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Metal-Free Transfer Hydrobromination of C−C Triple Bonds

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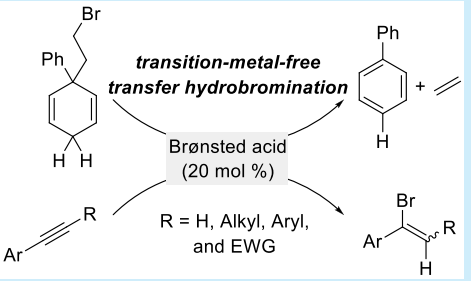
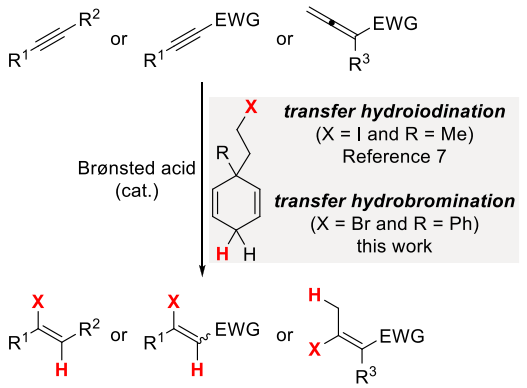
Supporting Information

ABSTRACT: A transfer hydrobromination of C−C triple bonds inititated by Brønsted acids is reported. Hydrogen bromide is released stepwise from a bench-stable cyclohexa-1,4-diene-based surrogate, generating biphenyl and ethylene as waste. A range of vinyl bromides was prepared from terminal and internal, mainly acceptor-substituted alkynes with good functional-group tolerance.



Transfer hydrofunctionalization of unsaturated compounds is a practical strategy for the synthesis of fine chemicals without handling hazardous reagents.[1,2] Our group introduced adequately substituted cyclohexadienes as surrogates for the transition-metal-free ionic transfer hydrofunctionalization of various double and triple bonds.[3−6] We recently designed a bench-stable surrogate for hydrogen iodide by installing an ethylene tether between the cyclohexa-2,5-dien-1-yl unit and the halogen atom to prevent spontaneous aromatization.[7] Transfer hydroiodination of a broad range of alkynes and allenes was achieved using Brønsted acids as initiators (X = I and R = Me; Scheme 1). The surrogate fragments into toluene and ethylene as byproducts. We wondered whether this strategy could be extended to hydrobromination (X = Br and R = Ph; Scheme 1). Hydrobromination is an important process for the preparation of vinyl and alkyl bromides which are versatile building blocks in organic synthesis. The direct addition of hydrogen bromide to unsaturated hydrocarbons is an attractive synthetic approach for due to its atom economy. However, using corrosive and gaseous hydrogen bromide (HBr) is of limited applicability on a laboratory scale. Hence, alternative processes using in situ generated HBr were developed with[8] and without[9] the aid of transition metals. In addition, transfer hydrobromination of 1,6-enynes was reported by Lautens and co-workers using Et_3N·HBr as a source of HBr.[10]

Scheme 1. Brønsted Acid Initiated Transfer Hydrohalogenation of C−C Multiple Bonds[a]



[a]EWG = electron-withdrawing group.

Low-molecular-weight HBr surrogates **1** or **2** that would release toluene or mesitylene along with ethylene gas as waste would have been ideal choices for the transfer hydrobromination (**4a** → **5a**, Table 1). However, subjecting **1** and **2** to the optimized procedure of our earlier transfer hydroiodination of phenylacetylene[7] led to no conversion (entries 1−3). We explain this by the stronger C(sp^3)−Br compared to the C(sp^3)−I bond. Conversely, the easily accessible surrogate **3**[11] furnished 13% yield of the hydrobromination product **5a** with biphenyl as a byproduct (entry 4). We tentatively attribute this increase in reactivity to the formation of the more stabilized Wheland complex intermediate.[12] Higher reaction temperature and catalyst loading resulted in improved conversion (entries 5 and 6). In turn, Brønsted acids stronger than TsOH, e.g., TfOH and Tf_2NH, decomposed either the substrate or the reagent (entries 7 and 8). A further increase in temperature and the amount of the surrogate eventually afforded to the desired vinyl bromide **5a** in 80% yield (entries 9 and 10). No conversion was observed in the absence of the Brønsted acid initiator.

