Hydroarylation of alkenes by protonation/Friedel-Crafts trapping – HFIP-mediated access to per-aryl quaternary stereocentres

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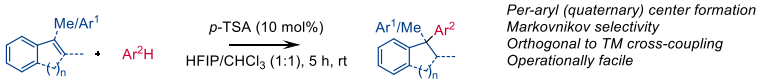


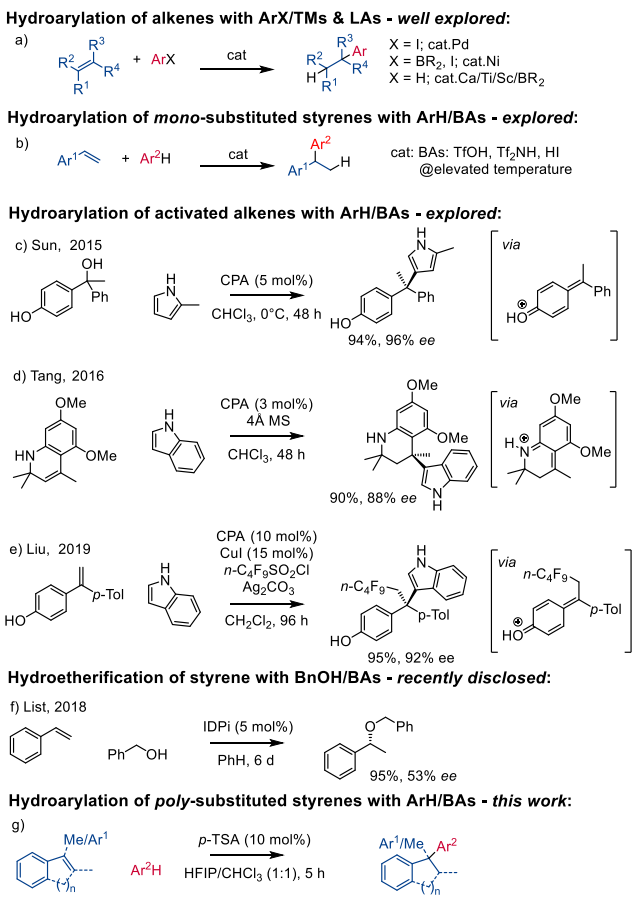
ABSTRACT: Upon treatment with a combination of HFIP and a strong Brønsted acid, alkenes behave as Brønsted bases and protonate to give carbocations which can be trapped by electron rich arenes. The reaction constitutes a Friedel-Crafts (FC) hydroarylation which proceeds with Markovnikov selectivity and is orthogonal to traditional metal catalyzed processes. The products contain polyarylated quaternary carbon atoms which are difficult to obtain *via* alternative methods. Intermolecular transfer hydrogenation and hydrothiolation are also demonstrated.

Alkenes are a ubiquitous functional group (FG), the installation of which can be achieved using a suite of venerable methods including carbonyl alkenylation, alkene metathesis, C-C cross-coupling, alkyne reduction and elimination reactions.[1] However, functionalization of alkenes, *e.g. via* addition reactions, generally requires high energy reagents like organometallic species promoted by transition metals or Lewis acids (*e.g.* Scheme 1).[2] Exceptions are intramolecular reactions and/or reactions of alkenes polarized by conjugation to heteroatoms (*e.g.* Scheme 1c-e). This situation reflects the intrinsically strong and unpolarized nature of the C-C double bond. The ability to selectively functionalize alkenes by a hydroarylation protocol which could operate in the absence of overt substrate bias and moreover tolerate pre-installed halide substituents for subsequent transition metal oxidative addition-initiated coupling protocols, would constitute a useful addition to the synthetic chemist's reaction arsenal.

We recently reported the use of HFIP to stabilize benzylic carbocations in an oxonium-Prins approach to the synthesis of furanochromanes.[3] We considered applying similar reaction conditions to enable *inter*molecular alkene functionalization. More specifically, we reasoned that protonation of a styrenyl alkene to unveil a HFIP stabilized benzylic carbocation could induce external trapping by an arene nucleophile. The result would be a Markovnikov selective Friedel-Crafts (FC) type hydroarylation. Although carbocations accessed from alcohols, epoxides, halides and even by C-C bond cleavage are known to participate in FC reactions,[4,5] entry to this reaction manifold from alkenes is rare (see below) and leverages the aforementioned ready synthetic access to this structurally diverse FG.

