard reaction conditions, whereas phosphoric acid **7g** and disulfonimide[34] **7h** showed no reactivity (Table 1, entries 8-10). This demonstrates that aryl-substituted alkynylnaphthols **1** are weaker Lewis bases compared to the tertiobutyl analogues used by the group of Tan (Scheme 2, eq. 2).[27] The use of catalysts with other diol backbones such as **7i** and **7j** was not beneficial in terms of both activity and enantioselectivity (Table 1, entries 11,12). Selecting catalyst **7e**, a screening of solvent, temperature, catalyst loading and concentration was performed (see supporting information for details). Increasing the concentration to 0.25 M improved both the yield and the enantioselectivity of the cycloisomerization product (Table 1, entry 14). Lowering the temperature to -10°C resulted in a complete loss of catalytic activity (Table 1, entry 16). As expected, the use of the 2-naphthol moiety as a directing group turned to be mandatory to reach high activity and selectivity. Indeed, employing substrate **3a** (where the hydroxyl was substituted by a methoxy group) produced racemic cyclized phenanthrene **4a** in a very low yield (Table 1, entry 17). In the same way, no cyclization to **6a** was observed in the presence of **7a** when using substrate **5a**, which possessed a benzylic alcohol function instead of the hydroxyl group (Table 1, entry 18). Thus, stabilization of the vinyl cation by conjugation with the aryl substituent or creation of hydrogen bonding between the catalyst and the substituent are not sufficient factors to observe an enantioselective cycloisomerization, the combination of the two factors is needed to enable the chiral induction.

Table 1. Optimization of reaction conditions.[a]



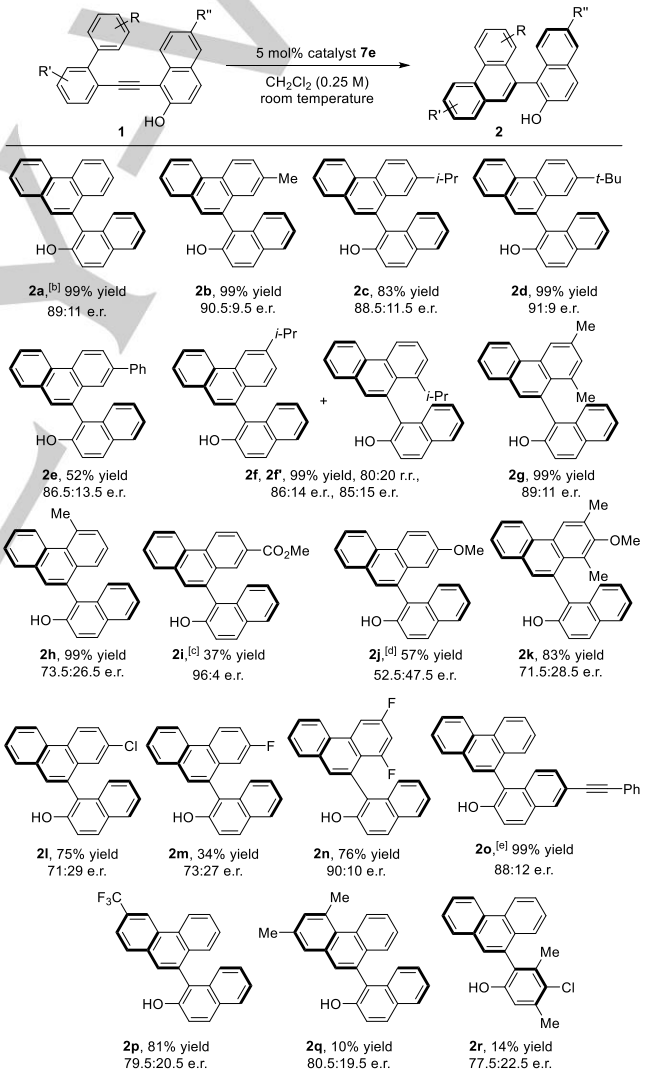


Entry[a]	Catalyst	Conc.	Yield[b]	e.r.[c]
1	quinine	0.05 M	0	-
2	CF_3SO_3H	0.05 M	99	-
3	**7a**	0.05 M	99	-
4	**(*R*)-7b**	0.05 M	99	62.5:37.5
5	**(*R*)-7c**	0.05 M	71	54:46
6	**(*R*)-7d**	0.25 M	4	52.5:47.5
7	**(*R*)-7e**	0.05 M	18	82.5:17.5
8	**(*R*)-7f**	0.05 M	traces	n. d.
9	**(*R*)-7g**	0.05 M	0	-
10	**(*R*)-7h**	0.05 M	traces	n. d.
11	**(*S*)-7i**	0.05 M	8	32:68
12	**(*R*)-7j**	0.05 M	20	67:33
13	**(*R*)-7e**	0.1 M	73	81:19
14	**(*R*)-7e**	0.25 M	90	86:14
15	**(*R*)-7e**	0.5 M	84	76.5:23.5
16[d]	**(*R*)-7e**	0.05 M	0	-
17[e,f]	**(*R*)-7e**	0.25 M	4	50:50
18[g]	**7a**	0.25 M	0	-