For isolated yields, we chose less toxic and less volatile toluene as solvent instead of benzene. The scope of the proton-initiated transfer hydrobromination of C−C triple bonds was then examined (Scheme 2). The purification of the obtained α-bromostyrenes was challenging and only successful in a few cases. Sterically hindered **4b** yielded **5b** in moderate 48%. The

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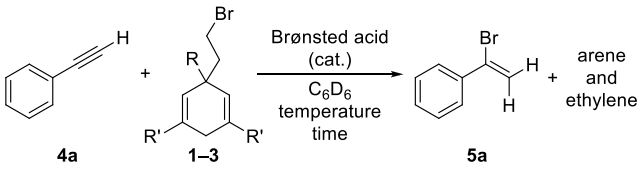
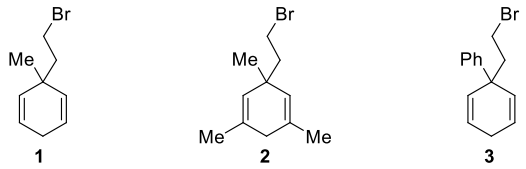
Table 1. Surrogate Screening and Reaction Optimization

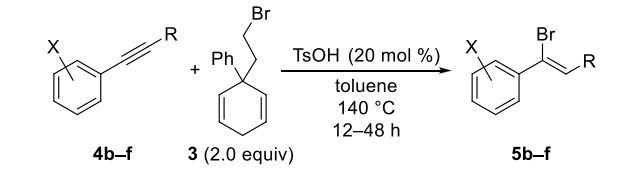


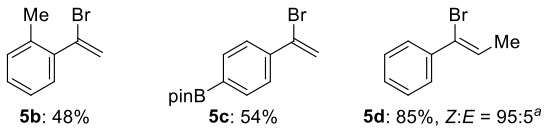


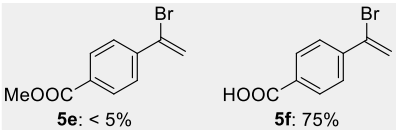
entry	surrogate	acid	T (°C)	yield[b] (%)
1	**1** (1.3 equiv)	TsOH (10 mol %)	100	<1
2[c]	**1** (1.3 equiv)	Tf_2NH (10 mol %)	120	<1
3	**2** (1.3 equiv)	TsOH (10 mol %)	100	<1
4	**3** (1.3 equiv)	TsOH (10 mol %)	100	13
5	**3** (1.3 equiv)	TsOH (10 mol %)	120	33
6	**3** (1.3 equiv)	TsOH (20 mol %)	120	57
7[d]	**3** (1.3 equiv)	Tf_2NH (20 mol %)	120	<1
8[e]	**3** (1.3 equiv)	TfOH (20 mol %)	120	<1
9[d]	**3** (1.3 equiv)	TsOH (20 mol %)	140	66
10	**3** (2.0 equiv)	TsOH (20 mol %)	140	80
11	**3** (2.0 equiv)	none	140	<1

[a]Unless otherwise noted, reactions were performed on a 0.030 mmol scale in 0.5 mL of the indicated solvent. [b]Determined by ^{1}H NMR spectroscopy by the addition of 1,4-dioxane as internal standard after the indicated time. [c]Performed in C_6D_5Cl as solvent. [d]Degradation of surrogate **3** in significant amounts. [e]Decomposition of **4a**.

Scheme 2. Scope I: Brønsted Acid Initiated Transfer Hydrobromination of Unactivated Alkynes





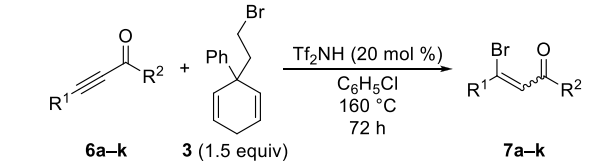


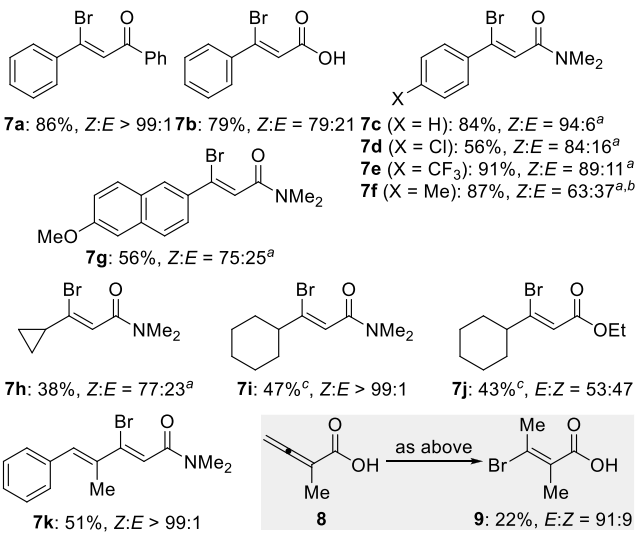
[a]75% with Z/E = 83:17 were obtained on a 1.0 mmol scale after 24 h; biphenyl was isolated as the byproduct in 91% and recycled in the preparation of surrogate **3**.

borylated derivative **5c** was obtained from **4c** in decent yield. Compound **4d** with an internal triple bond furnished **5d** in excellent yield predominantly with Z geometry.[13] It is noteworthy that **4f** bearing a free carboxylic acid showed good reactivity, while the corresponding methyl ester in **4e** essentially thwarted any conversion; **5f** was isolated in 75% yield, and trace amounts were detected of **5e**.

