CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201003759

# Electrophilic Carbocyclization of Hydroxylated Enynes

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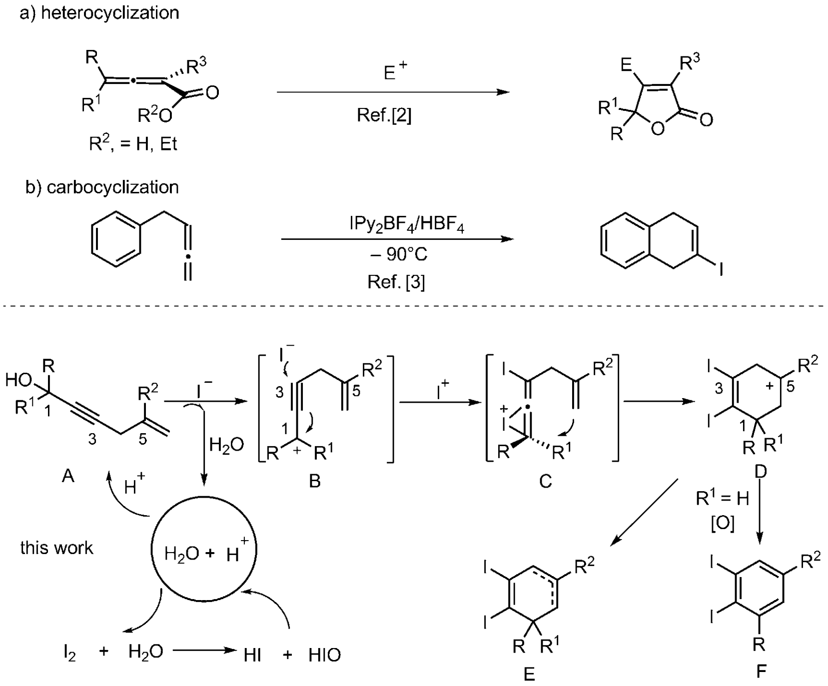

Scheme 1. The domino process. E = electrophile, Py = pyridine.

The electrophilic cyclization of nucleophiles, such as oxygen, nitrogen, sulfur, and carbon with alkynes was studied in detail by Barluenga, Larock, Kirsch, and others and has proved to be an effective method for the construction of cyclic compounds.[1,2] However, electrophilic additions to allenes have often been considered to be synthetically less attractive because of to the lack of efficient control of the regio and stereoselectivity. Examples of electrophilic cyclization of allenes with nucleophiles for the construction of C–X (C, N, and O) bonds include the cyclization of oxygen nucleophiles with allenes for the direct formation of a C–O bond (Scheme 1a).[3] Some important 4-iodofuran-2(5*H*)-ones, most of which employ iodine to trigger the cyclization, have been developed using this method, while in an early report, Barluenga et al. have used $IPy_2BF_4/HBF_4$ to promote the arylation of allenes at −90 °C (Scheme 1b).[4] However, the reaction conditions still need further improvement as the expensive $IPy_2BF_4$ electrophile is now used and low temperatures are still required.

Simple olefins have not been used as internal carbon nucleophiles in this manner.[2d,5] In the context of our ongoing efforts to construct C–X (C, N, and O) bonds by the use of alkynes with nucleophiles in domino reactions,[6] we found that several transition metals, such as gold and platinum, show similar behavior with electrophiles as $I^+$.[6c,f,7] The gold-catalyzed cycloisomerization of 1,*n*-enynes has become an effective way to construct various carbocyclic products.[8] However, the electrophilic cyclization of simple hydroxylated enynes is a particularly challenging chemical transformation. According to our previous work,[6] we envisioned that this type of propargyl alcohols **A** could eliminate the hydroxyl group to give the intermediate **B** in the presence of $I_2$ (**A**–**F**, Scheme 1). Herein, we present preliminary results of a metal-free preparation of diiodocyclohexadienes and 2,3-diiodobenzenes, in which the key cyclization step is the attack of unactivated olefins on allenes promoted by the iodonium ion at room temperature.

Initially, we started by using the hydroxylated enyne **1a** (0.2 mmol) and $I_2$ (1.2 equiv) in $CH_3NO_2$ at room temperature. To our delight, the desired products diiodocyclohexadiene (**2a** and **3a**) were isolated in 70 % yield after 24 h (Table 1, entry 1). On increasing the amount of $I_2$

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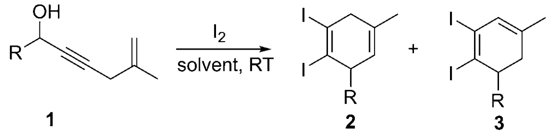
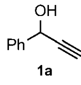
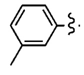
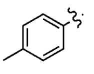
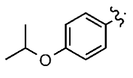
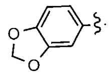
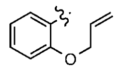
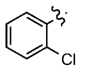
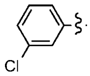
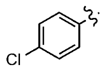
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003759.