[a] 0.1 mmol of **1a** in CH_2Cl_2 at rt. [b] yields determined by ^{1}H NMR. [c] (*R*):(S) enantiomeric ratios determined by chiral HPLC. Configuration of the *R*-enantiomer determined by circular dichroism (see SI). [d] reaction performed at -10°C. [e] substrate **3a** used. [f] 10 mol% of catalyst used [g] substrate **5a** used. conc: concentration.

With these optimized conditions in hand, we next examined the scope of the transformation (Table 2). The reaction proceeded well with a variety of alkyl and aryl substituents on the para position of the aryl nucleophile (**2b**-**2e**), furnishing atropisomeric products in good to excellent yields (52-99%) and high enantioselectivities (86.5:13.5 to 91:9 e.r.). The reaction of a substrate bearing an isopropyl substituent at the meta position of the aryl nucleophile delivered a mixture of regioisomers **2f** and **2f'** in a 4:1 ratio with good enantioselectivities (86:14 and 85:15 e.r., respectively). The 3,5-disubstitution was also well tolerated (**2g**). In contrast, with an aryl nucleophile possessing an ortho substituent, a significant drop of enantioselectivity was observed (**2h**). Interestingly, the presence of an electron-withdrawing substituent on the nucleophilic ring resulted in a diminished conversion but an excellent enantioselectivity (**2i**, 96:4 e.r.). In contrast, the presence of electron-donating substituents, such as a 4-methoxy group, resulted in diminished enantioselectivities (**2j-k**). Halogen substituents were well tolerated and resulted in cyclized products in high yields and moderate (**2l-m**) to good (**2n**) enantioselectivities (up to 90:10 e.r.).

Table 2. Substrate scope.[a]

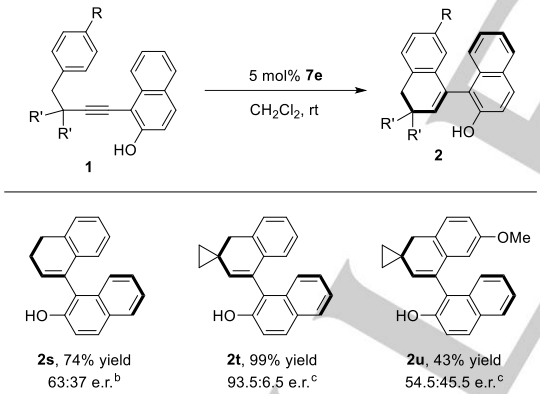


[a] The reaction was performed with 0.1 mmol of substrate **1**, 5 mol% of catalyst **7e** at r.t. in CH_2Cl_2 (0.25 M) for 70h. [b] Reaction run at 6°C using 10 mol% of catalyst **7e**. [c] Reaction run for 100h, 40% conversion. [d] Reaction run for 24h. [e] Reaction run at 40°C.

The introduction of a substituent on the naphthol ring was also investigated. Remarkably, in the case of substrate **1o** possessing two alkyne functions on the naphthol moiety, the electrophilic activation occurred selectively on the carbon-carbon triple bond placed on position 1. The substitution on the internal aryl ring was also studied and moderate enantioselectivities were obtained both for the 4-trifluoromethyl and the 3,5-dimethyl substitution patterns. Finally, the use of a substituted phenol as a directing group was also evaluated: the cycloisomerization delivered product **2r** in low yield (14%) and enantioselectivity (77.5:22.5 e. r.). This result obtained with unoptimized conditions/catalytic system already demonstrates that this new mode of activation of alkynes using Brønsted acid catalysts is not restricted to 2-naphthol directing groups.

