Carbocyclization

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Electrophilic Cyclization of 1,5-Enynes**

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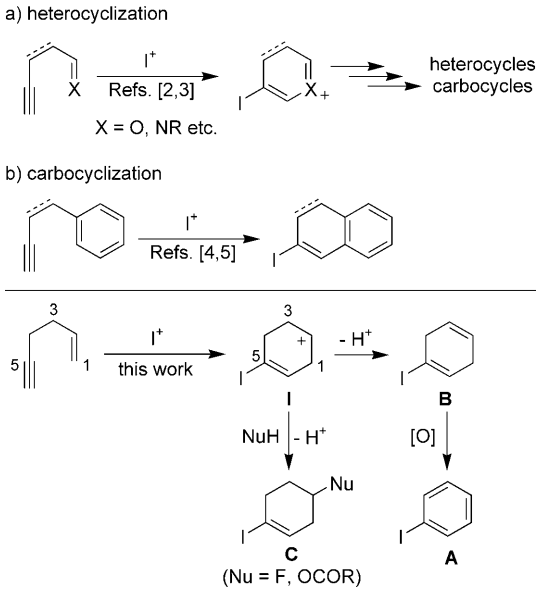
Dedicated to Professor Horst Kessler on the occasion of his 70th birthday

The electrophilic cyclization of alkynes was studied in detail by Barluenga, Larock, and others and has thus emerged as a broadly applicable strategy for the efficient synthesis of small-molecule targets.[1] For instance, the cyclization of heteroatom nucleophiles with tethered alkynes is useful for the direct formation of carbon–heteroatom bonds (Scheme 1 a). Several



Scheme 1. Iodonium-induced cyclizations of alkynes.

important syntheses of carbocycles and, in particular, heterocycles have been developed using this approach,[2,3] most of which employ iodine electrophiles to trigger the heterocyclization. Despite an early report by Barluenga et al.,[4] iodonium-induced carbocyclization has been demonstrated only for the intramolecular arylation of alkynes (i.e., arene nucleophiles; Scheme 1 b)[5] and when malonates are used as nucleophiles.[6] Remarkably, simple olefins have apparently not been used as internal carbon nucleophiles in this way.[7] Here we show that 1,5-enynes are powerful substrates in iodonium-induced carbocyclizations yielding six-membered carbocycles with great structural diversity (**A**–**C**; Scheme 1). The reaction outcome is predictable over a broad range of densely functionalized substrates.

The transition-metal-catalyzed cycloisomerization of 1,5-enynes has evolved into a broadly useful transformation that delivers various carbocyclic products of high complexity.[8,9] As part of our ongoing studies on the use of enynes in domino reactions,[10] we found that several transition-metal-catalyzed processes can be run with traditional electrophiles such as I^+ in an analogous way incorporating I rather than H in the final product.[11] However, the electrophilic cyclization of simple 1,5-enynes is a particularly challenging chemical transformation given the fact that a range of background reactions can arise from the positively charged intermediate **I**. Furthermore, reactive olefins may compete with the tethered alkyne for the electrophile,[12] while olefins that lack the required nucleophilicity do not undergo cyclization with the activated alkyne.

Our initial attempts to react various 1,5-enynes with I_2 in CH_2Cl_2 at 23 °C resulted in the formation of complex mixtures. We then discovered that potential side reactions can be suppressed if an excess of *N*-iodosuccinimide (NIS) is used at 50 °C. As shown in Table 1, treating a variety of 1,5-enynes **1** with NIS (3 equiv) under aerobic conditions gave the iodobenzenes **2** in high yields. Oxidative aromatization was accomplished with R^1 being aryl, alkyl and hydrogen substituents (Table 1, entries 1–10). Particularly notable is the smooth reaction of bromoalkyne **1k** to produce the 1-bromo-2-iodobenzene derivative **2k** (Table 1, entry 11).

A wide range of 1,5-enynes with different substituents R^2–R^5 were effectively converted into the corresponding benzenes. Unfortunately, substrates lacking a substituent at C2 (i.e., $R^4 = H$) turned out to be unreactive under the reaction conditions. This result indicates that the substituent at C2 is required to stabilize the positive charge in the cyclic intermediate **I**. The reaction tolerates the presence of a number of functional groups such as ester, ether, silyl ether, nitro, and azide groups, although enynes containing a free hydroxy or aldehyde group reacted in only poor yields. Most remarkably, we found that even fully substituted benzenes could be accessed in good yields (Table 1, entry 24).