Alkene hydroarylation has been achieved using Pd(0) catalysis with aryl iodides and more recently using Ni(0) catalysis with organoboron derivatives.[6–8] A Ni/Fe radical approach has also been used to allow arylation (and even alkylation) with aryl (or alkyl) iodides.[9,10] However, alkene hydroarylation using non pre-functionalized arenes (*i.e.* simple arenes without halogen/other reactive handles) has generally been achieved by promotion using metal-based Lewis acids[11] (Scheme 1a).[12–16] Previous reports of Brønsted acid catalyzed intermolecular alkene hydroarylation fall into two categories. Monosubstituted styrenes can be arylated upon exposure to strong acids for extended periods at elevated temperatures (*e.g* refluxing TfOH, 20 h), (Scheme 1b).[11,17–22] Alternatively, alkenes that are polarized by conjugation to heteroatoms and therefore readily protonate at carbon [*e.g.* enamines, enol ethers, *o*/*p*QM(I)s] may be arylated under milder conditions.[23] Pertinent recent (asymmetric) examples of this latter class include Sun's arylation of a *p*QM formed by chiral phosphoric acid (CPA)-catalyzed dehydration (Scheme 1c),[24] Tang's arylation of an *o*QMI formed by protonation (Scheme 1d),[25] and Liu's arylation of a styrene-derived *p*QM *via* benzylic radical formation/oxidation (Scheme 1e).[26] However, in all these CPA-mediated transformations the only arene nucleophiles able to successfully trap the cationic intermediates were indoles and pyrroles due to their ability to H bond with the CPA promotors.

Scheme 1. Context of the reaction.[a]



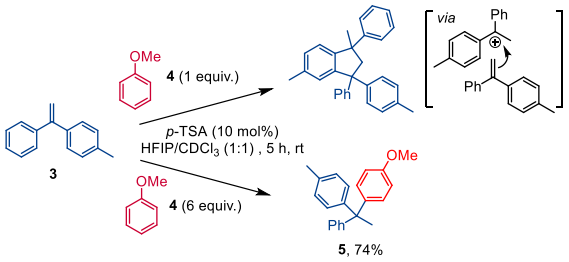
NB: TM = Transition Metal complex catalyst, LA - Lewis Acid catalyst, BA - Bronsted Acid catalyst

Although not a hydroarylation, List has recently demonstrated that non-heteroatom conjugated 1,1-disubstituted alkenes can undergo proton-induced intramolecular hydroetherification mediated by a highly acidic imidodiphosphorimidate (IDPi) catalyst to give THFs[27] and, tantalizingly, disclosed a single *inter*molecular variant – the coupling of benzyl alcohol with styrene (Scheme 1f).

Herein we disclose a mild and operationally simple method to activate and intermolecularly arylate multiply substituted styrenyl alkenes. Key to this protocol is the use of HFIP to stabilize the intermediate carbocations.[28] The conditions contrast with the aforementioned previous protocols which required harsh conditions and were only applicable to mono-substituted styrenes.

We initiated our investigation with 1-*para*-tolyl-1-phenylethylene **3** as the alkene (latent electrophile) and anisole **4** as the arene (nucleophile). To trigger protonation, we used *p*-TSA·H_2O as it is a cheap and easy to handle solid which is soluble in HFIP. We saw quantitative alkene dimerization when employing one equivalent of anisole as has also been observed when alkenes are treated with boron based Lewis acids (Scheme 2).[29,30] Undaunted, and drawing inspiration from the pioneering work of Jacobsen in which benzylic carbocations were successfully trapped by excess allyltrimethylsilane (6 equiv.),[31] we increased the equivalents of anisole. Gratifyingly, this led to the formation of the desired triarylethane **5** in 74% yield when using 6 equiv. of anisole (Scheme 2), with reduced amounts of dimerization.

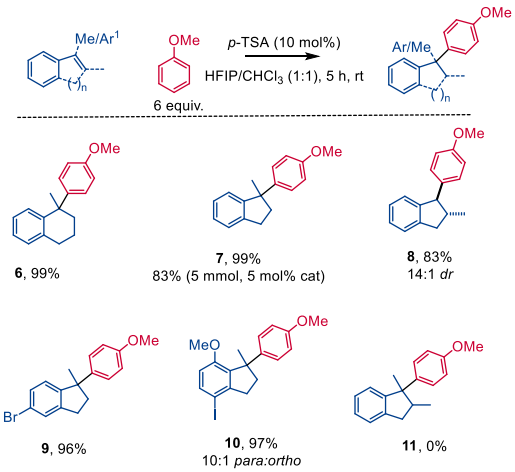
Scheme 2. Initial attempts at alkene protonation and arylation.[a]



[a]Isolated yield.

