

Brønsted Acid-Catalysed Hydroarylation of Unactivated Alkynes in Fluoroalcohol–Hydrocarbon Biphasic System: Construction of Phenanthrene Frameworks

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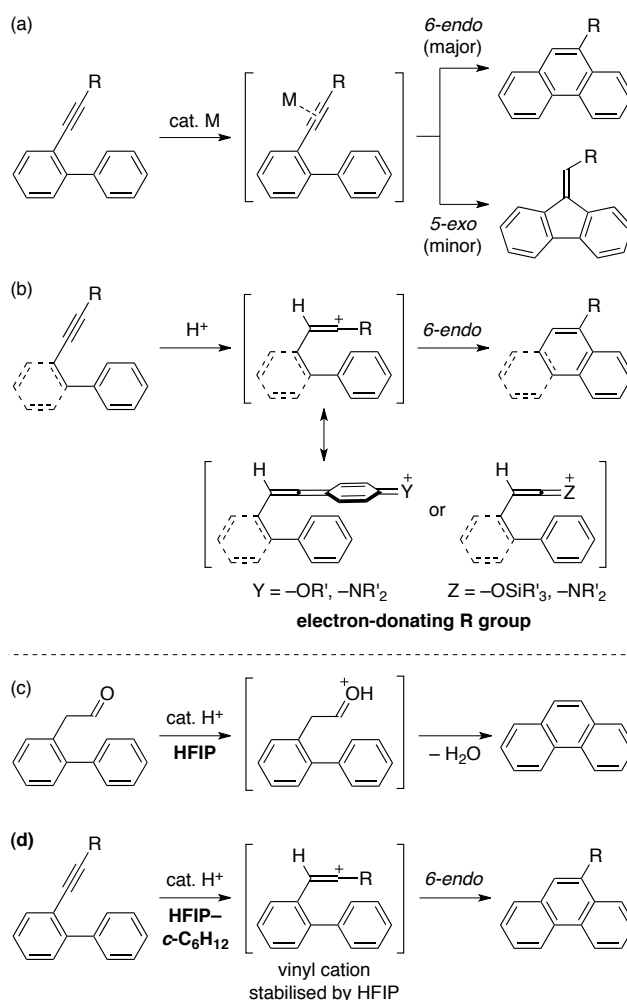
Ikko Takahashi, Takeshi Fujita, Noriaki Shoji and Junji Ichikawa*

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Transition metal-free hydroarylation of unactivated alkynes was achieved by combining a Brønsted acid catalyst and a two-phase solvent system consisting of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) and cyclohexane. This protocol is applicable to a wide variety of 2-alkynylbiaryls and leads to the synthesis of substituted phenanthrenes via 6-*endo*-selective ring closure. The biphasic system achieves highly efficient ring closure by appropriate separation of cationic intermediates from neutral compounds. The vinylic carbocation intermediates might be stabilised in the HFIP phase, while the substrates and products are distributed in the cyclohexane phase to suppress intermolecular side reactions.

Electrophilic activation of alkynes has occupied a significant position in synthetic organic chemistry, because it allows carbon–carbon and carbon–heteroatom bond formation at alkyne moieties.¹ Particularly, intramolecular hydroarylation of alkynes via electrophilic activation has been widely studied as one of the most effective methods for constructing carbocycles, including polycyclic aromatic hydrocarbons (PAHs).² Hydroarylation of 2-alkynylbiaryls has been conducted mostly via electrophilic activation by transition metal catalysts,³ which yields phenanthrenes via 6-*endo* cyclisation or dibenzofulvenes via 5-*exo* cyclisation (Scheme 1a).⁴ To date, however, Brønsted acid-mediated hydroarylation has shown limited success with an electron-donating group and/or an excess amount of acid,^{3m,5,6} probably because unstable vinyl cation intermediates are required to be generated via protonation of alkynes.^{7,8} For example, Swager and Chalifoux reported Brønsted acid-mediated hydroarylation of alkynes by using an excess amount of Brønsted acid and placing aryl groups with electron-donating alkoxy or amino substituents (Y),⁵ which stabilised the vinyl cation intermediates (Scheme 1b). Kozmin and Hsung succeeded in Brønsted acid-catalysed carbocyclisation of alkynes, which again required installing

electron-donating siloxy and amino substituents (Z), respectively, adjacent to the vinyl cation centre (Scheme 1b).⁹



Scheme 1 Cyclisation via electrophilic activation. (a) Transition metal-catalysed hydroarylation of alkynes. (b) Acid-mediated (or -catalysed) hydroarylation of alkynes bearing an electron-donating group. (c) Acid-catalysed dehydrative cycloaromatisation of carbonyl compounds. (d) Acid-catalysed hydroarylation of alkynes (this work).

