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Aminium cation-radical catalysed selective hydration of (*E*)-aryl enynes†

Marie-Claire Giel,[a] Andrew S. Barrow,[a] Christopher J. Smedley,[a] William Lewis[b] and John E. Moses*[cd]

The hydration of carbon–carbon triple bonds is an important and atom economic synthetic transformation. Herein, we report a mild and selective method for the catalytic Markovnikov hydration of (*E*)-aryl enynes to the corresponding enones, mediated through the bench-stable aminium salt, tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA). The chemoselective and diastereoselective method proceeds under neutral metal-free conditions, delivering excellent product yields from terminal and internal alkyne units. The synthesis of biologically important (*E*)-3-styrylisocoumarins, including a formal synthesis of the natural product achlisocoumarin III, demonstrates the utility of this novel transformation.

Alkyne hydration[1] is an important, atom economical[2] reaction with enormous significance in organic synthesis. First reported over 150 years ago, classical hydration reactions require strong protic acids such as H_2SO_4 to overcome the activation barriers of the otherwise exergonic process.[3]

Mechanistically, the hydration of a terminal alkyne follows either a Markovnikov addition pathway to give the ketone or the anti-Markovnikov route to an aldehyde; non-symmetrical internal alkynes, on the other hand, can lead to mixtures of both possible ketone regioisomers (Fig. 1). The discovery by Kucherov in 1881[4] of the rate acceleration of alkyne hydration by mercury(II) salts had a significant impact in synthetic[1] and industrial applications.[5] However, the use of toxic mercury salts is undesirable, particularly for large-scale applications, and several environmentally friendlier protocols have emerged.[1,6–16]

Herein, we report a mild, atom economical, and metal-free protocol for the hydration of aryl enynes using aminium ion catalysis. The (*E*)-enyne selective method delivers the Markovnikov hydration products with (*E*)-configuration in excellent yield.

The selective hydration of enynes to enones presents a significant challenge due to competing alkene hydration potential.[15] The few examples that have been reported require either strong Brønsted acids[15a] or mercury(II) salt catalysts.[17] During our work on single-electron transfer reactions,[18] we made an observation that led us to envisage a new approach for enyne hydration mediated through a cation-radical initiated pathway. In the presence of the aminium cation-radical salt tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA; Ledwith–Weitz salt),[19] (*E*)-1-(but-1-en-3-yn-1-yl)-4-methoxybenzene (**1**) underwent hydration to the aryl enone **2** in trace quantities (Table 1). The following optimised protocol was subsequently developed: [0.1 eq. of TBPA, stirring for 2 h at 40 °C in reagent grade acetone that had been purged with nitrogen gas] that increased the overall yield of the enone **2** to 74% (Table 1, entry 5). A trace quantity of product **3**, thought to arise through an aldol condensation process between **2** and acetone was also observed.

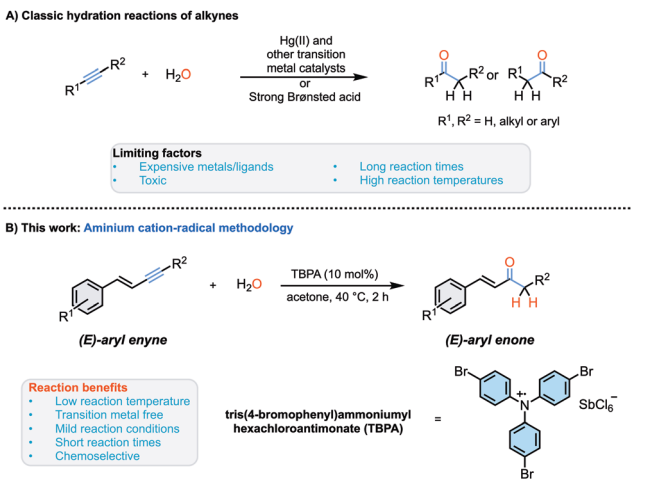

Fig. 1 (A) Classical Brønsted acid and Kucherov-type alkyne hydration protocols; (B) this work: TBPA aminium cation-radical mediated hydration of (*E*)-aryl enynes.