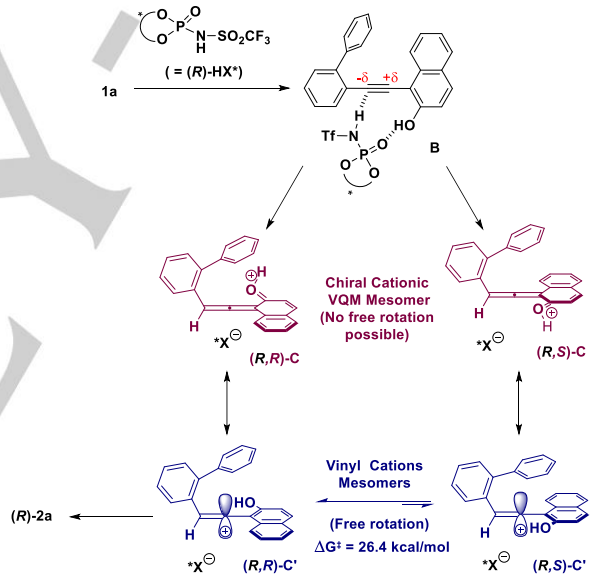
We also investigated the cycloisomerization of alkyl-substituted alkyne substrates (Table 3). The cyclization of substrate **1s** proceeded smoothly to deliver the atropisomeric dihydronaphtalene **2s** in good yield and a disappointing 26% ee. Considering the results obtained in the intermolecular hydroarylation of alkynes with the tert-butyl substituent,[27] we studied the reactivity of a substrate bearing a cyclopropyl group at the propargylic position: the tricycle **2t** was obtained with an excellent yield and a very good enantioselectivity. Once more, the nucleophilicity of the aryl nucleophile has a strong influence on the selectivity: substrate **1u** bearing a 4-methoxyphenyl substituent reacts in the presence of **7e** to give the product **2u** with a very low ee.

Table 3. Cycloisomerization of alkyl-substituted alkynes.[a]



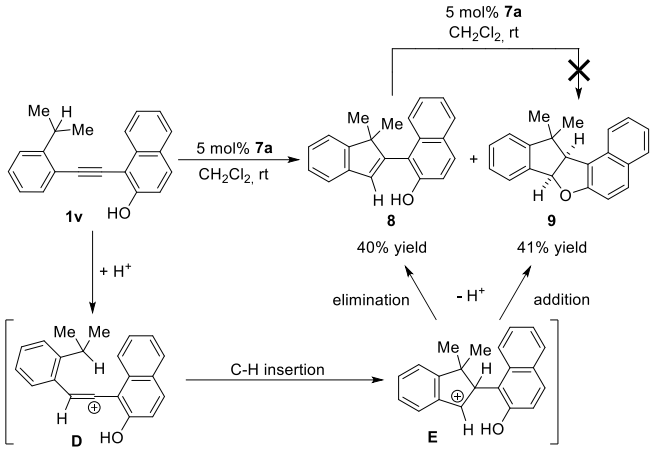
[a] The reaction was performed with 0.1 mmol of substrate **1**, 5 mol% of catalyst **7e** at r.t. in CH_2Cl_2 for 40h. [b] [**1s**] = 0.1 M. [c] [**1t-u**] = 0.25 M.

In accordance with these results, a postulated mechanism was suggested in Scheme 2 for the reaction of **1a** in the presence of BA catalysts. At the initial stage of the catalytic cycle, the presence of the naphthol directing group both increases the basicity of the alkyne function and polarizes the carbon-carbon triple bond leading to a regioselective protonation that delivers an intermediate that can be viewed either as (*i*) a protonated VQM[27, 35] **C** or (*ii*) a stabilized vinyl cation[36] **C'** that can react as a stronger electrophile compared to its neutral counterpart **A** (Scheme 1). The origin of the enantioselectivity observed with a chiral catalyst may result from a chiral protonation step delivering a stabilized single pseudo diastereoisomer **C** that cyclizes upon attack of the nucleophilic aryl substituent.[27] Alternatively, a non-selective protonation step may result in the formation of two pseudo diastereoisomeric ion pairs **C'** in equilibrium upon rotation along the naphthol/vinyl cation axis. In this case, the enantioinduction would result from a nucleophilic attack of the aryl group on the more stable of these two intermediates. The latter hypothesis is backed up by the relationship linking reaction rate and enantioselectivity with nucleophilic strength, as demonstrated by the trend observed with substrates **1j**, **1a** and **1i** bearing –OMe, -H and $–CO_2Me$ groups at the para position of the aryl nucleophile. Indeed, full conversion was achieved for the first substrate in less than 24h, whereas 40h was needed for the second one and only 40% conversion of **1j** was obtained after 100h. Concomitantly, the enantiomeric excesses increased from 5%, to 80% and 92%, respectively. Interestingly, the same trend was also observed with substrates **2t** and **2u**, which are devoid of undesired electronic effects onto the alkyne originating from the substitution of the nucleophilic aryl moiety (87% e.e. for $-C_6H_5$ *vs* 9% e.e for $-C_6H_4-OCH_3$, respectively).