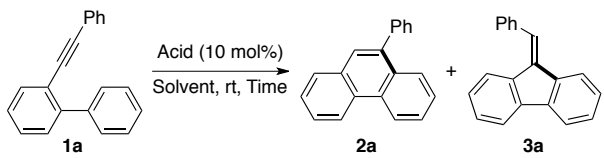
Division of Chemistry, Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan. E-mail: junji@chem.tsukuba.ac.jp

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Recently, we demonstrated Brønsted acid-catalysed dehydrative cycloaromatisation of carbonyl compounds and their analogues by using 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a solvent,¹⁰ which exhibits a cation-stabilising effect (Scheme 1c).^{11,12,13} The key to success in this reaction was to stabilise oxocarbenium ion intermediates in HFIP. We thus assumed that HFIP could stabilise even more unstable vinyl cations in a similar manner and enable Brønsted acid-catalysed hydroarylation of *unactivated* alkynes. By careful examination, the use of cyclohexane as a co-solvent with HFIP, which forms a biphasic solvent system, was found to be the best system for 6-*endo*-selective hydroarylation of 2-alkynylbiaryls (Scheme 1d). This protocol thus offers one of the most simple and atom-economical approaches to phenacenes.¹⁴

The combination of trifluoromethanesulfonic acid (TfOH) as a catalyst and HFIP as a solvent,¹⁵ which was the most effective for dehydrative cycloaromatisation of carbonyl compounds,¹⁰ was initially tested for intramolecular hydroarylation of 2-(phenylethynyl)biphenyl (**1a**) as an unactivated alkyne. Hydroarylation of **1a** proceeded to afford 6-*endo* cyclisation product **2a** and 5-*exo* cyclisation product **3a** in 53% and 7% yields, respectively (Table 1, Entry 1). To improve the yield of **2a**, several other Brønsted acids, such as methanesulfonic acid (MsOH), tetrafluoroboric acid (HBF₄), 10-camphorsulfonic acid (CSA), and *p*-toluenesulfonic acid monohydrate (TsOH·H₂O), were examined as catalysts, affording **2a** in 44%–54% yields (Table 1, Entries 2–5). Since cheap and easily handled TsOH·H₂O gave the best result, several solvents were screened in the presence of a catalytic amount of TsOH·H₂O (Table 1, Entries 6–9). As expected, HFIP was found to be the most effective among the solvents examined. To suppress side reactions, biphasic systems consisting of HFIP and aliphatic hydrocarbons, such as hexane, decalin, and cyclohexane (*c*-C₆H₁₂), were employed in the hydroarylation (Table 1, Entries 10–12, *vide infra*).¹⁶ When using *c*-C₆H₁₂ as a co-solvent, 6-*endo* product **2a** was obtained in 85% yield with high selectivity (Table 1, Entry 12). Furthermore, this reaction proceeded smoothly even in air (Table 1, Entry 13).

Table 1 Screening of conditions for hydroarylation of **1a**



Entry	Acid	Solvent	Time (h)	2a (%) ^a	3a (%) ^a
1	TfOH	HFIP	9	53	7
2	MsOH	HFIP	9	47	7
3	HBF ₄ ^b	HFIP	9	48	9
4	CSA	HFIP	9	44	5
5	TsOH·H ₂ O	HFIP	9	54	5
6	TsOH·H ₂ O	Hexane	60	N.D. ^c	N.D. ^c
7	TsOH·H ₂ O	CH ₂ Cl ₂	60	trace	N.D. ^c
8	TsOH·H ₂ O	CH ₃ NO ₂	60	1	N.D. ^c
9	TsOH·H ₂ O	<i>i</i> -PrOH	60	N.D. ^c	N.D. ^c

10	TsOH·H ₂ O	HFIP–Hexane (1/2)	9	78	9
11	TsOH·H ₂ O	HFIP–Decalin (1/2)	9	67	11
12	TsOH·H ₂ O	HFIP– <i>c</i> -C ₆ H ₁₂ (1/2)	9	85	13
13 ^d	TsOH·H ₂ O	HFIP– <i>c</i> -C ₆ H ₁₂ (1/2)	9	85	11

^a Yield was determined by ¹H NMR measurement using CH₂Br₂ as an internal standard. ^b HBF₄ was used as an aqueous solution (48 wt%). ^c N.D. = Not detected. ^d Reaction was conducted in air.

