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Selective Formation of Six-Membered Oxa- and Carbocycles by the In(III)-Activated Ring Closure of Acetylenic Substrates

Wen-Wei Qiu, Karavadhi Surendra, Liang Yin, and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University Cambridge, Massachusetts 02138, United States

corey@chemistry.harvard.edu

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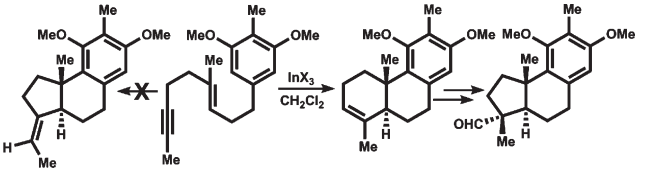
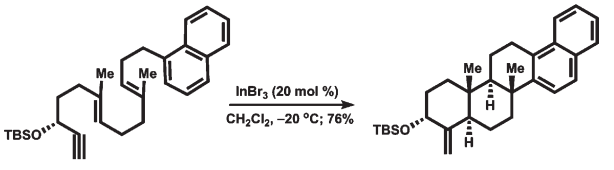
ABSTRACT



Fifteen examples are disclosed of efficient In(III)-catalyzed six-membered ring closure leading to bi-, tri-, and tetracyclic products.

We recently published a demonstration that indium bromide and iodide possess unusually high affinity for carbon−carbon triple bonds and that this interaction effectively bestows electrophilic reactivity on a C≡C subunit. Such activation has enabled the use of C≡C to initiate enantioselective cationic polycyclization reactions for example **1** → **2** (Scheme 1).[1]

Scheme 1. In(III)-Catalyzed Enantioselective Cationic Polycyclization



1 **2**

The idea for this approach arose from the hypothesis that the 5d orbitals of In(III) may be sufficiently lowered in energy to allow some mixing with the vacant 5p orbital and the possibility that the resulting p−d hybrids could coordinate in a bidentate mode with the two orthogonal π-bonding orbitals of C≡C so as to favor complexation. Some support for this approach came from the observation that $InBr_3$ and InI_3 are considerably more soluble in solutions of 1-heptyne in CH_2Cl_2 than in CH_2Cl_2 alone.

In this paper we report a range of new examples of In(III)-promoted cyclization reactions of unsaturated and aromatic acetylenes. These studies have revealed a strong preference for the formation of six-membered over five-membered rings in substrates for which both cyclization pathways are possible. Nine examples of such cyclization reactions in dry CH_2Cl_2 forming bicyclic benzenoid products are shown in Table 1.

In each case the In(III)-promoted cyclization involves an aryl acetylene as substrate, and in each case the product is a bicycle in which a six-membered ring is fused to the aromatic ring. The cyclization shown in entry 1 of Table 1 proceeded with translocation of hydrogen to furnish a β-tetralone rather than an unsaturated β-tetralol, possibly because the latter undergoes isomerization under the reaction conditions. Most of the cyclizations shown in Table 1 occur readily at room temperature. However, the transformations summarized in entries 3 and 4 required heating to ca. 55 °C. The cyclization can occur with either a TBS ether or the corresponding alcohol (entries 4 and 5).

(1) Surendra, K.; Qiu, W.-W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724–9726.

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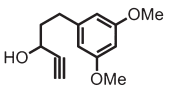
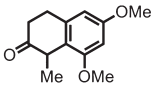
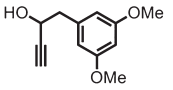
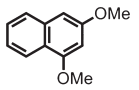
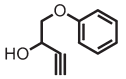
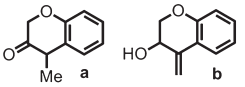
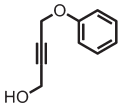
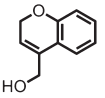
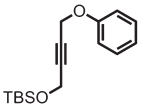
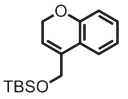
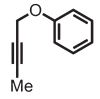
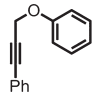
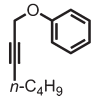
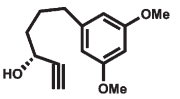
Table 1. In(III)-Catalyzed Polycyclization in CH_2Cl_2 at 23 °C

entry	substrate	product	time (h)	yield (%)[a]
1			2	91
2			2	85
3			2	99[b,c]
4			2	97[c]
5			12	63
6			4	55[d]
7			4	91[d]
8			12	83
9			12	80

[a] Isolated yields of products fully characterized by NMR and MS. [b] The ratio of cyclization products was a:b = 93:6. [c] Reaction was carried out at 55°C. [d] Reaction was carried out at −20 °C.

In the examples outlined in entries 1 and 3 of Table 1, cyclization is followed by a prototropic rearrangement to a ketone. These reactions illustrate a new and useful one-step route to β-tetralones. The transformation shown in the example in entry 2 of Table 1 is the result of dehydration of the initial bicyclic allylic alcohol. The substrates used for the reactions summarized in Table 1 are readily available as described in the Supporting Information.

The preference for six- over five-membered ring formation has also been observed for In(III)-activated triple bonds proximate to an ethylenic linkage. Table 2 summarizes six examples of such bicyclization processes (with InI_3 in dry CH_2Cl_2) leading to tri- and tetracyclic products (racemic) with the exclusive formation of six-membered rings and with complete diastereoselectivity. As with the cases disclosed in Table 1, the initiating triple bond may be either terminal or disubstituted. The efficiency of the cyclization reactions shown in Table 2 is noteworthy, generally corresponding to ca. 90% per ring formed. These bicyclizations are very easy to perform, as is apparent from a sample procedure.[2]



3

Figure 1. Unreactive acetylenic substrate.