Table 1. Carbocyclization of hydroxylated enynes for the synthesis of 1,2-diiodo-4-methylcyclohexadiene.[a]



| Entry | Substrates R | Solvent | $I_2$ [equiv] | Products **2**/**3**[b] | Yield [%][c] |
|---|---|---|---|---|---|
| 1 |  **1a** | $CH_3NO_2$[d] | 1.2 | 35:1 | 70 |
| 2 | | $CH_3NO_2$ | 1.5 | 40:1 | 84 |
| **3** | | $\mathbf{CH_3NO_2}$ | **1.8** | **50:1** | **90** |
| 4 | | $CH_3NO_2$ | 2.0 | 35:1 | 81 |
| 5 | | $CH_3NO_2$ | 2.5 | 20:1 | 76 |
| 6 | | $CH_2Cl_2$ | 1.8 | 30:1 | 82 |
| 7 | | DCE | 1.8 | 30:1 | 80 |
| 8 | | THF | 1.8 | – | –[d] |
| 9 | | DMF | 1.8 | – | 0 |

| | | | | |
|---|---|---|---|---|
| R |  |  |  |  |
| | 85% **2c**/**3c** (9:1) | 90% **2d**/**3d** (6:1) | 89% **2i**/**3i** (6:1) | 84% **2j**/**3j** (9:1) |
| R |  |  |  |  |
| | 65% **2m**/**3m** (11:2)[e] | 52% **2p**/**3p** (5:1) | 53% **2q**/**3q** (5:1) | 70% **2af**/**3af** (5:1) |

[a] Reaction conditions: **1a** (0.2 mmol), $I_2$ (1.8 equiv) in solvent (3.0 mL) at room temperature. [b] The ratio of **2/3** is determined by NMR analysis. [c] Yield of isolated product. [d] The $CH_3NO_2$ is untreated. [e] $I_2$ (1.5 equiv).

(1.8 equiv), a 90% yield was obtained after 2 h, the ratio of **2a**/**3a** was 50:1 (Table 1, entry 3). A further increase of the amount of $I_2$ gave no better results (Table 1, entries 4 and 5). Changing the reaction media was also not fruitful (Table 1, entries 6–9). Various representative hydroxylated enynes with different R groups were then subjected to the optimized conditions, as depicted in Table 1. Thus, a tandem carbon–carbon bond formation of hydroxylated enynes proceeded smoothly to give the corresponding products in moderate to excellent yields. The reaction worked well with aromatic R groups. Unfortunately, substrates with only one aliphatic group at C1 did not react owning to the poor stabilization of the intermediate **B**, as delineated in Scheme 1. Electron-rich aryl groups showed better results than those with electron-withdrawing groups (**1c** versus **1p**). The molecular structure of the representative product **2c** was determined by X-ray crystallographic analysis (Figure 1).[9] Interestingly, it was found that substrate **1m** with an *o*-(allyloxy)benzene group gave the corresponding product in the presence of $I_2$ (1.5 equiv), and the double bond in the R group was selectively retained in this reaction.

We also investigated a wide range of hydroxylated enynes (**1a**–**v**) with different R and $R^2$ substituents in the presence of $I_2$ with DDQ as oxidant. It was found that these substrates were effectively converted into the corresponding 2,3-diiodobenzenes **4** in moderate to good yield, as depicted in Table 2. The molecular structure of the representative product **4a** was determined by X-ray crystallographic analysis (Figure 2).[10] The reaction tolerates the presence of different electron-rich and electron-withdrawing aryl groups. The steric effect was also tolerated in this reaction. Unfortunately, substrate **1t** with a heteroaromatic R group (a furan nucleus), did not lead to the desired product. This might be resulting from the fact that the furan nucleus is not stable in this reaction system. Also, substrates **1v**, which lacks a substituent at C5 (i.e., $R^1{=}H$) turned out to be unreactive under the given reaction conditions, thus demonstrating that the substituent at C5 is required to stabilize the positive charge in the cyclic intermediate **D**.