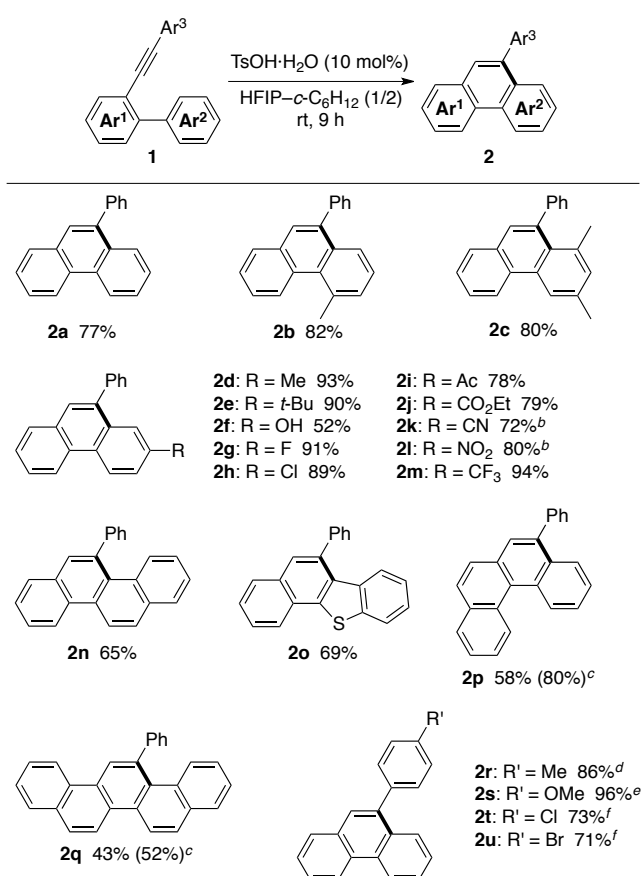
The optimal conditions obtained above for synthesising **2a** from **1a** were then successfully applied to the hydroarylation of (phenylethynyl)biaryls **1** bearing various substituents (Table 2). Hydroarylation of (phenylethynyl)biaryls **1b–1e** bearing electron-donating alkyl groups on the nucleophilic aryl group proceeded smoothly to afford the corresponding substituted phenanthrenes **2b–2e** in high yields. Despite the acidic conditions, the *tert*-butyl group was neither removed nor rearranged through the retro-Friedel–Crafts alkylation (**2e**). Hydroxy, fluorine, and chlorine substituents were tolerated in the reaction, providing phenanthrenes **2f–2h**. (Phenylethynyl)biaryls **1i–1m** bearing electron-withdrawing acetyl, ethoxycarbonyl, cyano, nitro, and trifluoromethyl groups also underwent successful hydroarylation. It is noteworthy that cyclisation of substrates **1k–1m** bearing strongly electron-withdrawing groups proceeded in high to excellent yields. Furthermore, tetracyclic benzenoids such as chrysene **2n** ([4]phenacene), naphtho[1,2-*b*]benzothiophene **2o**, and [4]helicene **2p** were synthesised in high yields. Additionally, this method provided substituted picene **2q** ([5]phenacene), which was expected to serve as an organic semiconductor.¹⁷ Installation of electron-donating methyl and methoxy groups on the benzene ring on the side opposite to the biphenyl group across the C–C triple bonds accelerated the reaction to afford the corresponding 9-arylphenanthrenes **2r** and **2s**, respectively, in high yields, because the substituents could effectively stabilise the intermediary vinyl cations. Furthermore, (arylethynyl)biphenyls **1t** and **1u** bearing electron-withdrawing chlorine and bromine substituents also afforded phenanthrenes **2t** and **2u** in 73% and 71% yields, respectively. These results suggested that even electron-withdrawing halogen substituents did not prohibit the formation of vinyl cations adjacent to the haloaryl groups.

To determine the effect of the biphasic solvent system, the distribution ratios of substances between fluoroalcohol and hydrocarbon phases were examined. The distribution ratios of 2-(phenylethynyl)biphenyl (**1a**), 9-phenylphenanthrene (**2a**), and TsOH between HFIP and *c*-C₆H₁₂ were independently determined by ¹H NMR measurement of the *c*-C₆H₁₂ layer (Table 3). As listed in Table 3, 88% of the substrate alkyne **1a** was dissolved in *c*-C₆H₁₂, while 12% of **1a** was dissolved in HFIP. Phenanthrene (**2a**) and TsOH were completely separated in the *c*-C₆H₁₂ and HFIP layers, respectively.

Based on the observations described above, plausible behaviours of alkynes **1**, phenacenes **2**, and TsOH during hydroarylation in the fluoroalcohol and hydrocarbon biphasic

solvent system are shown in Scheme 2. Alkynes **1** and phenacenes **2** were mainly dissolved in the *c*-C₆H₁₂ phase, while TsOH was dissolved in the HFIP phase. A portion of alkynes **1** was protonated by TsOH in the HFIP phase to generate vinyl cation intermediates **A**, which settled in the HFIP phase.¹⁸ Subsequent intramolecular cationic cyclisation of vinyl cations **A** proceeded in a 6-*endo* fashion in the HFIP phase to afford phenacenes **2** as major products, which moved from the HFIP phase into the *c*-C₆H₁₂ phase. Thus, the biphasic system successfully separated alkynes **1** and phenacenes **2** from the vinyl cations to prevent undesirable intermolecular reactions.