Substrates containing activated C−C multiple bonds such as alkynes **6a−k** and allene **8** were then subjected to the hydrobromination protocol (Scheme 3). The stronger acid

Scheme 3. Scope II: Brønsted Acid-Initiated Transfer Hydrobromination of Activated Acceptors





[a]The geometrical isomers were separable by flash chromatography on silica gel and were isolated individually (see the Supporting Information for details). [b]55% with Z/E = 87:13 along with 36% unreacted starting material were obtained on a 1.0 mmol scale after 5 days. [c]Along with unreacted starting material.

Tf_2NH was necessary as a result of the intrinsically electron-poor nature of the substrates. Different electron-withdrawing groups were tested, and α,β-unsaturated ketone, carboxylic acid, and amide **6a−c** reacted in good yields to afford **7a−c** with moderate to high diastereocontrol.[14] Electronic modification of the aryl ring in amide **7c** was possible but with eroded Z/E ratios (**6d−f** → **7d−f**); an electron-rich β-naphthyl group was tolerated as well (**6g** → **7g**). The double-bond isomers could be separated by flash chromatography in all these cases. Replacing the aryl substituent with an alkyl group led to lower isolated yields (**6h/i** → **7h/i**). Interestingly, amide **6i** with a cyclohexyl group was isolated with Z selectivity exclusively, but the corresponding ester **6j** was not (E/Z = 53:47 for **7j**). We were also able to prepare diene **7k** from the corresponding enyne **6k** in a synthetically useful yield. The preparation of tetrasubstituted vinyl bromide **9** was achieved by transfer hydrobromination of **8** in 22% isolated yield (gray box).

In accordance with our previously reported hydroiodination, we propose the mechanism outlined in Scheme 4 (shown for **4a** to **5a** with **3**). The catalysis is initiated by protonation of the alkyne to transiently generate the vinyl cation **10a**. We believe that **10a** and surrogate **3** then form the bromonium ion **11a**.[15] That intermediate then fragments into the vinyl bromide **5a**, ethylene, and Wheland complex **12** by concerted cleavage of

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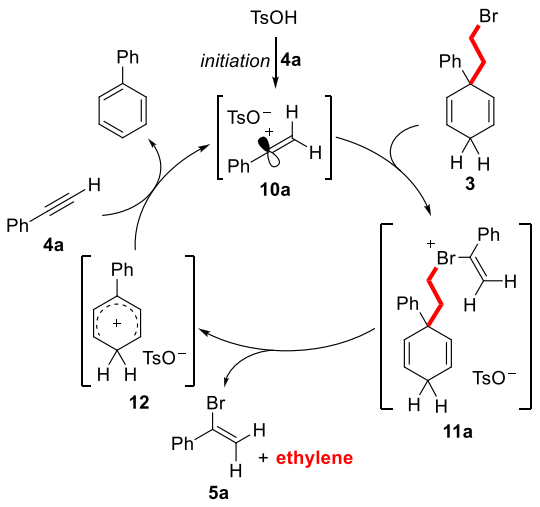
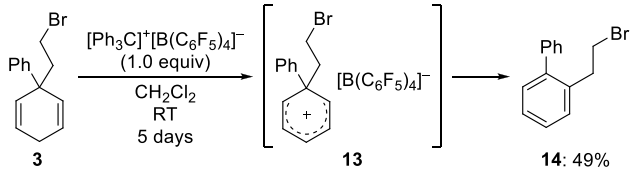
Scheme 4. Example of the Assumed Catalytic Cycle



the C−Br bond and the vicinal C−C bond. Compound **12** is protonated biphenyl and, as such, a strong Brønsted acid that will drive the catalytic cycle by protonation of substrate **4a**.

Either the bromine atom in **3** or one of the bis-allylic hydrogen atoms of the cyclohexa-1,4-diene could, in principle, act as the nucleofuge in the reaction with the vinyl cation. However, we knew from our previous study[7] that hydride abstraction leads to Wagner−Meerwein rearrangement[16] of the surrogate, and we did not observe any of that with surrogate **3**. To probe the possibility of this reaction pathway, we treated **3** with the triyl cation that would chemoselectively abstract the hydride (Scheme 5). Indeed, rearranged **14** did form in 49%

Scheme 5. Rearrangement of the HBr Surrogate Induced by Hydride Abstraction



yield after 5 days; the reaction likely involves the intermediacy of Wheland complex **13**.[16] This suggests that hydride abstraction is not competing with the bromonium-ion formation in the transfer hydrobromination.

To summarize, we have reported here a metal-free hydrobromination of terminal, internal, and especially electron-deficient alkynes. The reaction is less general than the related transfer hydroiodination[7] as it requires even higher reaction temperatures (140 and 160 °C instead of 80−120 °C). However, the new method avoids handling of gaseous hydrogen bromide or its aqueous solution, thereby allowing for the hydrobromination of a useful subset of C−C triple bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01431.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1907791 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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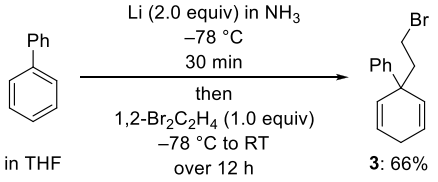
(11) See the Supporting Information for experimental details (one-step as well as three-step preparation) and characterization data, including crystallographic data.



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