The reaction could be run open to air and did not require dried solvents. Use of $CDCl_3$ allowed reaction tracking by ^1H NMR. To explore the structural scope of this reaction, we tested a range of non-terminal styrenes (Scheme 3).

Scheme 3. Reaction scope with respect to the alkene.[a]

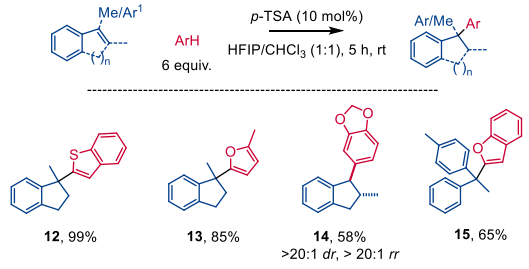


[a]Isolated yields.

A range of more substituted alkenes **6**-**10** were found to be amenable to arylation. Both indane and tetralin derivatives were hydroarylated in excellent yield. 1,2-Disubstituted indane **8**, was formed with high stereo- and regioselectivity, as the result of *trans*-selective trapping following protonation to give the *sec*-benzylic carbocation *cf.* the alternative tertiary carbocation. The reaction was tolerant of a bromine substituent situated *para* to the incipient carbocation (→ **9**) and an iodide substituent *meta* to the incipient carbocation (→ **10**). The bromine and iodine functions in compounds **9** and **10** are of potential utility for further functionalization and the syntheses of these compounds *via* the aforementioned metal catalyzed hydroarylation protocols would be challenging by virtue of requiring chemoselective oxidative insertion into one halogenated substrate over the other. All previous compounds (**5**-**9**) reacted with complete *para* selectivity with respect to the anisole methoxy substituent but the adjacent methoxy group en route to **10** is predicted to be responsible for the slight diminishing of this. Unfortunately, hydroarylation of the tetrasubstituted alkene that would have led to compound **11** was unsuccessful with no reactivity observed. An additional allylic side chain in **3** (with protonation leading to the biaryl homoallylic carbocation) was also not hydroarylated with decomposition observed.

Next, we explored variation of the nucleophilic arene component (Scheme 4).

Scheme 4. Reaction scope with respect to the arene.[a]



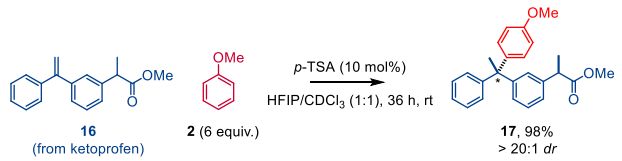
[a]Isolated yields.

Benzothiophene was successfully installed to give compound **12** in near quantitative yield, which could potentially undergo further elaboration to difunctionalized benzothiophenes *via* interrupted Pummerer chemistry.[32] 2-Methylfuran, which is prone to polymerization, was successfully coupled with the 1-methylindene to give furan derivative **13**. 1,3-Benzodioxole, a common motif within natural products, could be installed with high stereo- and regioselectivity to give biaryl **14** as the single isolated compound. Finally, benzofuran could be coupled with alkene **3** to yield the 1,1,1-triarylethane **15**.

Notable limitations of this method are the need to use an electron rich aryl as the nucleophilic component - less electron rich π-systems, such as *tert*-butylbenzene, led to alkene dimerization and decomposition. Moreover, basic groups such as amides are generally not tolerated in the superstoichiometric arene nucleophile, presumably because they present lone pairs that can act as a kinetic *cul-de-sac* for preferential protonation over the alkene. Additionally, indoles were not suitable allowing a complimentary approach to those already established (Scheme 1).

To illustrate how this new hydroarylation procedure can be used to enable rapid access to more complex and synthetically useful structures, we prepared a triaryl analogue **17** from alkene **16**, which is a derivative of the non-steroidal anti-inflammatory (NSAID) drug ketoprofen (Scheme 5).