[a] *La Trobe Institute for Molecular Science, Melbourne, VIC, 3086, Australia*
[b] *School of Chemistry, The University of Sydney, Sydney, NSW, 2006, Australia*
[c] *Cancer Center, Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY, 11724, USA. E-mail: moses@cshl.edu*
[d] *Department of Chemistry, Stony Brook University, NY, 11794, USA*

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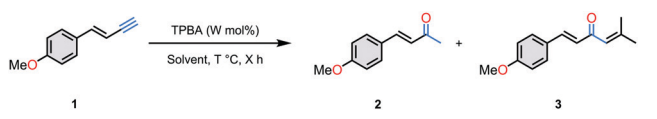
Table 1 Optimisation of aminium cation radical-mediated enyne hydration[a]



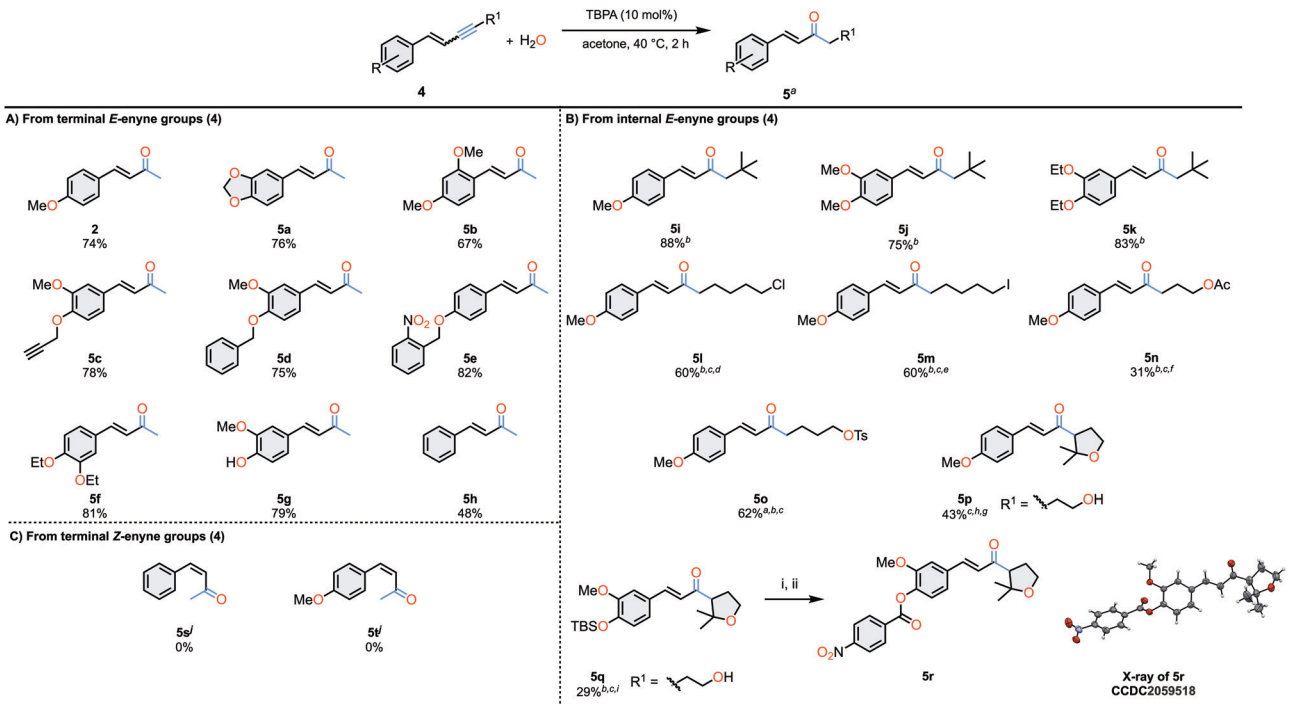
Entry	Solvent	*W* (mol%)	Temperature (*T*)/°C	Time (*X*)/h	Yield (%) of **2**	Yield (%) of **3**
1	CH_2Cl_2	10	0	1	Trace	0
2	CH_2Cl_2	10	40	1	Trace	0
3	THF	10	40	2	0	0
4	MeCN	10	40	2	14	0
5	**Acetone**	**10**	**40**	**2**	**74**	**Trace**

[a] The reactions were performed on a 0.20 mmol scale of enyne 1; isolated yields.