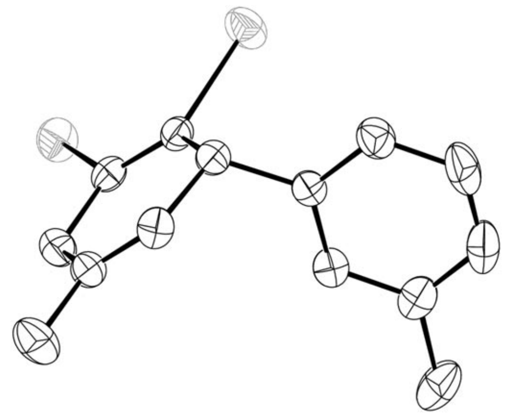


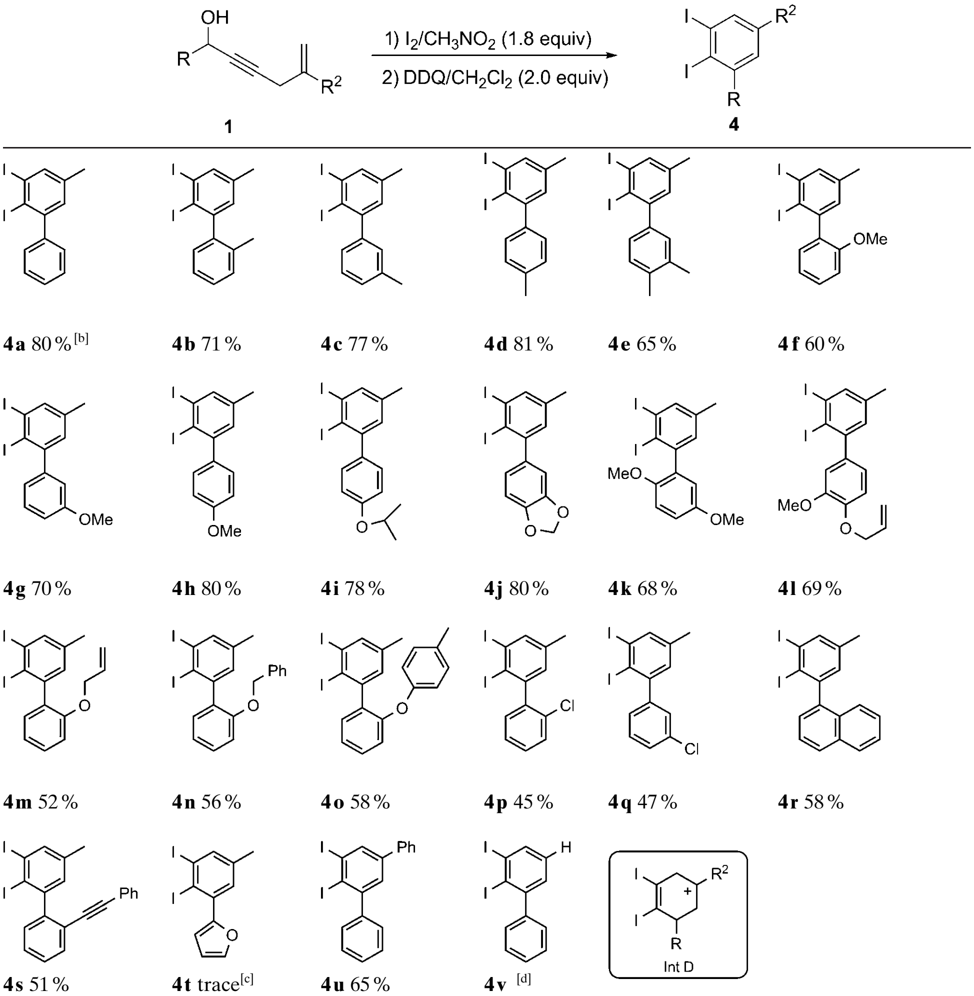
Figure 1. X-ray structure of **2c**. Ellipsoids set at 40% probability. Carbon: black; iodine: light gray; hydrogen atoms omitted for clarity.[9]

Fortunately, in the case of hydroxylated enynes **1w**,**x**, which contain styrene as R group and two olefin groups, the styrene group was selectively retained and a good yield of corresponding **4w**,**x** was obtained (Scheme 2) at the above reaction conditions at 0 °C.

Knowing the importance of multi-iodo-terphenyl derivatives in organic materials,[11] which are used for the preparation of many optical and conductive materials through palladium-catalyzed Sonagashira coupling, Suzuki coupling, and Heck coupling reactions, we also prepared hydroxylated enyne **1y**, and it was found that under the optimized conditions, the corresponding tetraiodo-1,1′:4′,1″-terphenyl **4y** was obtained in 51% yield (Scheme 3).