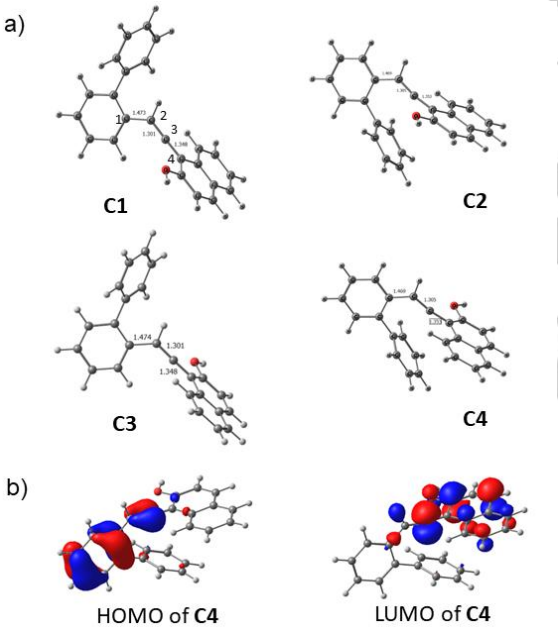
Scheme 2. Proposed mechanism of the catalytic asymmetric carbocycloisomerization of **1a** catalyzed by N-triflyl phosphoramide Brønsted acids.

To assess the vinyl cation character of intermediate **C/C'**, we decided to investigate its ability to promote C-H insertion. Indeed, as experimentally observed[5] and then rationalized by DFT studies,[37] vinyl cations possess a carbenic reactivity[38] resulting in their insertion into inert C-H bonds. We thus prepared substrate **1v** bearing an isopropyl chain and submitted it to cycloisomerization in the presence of 5 mol% of Brønsted acid catalyst **7a** as model catalyst (Scheme 3). Interestingly, the reaction delivered indene **8** and polycycle **9** in 40% and 41%, respectively.



Scheme 3. Brønsted acid-catalyzed alkyne-alkane cycloisomerization.

The postulated mechanism involves the protonation of the carbon-carbon triple bond to give the stabilized vinyl cation **D**. Further intramolecular C-H insertion at the benzylic position leads to the formation of carbocation **E,** that can react either *via* elimination of a proton to give indene **8**, or via O-addition of the naphthol hydroxyl to give **9**. Remarkably, when indene **8** was treated in the presence of Brønsted acid **7a**, no formation of **9** was observed.



Scheme 4. a) Four rotamers found on the PES (main distances in Ångström), b) HOMO and LUMO of rotamer C4.

DFT calculations on **1a** showed a favored protonation on the β-ethylenic carbon of the naphthol (~6 kcal/mol) compared to the α one, which was in agreement with the experimental observations. Four cationic rotamers were found on the potential energy surface (PES), and were calculated to be almost isoenergetic. They corresponded to the various possibilities of rotation of the carbon 1 – carbon 2 bond (rotamers **C1** and **C2**) and of the carbon 3 - carbon 4 bond (**C3** and **C4**) (Scheme 4, a). The barrier of rotation between **C1** and **C3** corresponds to a $\Delta G^{\ddagger}$ of 26.4 kcal/mol, showing that cationic VQM **C** exhibit a low configurational stability at room temperature on the time scale of the reaction, and that isomerization can occurs through rotation around the vinyl cation/naphthol axis of mesomer **C'**. The representation of the molecular orbitals (depicted in scheme 4, b for rotamer **C4** as an example) clearly shows a vacant p orbital (corresponding to the LUMO) strongly localized on the C3 central carbon and orthogonal to a π bond (corresponding to the HOMO). Such description is fitting perfectly with a carbenoïd structure, in accordance to the experimental results observed in C-H activation reactions (Scheme 3)

In conclusion, we have developed a catalytic asymmetric carbocyclization of 2-alkynylbiphenyls to atropisomeric phenanthrenes catalyzed by a Brønsted superacid catalyst. This method, based on the use of the 2-naphtholyl substituent, provides a metal-free alternative to the carbophilic late transition metals Lewis acids for cycloisomerization involving the electrophilic activation of alkynes as the initial step of the catalytic cycle. Mechanistic studies showed that the carbenic nature of the stabilized vinyl cation intermediate can be used to initiate an alkyne/alkane cycloisomerization reaction. Current studies are underway in our group to optimize the steric and electronic features for both the directing group and the catalyst in order to obtain higher levels of selectivity. The scope of nucleophiles that can be applied in such transformations is also under evaluation and results will be reported in due course.

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Keywords: asymmetric catalysis • Brønsted acid • cycloisomerization • atropoisomer • alkyne

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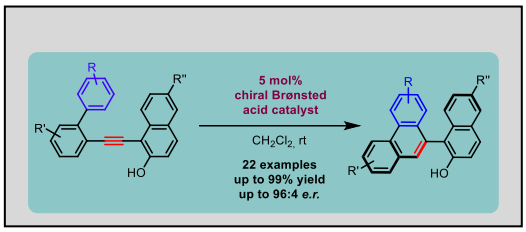

Chiral *N*-triflyl phosphoramides catalyze the asymmetric carbocyclization of alkynyl aryl substrates. The introduction of a 2-naphtolyl substituant on the alkyne enables the chemo- and regioselective protonation of alkynes and delivers atropisomeric phenanthrenes and dihydronaphtalenes enantioselectively.