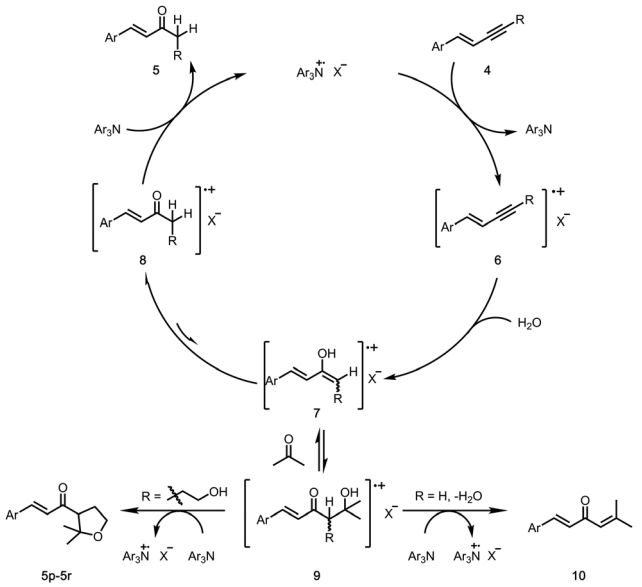
Interestingly, when high purity acetone[20] was used as the solvent, the yield of **2** was significantly reduced (28%). However, the addition of 1.0 equivalent of water to the high purity acetone resulted in 78% yield of the product (*cf.* 74% yield using reagent grade "wet" acetone). Gradually increasing the concentration of water to 5.0 equivalents led to a steady reduction in the yield (7%) (see ESI,† T1). TBPA is known to be degraded by water to tris (4-bromophenyl)amine, which itself, when used in place of TBPA, was inactive (see ESI†).[21,22] When the enyne **1** was taken into high purity acetone followed by the addition of 1.0 eq. of $H_2{}^{18}O$ and TBPA catalyst, the ^{18}O labelled hydration product was detected by electrospray ionization (ESI) mass spectrometry, suggesting water is the source of the incorporated oxygen (see ESI†).

The method performs well with both terminal and internal (*E*)-aryl enynes and is tolerant of several functional groups, including Cl (**4l**), I (**4m**), OAc (**4n**), OTs (**4o**); each giving consistently high yields of the aryl enone products (**5l–5o**) (Scheme 1A). The specificity for enynes over alkynes is particularly noteworthy—in the case of **4c**, the propynyloxy group was unaffected by the hydration conditions, giving the enone product **5c** in 78% yield. The TBPA mediated reaction of the enynol substrates **4p** and **4q** resulted in the 2,2-dimethyltetrahydrofuran-3-yl products **5p** (43%) and **5q** (29%), respectively. The tetrahydrofuran ring structure of **5q** was corroborated through single-crystal X-ray crystallography of the 4-nitrobenzoate derivative **5r** (Scheme 1B). Both **5p** and **5q** presumably incorporate acetone through an aldol-type process, followed by intramolecular cyclisation. Interestingly, when the (*Z*)-enynes **4s** and **4t** were exposed to the optimised reaction conditions, no hydration products were detected, suggesting a high level of selectivity (Scheme 1C).

Mechanistically, TBPA mediated reactions generally follow: (i) a cation-radical mediated pathway,[23] and/or (ii) a classic Brønsted acid directed process.[24] To investigate, we first performed the TBPA mediated hydration of enyne **1** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (20 mol%) according to Gassman's test.[23c,24] The outcome remained unchanged—the hydration



Scheme 1 Substrate scope for the aminium cation radical-mediated hydration protocol. [a] The reactions were performed on a 0.20 mmol scale of enyne **4**; isolated yields. [b] Reaction performed at 50 °C. [c] Reaction proceeded for 3 h. [d] Reaction performed on 0.40 mmol scale of enyne **4l**. [e] Reaction performed on 0.29 mmol scale of enyne **4m**. [f] Reaction performed on 0.41 mmol scale of enyne **4n**. [g] Reaction performed on 0.62 mmol scale of enyne **4p**. [h] Reaction performed at 45 °C. [i] Reaction performed on 0.94 mmol scale of enyne **4q**. [j] No product observed. Compound **5r** was synthesised from **5q** in two steps; i: TBAF (1.0 M in THF) (1.40 eq.), THF, r.t., 5 min, 94%, ii: 4-nitrobenzoyl chloride (1.00 eq.), Et_3N (2.05 eq.), CH_2Cl_2, 0 °C – r.t., 0.5 h, 70% (see ESI† for experimental procedures).