Additionally, hydroxylated enyne **1z** with an electron-withdrawing aryl group was also subjected to the above conditions (Scheme 4). To our delight, the corresponding product 4′-bromo-2,3-diiodo-5-methyl-1,1′-biphenyl (**4z**) was obtained in 52% yield. Then, we thought that if the olefin group was changed into an aryl group such as 1-(4-bromophenyl)-4-phenylbut-2-yn-1-ol (**1aa**), the corresponding 2,3-diiodo-1,4-dihydronaphthalene **4aa** could also be obtained. To our surprise, only (*E*)-1-(4-bromophenyl)-2,3-diiodo-4-phenylbut-2-en-1-ol (**5aa)** was selectively obtained in 56% yield.

Table 2. Synthesis of 2,3-diiodobenzenes **4** from hydroxylated enynes **1**.[a]



**4a** 80%[b]
**4b** 71%
**4c** 77%
**4d** 81%
**4e** 65%
**4f** 60%
**4g** 70%
**4h** 80%
**4i** 78%
**4j** 80%
**4k** 68%
**4l** 69%
**4m** 52%
**4n** 56%
**4o** 58%
**4p** 45%
**4q** 47%
**4r** 58%
**4s** 51%
**4t** trace[c]
**4u** 65%
**4v** [d]

[a] Reaction conditions: **1a** (0.2 mmol), $I_2$ (1.8 equiv) in $CH_3NO_2$ (3.0 mL) at room temperature. [b] Yield of isolated product. [c] Product **4u** was observed only in trace amount. [d] No reaction was observed.

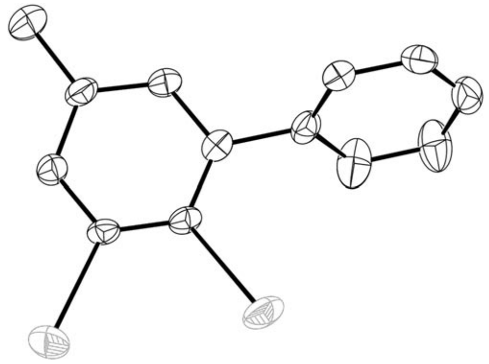
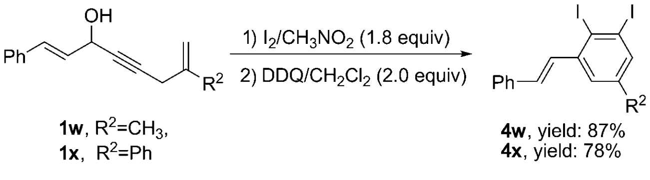


Figure 2. X-ray structure of **4a**. Ellipsoids set at 40% probability. Carbon: black; iodine: light gray; hydrogen atoms omitted for clarity.[10]

In the cases in which the aromatization process is blocked by a substituent at the C1 position, hydroxylated enynes **1ab–ae** gave the diene products in good yield as well, as depicted in Table 3. Notably, a substrate similar to **1ae**, with a styrene as R group was also obtained in 76% yield, whereas the styrene group was selectively retained in this reaction.

We next investigated the use of the iodine bromide reagent (IBr). To our surprise, IBr (1.5 equiv) in $CH_3NO_2$ at −25°C converted hydroxylated enyne **1u** into **2u**, which was oxidized to 5′-bromo-4′-iodo-1,1′:3′,1′′-terphenyl **5u** in 30% yield (Scheme 5). In this reaction, both the halogen atoms (I and Br) were used effectively.

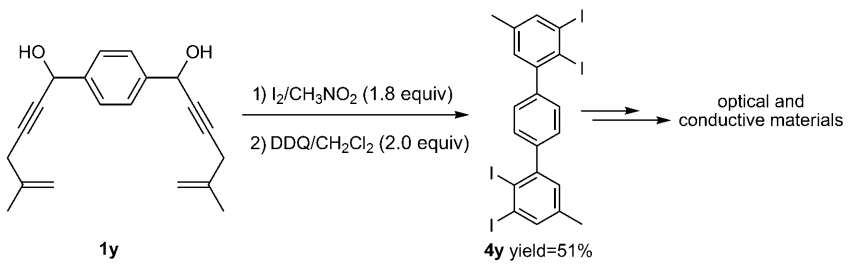
In conclusion, we have reported an iodonium-induced carbocyclizations of alkenes with hydroxylated alkynes. These transition-metal free reactions are mild, efficient, clean, and simple to perform and can convert hydroxylated enynes into six-membered cyclic products of high value including diiodocyclohexadiene and 2,3-diiodobenzene. In this process, several C−X (C, I, Br) bonds are formed. The reaction is atom economic and all the halogen atoms (I and Br) generated from the electrophiles are used effectively. The dihalogenated moiety can be readily introduced into the benzene in a position usually not easily to functionalize.