Table 2 Synthesis of PAHs via hydroarylation of **1**^a

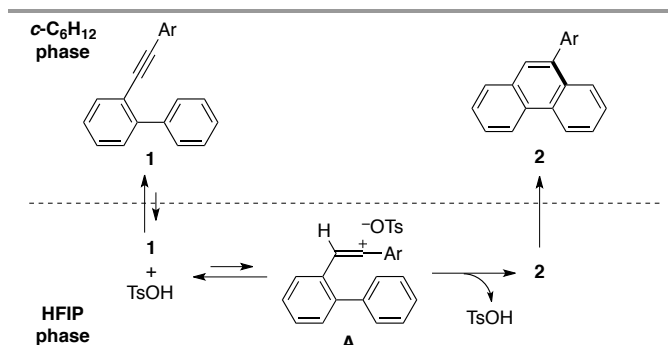


^a Reaction conditions: alkyne **1** (0.3 mmol), TsOH·H₂O (10 mol%), HFIP (1.5 mL), and *c*-C₆H₁₂ (3.0 mL). Isolated yield. Yield determined by ¹H NMR measurement using CH₂Br₂ as an internal standard is given in parentheses. ^b TfOH (10 mol%) was used instead of TsOH·H₂O. ^c Gel permeation chromatography (GPC) was performed for purification. ^d rt, 3 h. ^e rt, 1 h. ^f TsOH·H₂O (20 mol%), 60 °C, 3 h.

Table 3 Distribution Ratios of **1a**, TsOH, and **2a** between *c*-C₆H₁₂ and HFIP

	1a (%)	TsOH ^a (%)	2a (%)
<i>c</i> -C ₆ H ₁₂ layer	88 ^b	N.D. ^{b,c}	>99 ^b
HFIP layer	12 ^d	>99 ^d	<1 ^d

^a TsOH was added to the biphasic system as TsOH·H₂O. ^b Distribution ratio was determined by ¹H NMR measurement using CH₂Br₂ as an internal standard. ^c N.D. = Not detected. ^d Distribution ratio in the HFIP layer was calculated based on that in the *c*-C₆H₁₂ layer.



Scheme 2 Proposed behaviour of substances in HFIP–cyclohexane biphasic system.

In addition, we successfully recycled the HFIP solution of TsOH. After the reaction, the *c*-C₆H₁₂ layer containing **2a** and **3a** was separated from the HFIP layer containing TsOH, which was repeatedly reused by adding a new *c*-C₆H₁₂ solution of **1a**. When sequential reactions using the same HFIP layer containing TsOH were conducted five times with stirring under the same conditions, the corresponding phenanthrene **2a** and fulvene **3a** were obtained in 96% (1st cycle), 97% (2nd cycle), 94% (3rd cycle), 92% (4th cycle), and 91% (5th cycle) total yields (Table 4). Thus, the reactivity of the HFIP solution of TsOH·H₂O was confirmed to be maintained over five cycles, which fully demonstrated the feasibility of this procedure.¹⁹

Table 4 Recycling of HFIP solution containing TsOH for sequential hydroarylation^a

	Total yield of 2a and 3a (%) ^b	2a/3a ratio ^c
1st	96	92/8
2nd	97	92/8
3rd	94	91/9
4th	92	90/10
5th	91	90/10

^a Reaction conditions (1st cycle): alkyne **1a** (0.3 mmol), TsOH·H₂O (10 mol%), HFIP (1.5 mL), and *c*-C₆H₁₂ (3.0 mL) at room temperature for 9 h. Reaction conditions (2nd–5th cycles): alkyne **1a** (0.3 mmol), TsOH in HFIP (ca. 1.5 mL), and *c*-C₆H₁₂ (3.0 mL) at room temperature for 9 h. ^b Yield was determined by ¹H NMR measurement using CH₂Br₂ as an internal standard. ^c Ratio was determined by ¹H NMR measurement.

In summary, we have developed an efficient and atom-economical method for synthesising phenacenes through TsOH-catalysed intramolecular hydroarylation of *unactivated* alkynes with a wide variety of substituents. This reaction requires only a catalytic amount of Brønsted acid. Therefore, (i) there are no metal impurities in the phenacene products; (ii) quenching and workup are dramatically simplified, compared to conventional methods employing an excess amount of Brønsted acid. The two-phase *c*-C₆H₁₂/HFIP solvent system promoted the catalytic reaction via the vinyl cation intermediate and suppressed side reactions, which enabled recycling of expensive HFIP including the acid catalyst. Thus, we discovered the excellent potential of the two-phase solvent system containing HFIP.

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