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Efficient Hydroarylation and Hydroalkenylation of Vinylerenes by Brønsted Acid Catalysis†

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Brønsted acid Tf$_2$NH alone catalyzed both Friedel–Crafts-type hydroarylation and head-to-tail hydroalkenylation of vinylerenes under mild reaction conditions have been realized, providing a readily scalable, metal-free, and practical access to the 1,1-diarylalkane scaffolds and trans-1,3-diaryl-1-butene in high yields and excellent regioselectivities.

The direct catalytic hydroarylation and hydroalkenylation of vinylerenes are highly atom-economical and fundamental methods for the synthesis of 1,1-diarylalkane (branched) scaffolds, which are core fragments existing in a number of complex natural and synthetic molecules. These compounds always display some biological activities and are potential therapeutic agents against cancer, smallpox, and insomnia, as well as other diseases (Figure 1). Hence, much attention has been paid to achieve such transformations and numerous elegant developments have been reported (Scheme 1). According to the mechanism, the catalytic reactions can be classified into two major types: (1) hydroarylation through C-H activation by transition metal catalysts,2,3 and (2) Friedel–Crafts-type alkylation in the presence of Lewis or Brønsted acid.4 The former method usually requires a directing group on the arene and preferentially affords the linear adduct, with a few exceptions.5 In contrast, 1,1-diarylethanes are generally obtained from Friedel–Crafts-type hydroarylation due to the stability of positive charge on the α-position of styrenethat develops upon Lewis acid coordination4a–g or Brønsted acid protonation4h–k (Scheme 1, A and B). Recently, Pospech group reported a hydroarylation of styrene derivatives catalyzed by phosphate with indoles as reactive partner. However, the presence of hydroxyl group was necessary for forming more reactive quinonemethide-like intermediate to accomplish the whole reaction (Scheme 1, C). With the advent of modern ‘super acids’, especially triflimide (Tf$_2$NH, pKa = 0.67 in HOAc), we recognized that hydroarylation of simple vine larenes might be catalyzed by the strong Brønsted acid via the generation of the intermediate B (Scheme 1, i).

Additionally, hydroalkenylation of olefins is one of the current interesting and useful protocols to synthesize essential intermediates for fine and industrial chemicals.8 Generally, such reactions could be carried out following three ways to date: head-to-head (h-h),9 head-to-tail (h-t)10 and tail-to-tail (t-t)11. Since a new allylic carbon stereogenic center is formed, the h-t dimerization is considered more attractive. Although a range of metal catalytic systems have been developed for this transformation: Dawans10a and Yi10b disclosed that nickel-based catalytic systems...
that the Friedel–Crafts hydroarylation could take place with Tf$_2$NH as a catalyst. The screening of solvents showed that dioxane was superior to other solvent and the product was obtained in 71% yield at 80 °C with 4 mol % of Tf$_2$NH (entries 1-5). Lowering the temperature to 60 °C resulted in 38% yield (entry 6). Because of the challenge to separate two isomers 3a' of 2- and 4-regioselectivities with anisole 2a, and more importantly, for the development of a practical access to analogues of potential therapeutic agents I-III (figure 1), we finally selected 1,2,3-trimethoxybenzene 2b as the reactant to continue our study (entries 7-9), and the further improved reaction condition was obtained in a 5:1 molar ratio of arene 2b to 1a at 90 °C with a 4 mol % catalyst loading that led to 75% yield of product 3a exclusively (entry 9). No reaction occurred in the absence of acid catalyst (entry 10).

With the optimized reaction conditions established, we then examined the substrate scope of the hydroarylation between various vinylarenes 1 and 2b (Table 2). Significantly, besides 1a, the transformations took place smoothly to assemble (1-(3,4,5-trimethoxyphenyl)ethyl)-arenes exclusively with other substituted vinylarenes and self-dimerization of 1 was tremendously suppressed. Basically, the relatively electron-rich styrenes were more reactive than electron-deficient ones. For instance, styrenes 1b and 1c with ortho-para-methyl substituent converted into the corresponding adducts 3b and 3c in 86% and 82% yields, respectively (entries 2 and 3). Compound 3d was readily obtained in 88% yield employing 4-tert-butyl styrene 1d as the substrate (entry 4). The best result was obtained by introducing two methyl groups on 2,5-position of the benzene ring to furnish 3e in 92% yield (entry 5). When electron-withdrawing halogen atom was attached to the aromatic ring in styrenes, the good outcomes was gained. 4-halogen-containing (F, Cl, and Br) styrenes 1f-h were all compatible with this transformation and cleanly led to 3f-h in 75-50% yields (entries 6-8).