Even though seven-membered (Table 1, entries 1 and 3) or five-membered (entries 2, 4−9) ring formation could, in principle, have occurred, no such products were observed. Thus, it appears that coordination of In(III) to a C—C≡C subunit not only induces electrophilicity in the triple bond but also bends the C—C≡C angle in a way that facilitates six-membered ring formation. We also have found that acetylenic substrates that can potentially cyclize to form seven- or eight-membered rings undergo cyclization very slowly or not at all, as observed for instance with substrate **3** (Figure 1).

We have tested for the possibility that the reactions summarized in Tables 1 and 2 may involve In(III) activation by traces of H_2O present in the reaction mixture with the complex H_2O-InI_3 essentially behaving as a protic activation (i.e, Brønsted) catalyst. This was done by studying the cyclization in the presence of 2,6-di-*tert*-butylpyridine which would innhibit a proton donor but not InI_3 (which does not complex with this sterically encumbered base). It was determined that the cyclizations shown in Table 2, entries 2 and 3, proceed in the same way in the presence or absence of di-*tert*-butylpyridine to give the same product in >90% yield.

Although six-membered rings are formed preferentially in the cyclization reactions shown in Tables 1 and 2, it is possible to generate structures containing five-membered rings from the products shown in the tables by ring contraction. For instance, the product in Table 2, entry 5 (**4**) was readily transformed into the 5−6−6 fused ring structure **6** via the epoxide **5**, as shown in Scheme 2. The structures of **5** and **6** were established by spectroscopic measurements, including ^{1}H NMR and NOE measurements.

The details of the preparation of the acetylenic substrates shown in Table 2 are given in the Supporting Information. In brief, the various starting materials **9**

(2) Procedure for the cyclization shown in Table 2, entry 5: To a mixture of InI_3 (100 mg, 0.2 mmol) and CH_2Cl_2 (8.0 mL) was added substrate (286 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) via cannula at −20 °C. After stirring at −20 °C for 12 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to afford the tricyclic product in 83% yield (Table 2, entry 5).

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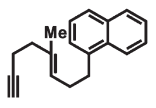
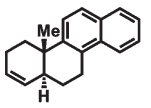
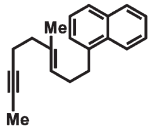
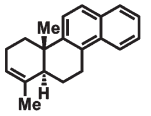
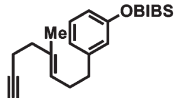
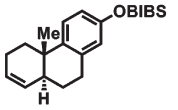
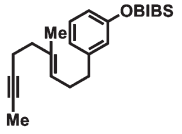
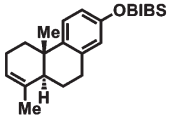
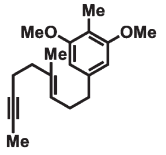
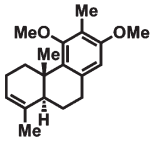
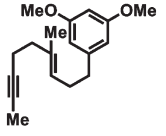
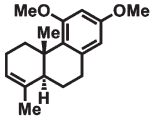
Table 2. InI_3-Catalyzed Cyclization (20 mol %, CH_2Cl_2, −20°C)

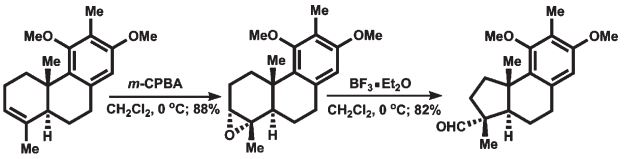
entry	substrate	product	time (h)	yield (%)[a]
1			4	79
2			4	83
3			4	96[b]
4			4	98
5			12	83
6			12	88

[a] Isolated yields of products fully characterized by NMR and MS. [b] BIBS = di-*tert*-butylisobutylsilyl.[3]

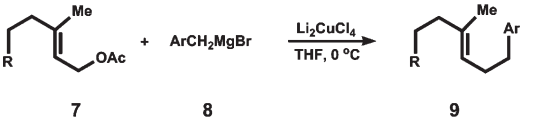
were made by the Li_2CuCl_4-catalyzed[4] process shown in Scheme 3, specifically coupling of an allylic acetate **7** with a benzylic Grignard reagent **8**.

In conclusion, the present research further demonstrates the utility of the $InBr_3$- or InI_3-activation of acetylenic substrates in cationic cyclization processes leading to useful polycyclic structures. The constructions described

Scheme 2. Ring Contraction To Generate a Five-Membered Ring



Scheme 3. Coupling Method for Preparation of the Substrates in Table 2



provide efficient and practical routes to the compounds specified in Tables 1 and 2. The complete selectivity of the acetylenic ring closure for six- over five-membered rings is especially noteworthy. Preferential formation of six-membered rings has also been noted for cyclizations of unsaturated acetylenes using Hg(II), e.g. $Hg(OTf)_2$, as a reagent.[5]

As noted earlier[1] indium(III) catalysis of cationic cyclizations of acetylenic substrates has substantial economic, environmental, and safety advantages over the use of Au(I), Pt(IV), or Ga(III) catalysis.[6–9]

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Supporting Information Available. Experimental procedures and characterization data for all reactions and products, including copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563–4565. (b) Imagawa, H.; Lyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451–453.

(6) Gold salts have recently been used to catalyze cationic cyclizations of acetylenic olefins. See: (a) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888–2891. (b) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277. (c) Lykakis, I. N.; Efe, C.; Gryparis, C.; Stratakis, M. *Eur. J. Org. Chem.* **2011**, 2334–2338.

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