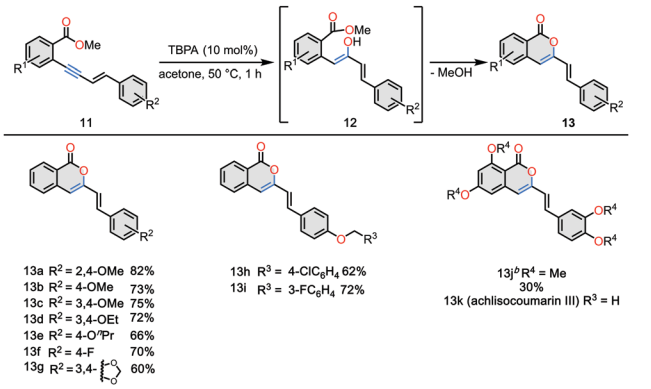
Scheme 2 A plausible working mechanism for the TBPA catalysed hydration of the (*E*)-aryl enynes.

product was obtained in a comparable 68% yield—suggesting Brønsted acid catalysis was unlikely. In the presence of the radical scavenger TEMPO (20 mol%), no hydration of **1** was observed. Similarly, introducing oxygen to the solvent resulted in lower product yields (see ESI†). Collectively, these control experiments lend support for a cation-radical pathway.

We tentatively propose the catalytic cycle illustrated in Scheme 2 to rationalise the selective hydration of (*E*)-aryl enynes and the formation of related products. Initiation of the cation-radical mediated process is presumed to proceed by oxidation of the (*E*)-enyne **4** by TBPA to give the cation-radical $[SbCl_6]^-$ intermediate **6**. Nucleophilic attack by water on intermediate **6** gives the cation-radical enol intermediate **7**, that upon tautomerisation delivers the ketone intermediate **8**. Reduction of **8** through single-electron transfer from the triarylamine (or an equivalent species) yields the (*E*)-aryl enone **5** along with regeneration of TBPA.[23,25] Alternatively, and consistent with the work of Mares and co-workers,[26] it is feasible that the cation-radical intermediates **7** and/or **8** (or related, *e.g.*, **6**) could be chain propagating species with TBPA functioning as the initiator.

The formation of the 2,2-dimethyltetrahydrofuran-3-yl products (*e.g.*, **5p**, where R = $-CH_2CH_2OH$) can be rationalised by the reversible aldol-type condensation of **7** with acetone to give intermediate **9**, followed by dehydrative cyclisation. When R = H, aldol condensation of **7** with acetone explains the origin of the side product **10**.

To showcase the potential utility of the new methodology, we selected the important 3-styryliscoumarin core, which is a prevalent motif in several natural products.[27–30] We envisaged a pathway where enyne hydration of **11** is followed by cyclisation of the enol tautomer **12** to deliver the 3-styryliscoumarin core **13** (Scheme 3). Using methyl (*E*)-2-(4-(2,4-dimethoxyphenyl)but-3-en-1-yn-1-yl)benzoate (**11a**) as a model substrate with 10 mol% TBPA at 50 °C for 1 h, the styrylisocoumarin (**13a**) was isolated



Scheme 3 Investigation into substrate scope of 1,4-diarylenynes **11**. [a] The reactions were performed on a 0.20 mmol scale; isolated yields. [b] Reaction performed on 0.66 mmol of 1,4-diarylenyne **11j** for 7 h.

in 82% yield. A selection of methyl (*E*)-2-(4-phenylbut-3-en-1-yn-1-yl)benzoate derivatives (**12**) were subsequently converted to the corresponding (*E*)-3-styrylisocoumarins (**13**) in good yield (30–82%) under the mild reaction conditions. Notably, the synthesis of (*E*)-3-styrylisocoumarin **13j** constitutes a formal synthesis of the natural product, achlisocoumarin III (**13k**).[28b]

In summary, we have developed a novel and selective method for the hydration of conjugated (*E*)-aryl enynes catalysed by the cation-radical salt TBPA. The new protocol abets the hydration of both terminal and internal conjugated enynes in good to excellent yield. The aryl enone hydration products are prized synthetic intermediates with the ability to undergo a range of valuable chemistries including intramolecular cyclisation to yield isocoumarin-type cores. The application of the methodology was showcased in the formal synthesis of the 3-styrylisocoumarin natural product, achlisocoumarin III. We believe the novel aminium radical mediated hydration method is a valuable addition to the toolbox of alkyne reactivity, offering a new mild and selective pathway to useful synthetic intermediates.

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Conflicts of interest

There are no conflicts to declare.

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