Scheme 5. Functionalisation of a ketoprofen derivative.[a]

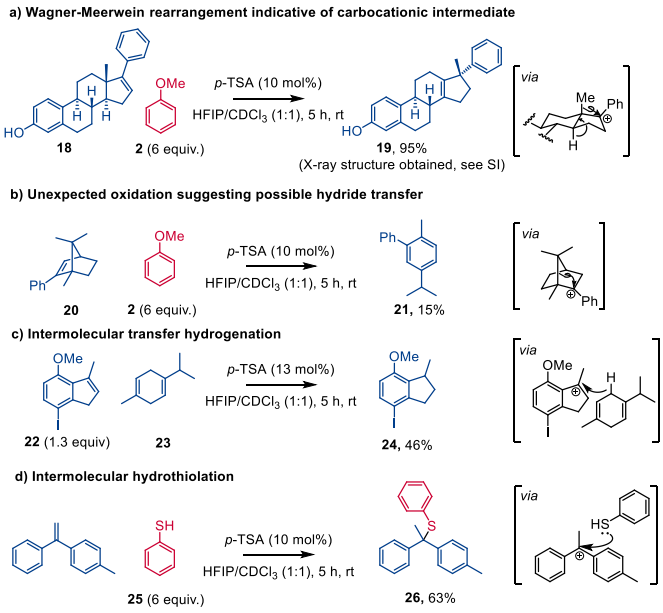


[a]Isolated yield. *Only one diastereomer formed, relative stereochemistry not established.

Surprisingly, the product was formed as a single, as yet unassigned, diastereomer. The origin of this diastereoselectivity is unknown but may be due the electrostatic field from the ester interacting with the positively charged transition state.[33] This method could allow rapid further investigations towards the effect of electronic and spatial geometry on the medicinal properties of profens.[34] It is noteworthy that for this substrate selective activation of the alkene was achieved in the presence of the ester moiety. This perhaps suggests that the ability of HFIP to stabilize carbocations renders the alkene more basic than the ester under these conditions. While such selective activation is rare, List has reported an IDPi-mediated intramolecular cycloetherifcation reaction in the presence of a traditionally basic sulfonamide with no involvement of HFIP.[27]

Seeking to confirm the intermediacy of carbocationic intermediates in these reactions, we considered intramolecular rearrangements as a potential diagnostic. As such, the estrone derivative **18** was prepared in which the adjacent quaternary center is primed for a 1,2-alkyl shift. Consistent with the formation of an intermediate carbocation, the tetrasubstituted alkene **19** arising from subsequent migration and elimination, was obtained from this substrate upon subjection to the standard hydroarylation conditions using anisole as potential trapping nucleophile (Scheme 6a).

Scheme 6. Carbocationic rearrangements, transfer hydrogenation and hydrothiolation. [a]



[a]Isolated yields.

Intrigued by potential other classic intramolecular carbocationic rearrangements we reasoned the camphor derived **20** would be prone to rearrangement. Indeed, complete consumption of this substrate was observed with isolation of the rearranged and aromatised phenyl substituted cymene derivative **21** (Scheme 6b). We postulated that alkene **20** was likely undergoing disproportionation and that therefore a suitable hydride source might also enable such reductive transformations – amounting to transfer hydrogenation under Brønsted acid catalysis. Such transfer hydrogenation would be orthogonal to known metal catalyzed protocols.[35] Pleasingly, use of γ-terpinene **23** as the hydride source and iodoindane **22** as alkenyl substrate led to the desired alkane **24** with the sensitive aryl iodide moiety still intact (Scheme 6c). Intramolecular 1,5-hydride transfer has been achieved by Chiba and Xiao using Brønsted acid catalysis,[36–38] but to the best of our knowledge this is the first example of an intermolecular transfer hydrogenation. While there are a plethora of reports of intermolecular hydride transfer to carbonyls and imines from Hantzsch esters,[39] this HFIP-mediated reaction is remarkable because alkene **22** is a poor electrophile and skipped diene **23** is a poor hydride donor as judged by their respective Mayr coefficients.[40]

Finally, we considered the use of a thiol as a carbocation scavenger. Application of our standard reaction conditions saw concomitant hydrothiolation of the alkene (Scheme 6d). It is noteworthy that such organocatalytic C-S bond formation traditionally requires similar alkene bias as previous arylation strategies.[41,42] Indeed, the formation of such S containing quaternary centers by nucleophilic addition has previously relied upon conjugate additions and Mannich-type reactions.[43]

We have described a facile method for the Brønsted acid catalyzed intermolecular hydroarylation of styrenes. The reaction exploits the ability of HFIP to enhance the Brønsted basicity of a styrene by stabilizing the benzylic carbocation. Friedel-Crafts trapping by electron rich arenes occurs at room temperature, open to air, and with short reaction times employing a cheap sulfonic acid. Conceptually, this work lays a general platform for Brønsted acid activation of alkenes by protonation and subsequent intermolecular functionalization by a nucleophile.[44]

Future work towards enantioselectivity and alternative reactivity are underway within our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H and ^{13}C NMR spectra of new compounds and single crystal X-ray structure determination for compound **19**.
FAIR data accessible at DOI: 10.14469/hpc/5091

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