Several additional observations merit note. Transformations of enynes **1** into benzenes **2** most likely proceed through dienes **B** as delineated in Scheme 1. For instance, if the cyclization of enyne **1t** is conducted under argon rather than under aerobic conditions, aromatization is slowed dramatically and accompanied by diene formation (argon: 8% yield

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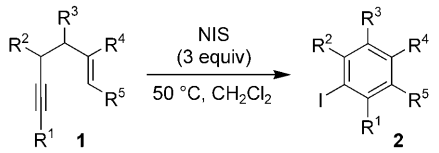
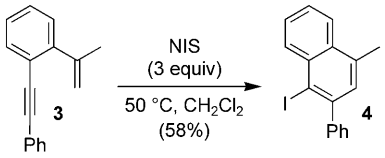
Table 1: NIS-mediated formation of iodobenzenes.[a]



Entry	Product						Yield [%][b]
	R^1	R^2	R^3	R^4	R^5		
1	Ph	H	TIPSO$(CH_2)_3$	Me	H	**2a**	96
2	4-MeO(C_6H_4)	H	TIPSO$(CH_2)_3$	Me	H	**2b**	93
3	4-$MeO_2C(C_6H_4)$	H	TIPSO$(CH_2)_3$	Me	H	**2c**	76
4	4-$O_2N(C_6H_4)$	H	TIPSO$(CH_2)_3$	Me	H	**2d**	59
5	4-Cl(C_6H_4)	H	TIPSO$(CH_2)_3$	Me	H	**2e**	70
6	2-naphthyl	H	TIPSO$(CH_2)_3$	Me	H	**2f**	95
7	2-thienyl	H	TIPSO$(CH_2)_3$	Me	H	**2g**	86
8	H	H	TIPSO$(CH_2)_3$	Me	H	**2h**	75
9	Me	H	TIPSO$(CH_2)_3$	Me	H	**2i**	81
10	CH_2Ph	H	Me	Ph	H	**2j**	88
11	Br	H	Me	Ph	H	**2k**	90
12	4-MeO(C_6H_4)	H	H	Ph	H	**2l**	82
13	4-MeO(C_6H_4)	H	Me	Ph	H	**2m**	93
14	H	H	Ph	Ph	H	**2n**	78
15	Ph	H	*n*Bu	Me	H	**2o**	92
16	Ph	H	MeO$(CH_2)_3$	Me	H	**2p**	92
17	Ph	H	TBSO$(CH_2)_3$	Me	H	**2q**	44[c]
18	Ph	H	HO$(CH_2)_3$	Me	H	**2r**	13[d]
19	Ph	H	OHC$(CH_2)_2$	Me	H	**2s**	19
20	Ph	H	$N_3(CH_2)_3$	Me	H	**2t**	76
21	Ph	H	TIPSO$(CH_2)_3$	*n*Bu	H	**2u**	74
22	4-MeO(C_6H_4)	H	Me	Ph	Me	**2v**	71
23	*E*-MeO_2CMeC=CH	H	Me	TIPSO$(CH_2)_2$	Me	**2w**	62
24	4-MeO(C_6H_4)	Me	Me	Ph	Me	**2x**	71

[a] Conditions: Substrate (0.1 M), NIS (3 equiv), 50 °C, CH_2Cl_2. [b] Yield of pure product after column chromatography. [c] Cleavage of silyl ether was observed (44% yield of **2q**, and 54% yield of **2r**). [d] A variety of by-products were obtained, some of which arise from intramolecular addition of the hydroxy group. TIPS = Si(*i*Pr)$_3$, TBS = Si*t*BuMe$_2$.

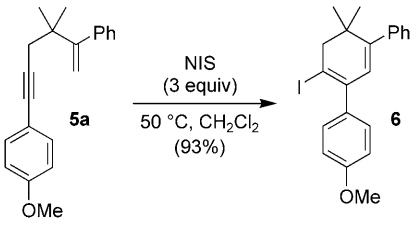
of **2t**, 63% yield of 1,4-diene **13t**, and unidentified compounds after 2 h; air: 76% yield of **2t** after 2 h). Iodonaphthalenes were produced from 1-alkenyl-2-alkynylbenzenes as indicated by the conversion **3**→**4** in 58% yield [Eq. (1)].