Scheme 2. Hydroxylated enynes **1w,x** with styrene as R group.

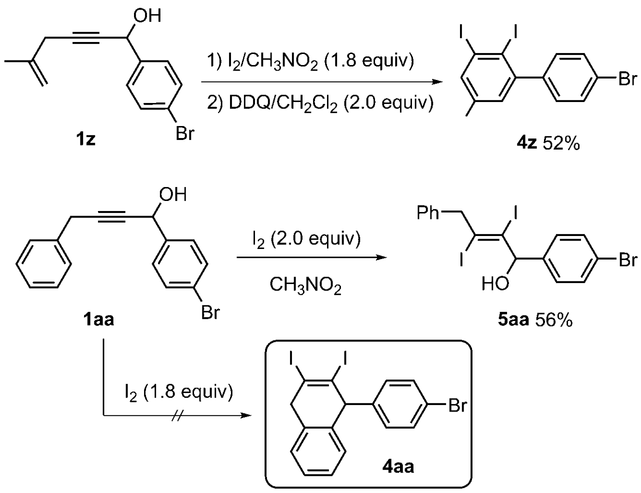
## Experimental Section

$I_2$ (92 mg, 0.36 mmol, 1.8 equiv) was added to a solution of hydroxylated alkynes **1** (0.20 mmol) in $CH_3NO_2$ (3.0 mL) at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was diluted with ethyl ether (40 mL), washed with water, saturated brine, dried over $Na_2SO_4$, and evaporated under reduced



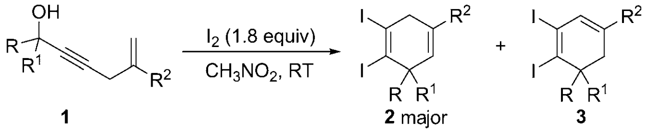
Scheme 3. Synthesis of 2,2′′,3,3′′-tetraiodo-5,5′′-dimethyl-1,1′:4′,1′′-terphenyl **4y**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

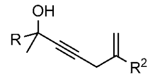
pressure. The residue was added in $CH_2Cl_2$ (6 mL) without purification, and then DDQ (90 mg, 0.40 mmol) was added and the reaction was stirred at room temperature. When the reaction was considered complete as determined by TLC analysis, $Na_2S_2O_3$ was added and the reaction mixture was diluted with ethyl ether (40 mL), washed with water, saturated brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding 2,3-diiodobenzenes **4**.



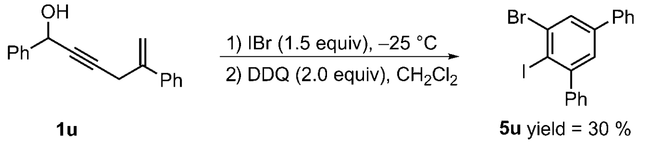
Scheme 4. Comparison of the substrates **1z** and **1aa**.

Table 3. Synthesis of 1,2-diiodo-4-methylcyclohexadiene from hydroxylated enynes**1ab–ae**.[a]



| Entry | Substrates R, $R^1$ | 2/3[b] | Yield[%][c] |
|---|---|---|---|
| 1 |  <br>**1ab** R, $R^2=CH_3$ | 5:2 | 55 |
| 2 | **1ac** R = Ph, $R^2=CH_3$ | 2:1 | 88 |
| 3 | **1ad** R = $CH_3$, $R^2$ = Ph | 5:2 | 88 |
| 4 | **1ae**[d] R = styrene $R^2=CH_3$ | 2:1 | 76 |

[a] Reaction conditions: **1a** (0.2 mmol), $I_2$ (1.8 equiv) in $CH_3NO_2$ (3.0 mL) at room temperature. [b] The ratio of **2**/**3** is determined by NMR analysis. [c] Yield of isolated product. [d] This reaction was carried out at 0°C.



Scheme 5. Synthesis of 5′-bromo-4′-iodo-1,1′:3′,1′′-terphenyl **5u** from hydroxylated enyne **1u**.

## Acknowledgements

We are grateful to the National Science Foundation (NSF-21072080) for financial support. We acknowledge the National Basic Research Program of China (973 Program), 2010CB833203 and the Fundamental Research Funds for the Central Universities.

**Keywords:** allenes · carbocyclization · electrophilic cyclization · iodine · olefins

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[10] The molecular structure of **3a** was determined by means of X-ray crystallographic studies; CCDC-798186 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Received: December 31, 2010