To highlight the potential application of the highly atom-economic hydroarylation process, we conducted the reactions of 2-vinylphenanthrene 1i with 2b (Scheme 2, eq 1), and 1f with benzofuran 2e and benzol[b]thiophene 2d to gram-scale (eq 2). Accordingly, treating 1i (3.0 mmol, 0.462 g) with 2b (15.5 mmol, 5 equiv), and 1f (6.0 mmol, 0.73 g) with 2c (5.0 mmol, 0.59 g) and 2d (5.0 mmol, 0.67 g) to the standard reaction conditions, readily provided the potent of tubulin polymerization 3i, 3j, and 3k in 80-84% yields. Notably, 3k is a very useful material for the synthesis of anti-insomnia agent benzothiophene IV.  

![Scheme 2 Gram-Scale Hydroarylations](image)

During the period of our studies on above hydroarylation between vinylarenes and anisole, it was found that a small quantity of homodimerized products generated. We reasoned that such dimerization of styrene derivatives might be also catalyzed by Brønsted acids (Table 3). Examination of usual Brønsted acids
in THF at 80 °C revealed that Tf$_2$NH is optimal which promoted the homodimerization successfully to provide the desired product 4a in 70% (entries 1-4). Changing the solvent THF to a mixed solvent of THF and cyclohexane in a 3:1 volume ratio increased the yield up to 82% (entry 5). Enlarging the Tf$_2$NH-loading to 6 mol % didn’t improve the reaction (entry 6). A sharp decrease of yield was observed from 80 °C to 60 °C, while raising the temperature to 90 °C didn’t afford improvement in the yield (entries 7 and 8).

Next, the scope and generality of this homodimerization were explored using various commercially available vinylarenes (Table 4). Besides styrene, both alkyl-substituted and halogenated vinylarenes were all able to participate in the dimerization to provide smoothly the corresponding products. Methyl group in ortho- and para-position had no apparent effect on the yields of products (entries 1-2). Notably, tert-butyl substituent could also tolerate the reaction conditions and provided 4d in 82% yield (entry 3). Gratifyingly, the fluorinated substrates underwent well the process, and gave the trans-1,3-diaryl-1-butenes 4f, and 4j-k in good yields regard less of the substituted position (entries 4-6). Yields of more than 60% were obtained when Cl and Br substituted vinylarenes were used as reaction substrates (entries 7 and 8). With 1-vinylnaphthalene 1l as substrate, the satisfied yield was achieved (entry 9). Prop-1-en-2-ylbenzene 1m and the bicyclic compounds 1n and 1H-indene 1o are also compatible with this transformation, providing 4m-o in acceptable yields (entries 10-12). It is noteworthy that the current homohydroalkenylation of 1o is easily scaled up to 10 mmol scale, producing 0.88 g of 4o in 76% yield (entry 12).

Remarkably, the cross-hydroalkenylation process occurred efficiently (Table 5). Treatment of 1f (5.0 equiv) with another vinylarenes, including 1b, 1d, 1p, and 1g, to the standard reaction conditions afforded the desired products 5b-e in 55-89% yields.

In conclusion, we described a readily scalable, mild, and efficient method for hydroarylation and head-to-tail hydroalkenylation of vinylarenes with Brønsted acid Tf$_2$NH as the same only catalyst, which provides an easy access to bioactive 1,1-diarylkamine scaffold and trans-1,3-diaryl-1-butenes. This is the first example of highly regioselective hydroarylation and hydroalkenylation with only one organic catalyst.

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Notes and references


2 For reviews, see: (a) F. Kakiuchi, N. Chatani, Angew. Chem., Int. Ed. 2006, 45, 32; (b) F. Kakiuchi, T. Kochi, Synthesis 2008, 3013; (c) D. A. Colby, R. G. Bergman, J. A. Ellman, Chem. Rev. 2010, 110, 624.


7 (a) The pKa Values in glacial acetic acid were measured by 1H NMR spectroscopy, see: B. M. Rode, A. Engelbrecht, J. Schantl, Z. Phys. Chem. (Leipzig) 1973, 253, 17; (b) The pKa Values of Tf2NH and HOTf in glacial acetic acid are 7.8 and 4.2, respectively, see: J. Foropoulos, D. D. DesMarre, Inorg. Chem. 1984, 23, 3720.


12 A recent review on strong Brønsted acids as catalysts, see: T. Akiyama, K. Mori, Chem. Rev. 2015, 115, 9277.