(1)

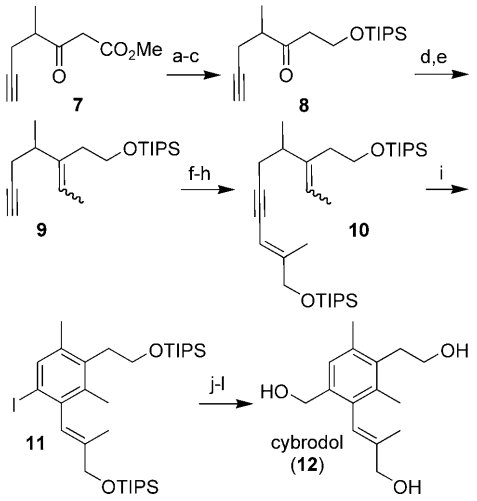
When aromatization is blocked through a further substituent at C3, enynes (e.g., **5a**) were found to give 1,3-diene products as well [Eq. (2)].

The application of the new annulation strategy,[13] in which the aromatic ring is assembled in a single step with all substituents already in place, to the synthesis of the sesquiterpenoid cybrodol illustrates the utility of this methodology. Isolated from the bird's nest fungus *Cyathus bulleri* by Ayer et al. in 1980, cybrodol (**12**) is a pentasubstituted benzene



(2)

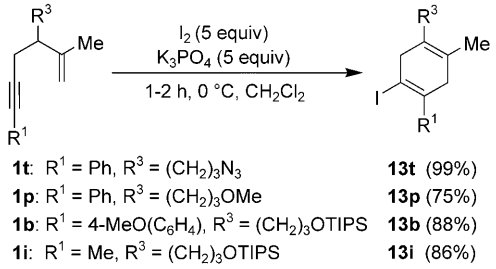
derivative.[14] As outlined in Scheme 2, we began our synthesis by transforming 3-oxo ester **7** into triisopropylsilyl (TIPS) ether **8** using standard protocols. Addition of EtMgBr and



Scheme 2. Total synthesis of cybrodol (**12**). Reagents and conditions: a) $LiAlH_4$, 0 °C, Et_2O; b) TIPSCl, imidazole, 23 °C, DMF, 97% over two steps; c) PCC, 23 °C, CH_2Cl_2, 73%; d) EtMgBr, 0 °C to 23 °C, THF, 81%; e) Martin's sulfurane, NEt_3, 23 °C, CH_2Cl_2, 98%; f) (*E*)-MeO_2C-MeC=CHBr, [$PdCl_2(PPh_3)_2$] (2 mol%), CuI (4 mol%), NEt_3, 50 °C, quant.; g) DIBAL-H, −78 °C, CH_2Cl_2; h) TIPSCl, imidazole, 23 °C, DMF, 99% over two steps; i) NIS, 50 °C, CH_2Cl_2, 89%; j) 1) *t*BuLi, −78 °C, THF, 2) MeOC(O)CN, −78 °C to 23 °C, 56%; k) DIBAL-H, −78 °C, CH_2Cl_2; l) HF, 23 °C, MeCN, 80% over two steps. PCC = pyridinium chlorochromate.

subsequent regioselective elimination by exposure to Martin's sulfurane ([$PhC(CF_3)_2O]_2SPh_2$)[15] produced 1,5-enyne **9** in 79% yield over two steps. Sonogashira coupling of **9** with (*E*)-methyl 3-bromo-2-methylacrylate[16] installed the last side chain, which was then elaborated to provide bis(silyl ether) **10**. In the pivotal step, oxidative cyclization with NIS in CH_2Cl_2 at 50 °C gave iodobenzene **11** in excellent 89% yield. Addition of the lithium species generated from **11** to methyl cyanoformate gave the fully constructed aromatic core, which was finally subjected to reduction and desilylation to furnish cybrodol in 45% yield over the three steps. The NMR data of synthetic **12** was identical to that reported for the natural substance.[17]

We also found that 1,5-enynes bearing a substituent both at C2 and C3 (R^3, $R^4 \neq H$) can be smoothly transformed into the corresponding cyclic 1,4-dienes **13** upon treatment with I_2 and K_3PO_4 in CH_2Cl_2 at 0 °C (Scheme 3). A reaction time of only 1–2 hours was required to reach completion. When the

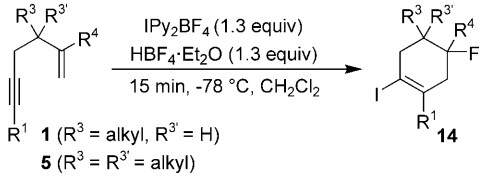


Scheme 3. Formation of 1-iodocyclohexa-1,4-dienes **13**.

reactions were run for a longer period of time, significant amounts of benzenes **2** arose from the subsequent aromatization of **13**.

We next investigated the use of the bis(pyridine)iodonium tetrafluoroborate reagent[18] (IPy_2BF_4) developed by the Barluenga group in reactions of 1,5-enynes. To our surprise, an equimolar mixture of IPy_2BF_4 and $HBF_4{\cdot}Et_2O$ at −78 °C in CH_2Cl_2 rapidly (15 min) converted 1,5-enynes into 4-fluoro-1-iodocyclohexenes **14** (Table 2). Under these optimized conditions, a range of substrates underwent fluorination in moderate to excellent yields to give cyclohexene products. Once again, only 1,5-enynes having a substituent at C2 reacted; enynes with $R^4 = H$ proved to be unreactive. This cyclization–fluorination reaction of 1,5-enynes represents an attractive and simple means of incorporating fluorine into complex organic molecules.[19,20]

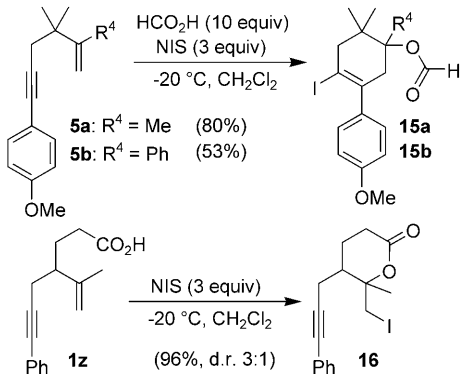
Table 2: Synthesis of 4-fluoro-1-iodocyclohexenes **14** by use of IPy_2BF_4.[a]



Entry	Substr.	Product R^1	R^3	$R^{3'}$	R^4		Yield [%][b]
1	**5a**	4-MeO(C_6H_4)	Me	Me	Me	**14a**	78
2	**5b**	4-MeO(C_6H_4)	Me	Me	Ph	**14b**	53
3	**5c**	Me	-$(CH_2)_5$-		Me	**14c**	33
4	**1r**	Ph	$HO(CH_2)_3$	H	Me	**14d**	59[c]
5	**1o**	Ph	*n*Bu	H	Me	**14e**	85[c]
6	**1t**	Ph	$N_3(CH_2)_3$	H	Me	**14f**	80[c]
7	**1y**	Ph	$MsO(CH_2)_3$	H	Me	**14g**	73[c]

[a] Conditions: Substrate (0.05 M), IPy_2BF_4 (1.3 equiv), $HBF_4{\cdot}Et_2O$ (1.3 equiv), 15 min, −78 °C, CH_2Cl_2. [b] Yield of pure product after column chromatography. [c] Obtained as a 1:1 mixture of diastereomers. Ms = CH_3SO_2.

Having established the feasibility of incorporating a nucleophile into the cyclohexene core, we sought to briefly investigate the introduction of oxygen nucleophiles. To our delight, when 1,5-enynes **5a** and **5b** were subjected to an excess of NIS (3 equiv) and formic acid (10 equiv) at −20 °C in CH_2Cl_2, the esters **15a** and **15b** were formed in 80% and 53% yield, respectively (Scheme 4). Of importance, an enyne with a tethered carboxylic acid does not react to form a cyclohexene derivative; as shown for the conversion of acid **1z**, only the iodolactonization product **16** was obtained.



Scheme 4. Formation of esters **15**.

In conclusion, we have developed iodonium-induced carbocyclizations of alkenes with appended alkynes. The transition-metal-free processes are experimentally simple to perform and convert 1,5-enynes into six-membered cyclic products of high value including highly substituted benzenes, 1,4-cyclohexadienes, and 4-fluorocyclohexenes. We are continuing to explore the enormous potential of electrophilic enyne cyclizations for the synthesis of diverse carbocyclic scaffolds.

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