

# Diiodoindium(III) Cation, $\text{InI}_2^+$ , a Potent Yneophile. Generation and Application to Cationic Cyclization by Selective $\pi$ -Activation of $\text{C}\equiv\text{C}$

Karavadhi Surendra and E. J. Corey\*

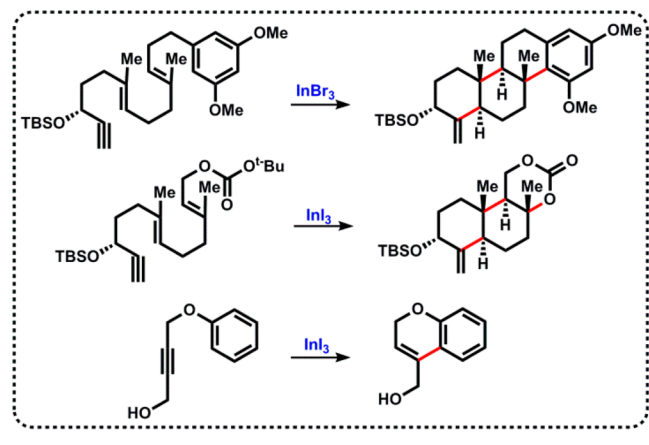
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

**S** Supporting Information

**ABSTRACT:** The removal of the iodide ion from indium triiodide by means of reactive Ag(I) salts leads to the formation of the highly reactive ligandless cation  $\text{InI}_2^+$ , which is unusual in having two vacant low-lying p-orbitals. This bivalent Lewis acidity leads to an especially high affinity for the two orthogonal  $\pi$ -bonds of carbon–carbon triple bonds. Consequently, the double-coordinating  $\text{InI}_2^+$  is an especially effective reagent for the selective activation of  $\text{C}\equiv\text{C}$  and the catalytic initiation of cationic cyclization processes. A number of such reactions are described to demonstrate synthetic utility.

We recently described a number of useful cationic  $\pi$ -cyclization and polycyclization reactions which are initiated by selective In(III) iodide or bromide complexation at a carbon–carbon triple bond.<sup>1,2</sup> Three examples are shown in Scheme 1. The In(III)-induced cyclization reactions are

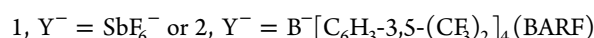
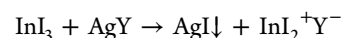
## Scheme 1. Indium(III)-Catalyzed Cationic Cyclizations



stereocontrolled, selectively initiated at  $\text{C}\equiv\text{C}$  vs  $\text{C}=\text{C}$ , and occur in the range of  $-20$  to  $+25$  °C over several hours using ca. 20 mol % of  $\text{InI}_3$  or  $\text{InBr}_3$  in dry  $\text{CH}_2\text{Cl}_2$  as solvent.<sup>1,2</sup>

In this communication, we report the generation of an even more effective catalyst for such cyclizations, the cation  $\text{InI}_2^+$ , which, because of its enhanced affinity for the acetylenic  $\pi$ -system, can be used in amounts as small as 1 mol % to effect faster cyclization at  $-20$  °C as compared to  $\text{InBr}_3$  or  $\text{InI}_3$ . The  $\text{InI}_2^+$ -initiated cyclizations were clean and afforded the same major product as from  $\text{InI}_3$  or  $\text{InBr}_3$  catalysis, in excellent yield.

The generation of the  $\text{InI}_2^+$  cation has been accomplished in two ways at 0 °C in dry  $\text{CH}_2\text{Cl}_2$  as solvent:



These reactions are rapid at 0 °C, and in the case of AgBARF, a precipitate of silver iodide and an orange solution of  $\text{InI}_2^+$  BARF<sup>−</sup> is formed (97% yield after 15 min). With  $\text{AgSbF}_6$  as a reactant, both products precipitate, i.e., AgI and  $\text{InI}_2^+$   $\text{SbF}_6^-$ , as an orange powdery mixture which has negligible solubility in  $\text{CH}_2\text{Cl}_2$ . So far, we have not succeeded in obtaining either of these as crystalline  $\text{InI}_2^+$  salts for X-ray diffraction structural analysis. However, we were able to generate from  $\text{InI}_3$  and 2 equiv of 1,10-phenanthroline a crystalline salt  $\text{InI}_2(\text{Phen})_2^+ \text{I}^-$  (3), with the X-ray crystallographic structure shown in Figure 1.

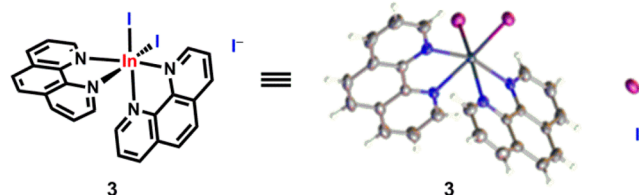
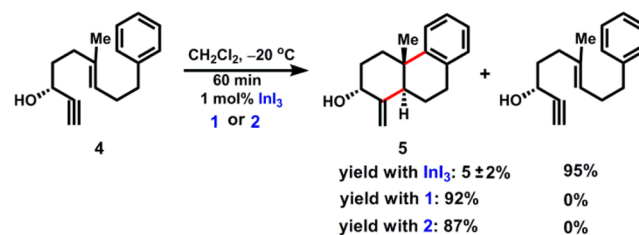


Figure 1. X-ray crystal structure of  $\text{InI}_2(\text{Phen})_2^+\text{I}^-$  (3).

The soluble  $\text{InI}_2^+$  BARF<sup>−</sup> salt 2 and insoluble  $\text{InI}_2^+$   $\text{SbF}_6^-$  salt 1 are both powerful catalysts for  $\text{C}\equiv\text{C}$  initiated  $\pi$ -cyclization reactions under anhydrous conditions in  $\text{CH}_2\text{Cl}_2$  and are much more reactive than  $\text{InI}_3$  or  $\text{InBr}_3$ , as indicated by the results summarized in Scheme 2.

## Scheme 2. Relative Reactivities of $\text{InI}_3$ , $\text{InI}_2^+$ $\text{SbF}_6^-$ (1), and $\text{InI}_2^+$ BARF<sup>−</sup> (2) in the Cyclization of 4 to 5<sup>1</sup>



Received: June 30, 2014

Published: July 24, 2014

We have also applied the diiodoindium cation as a catalyst for six of the polycyclization reactions described previously<sup>1</sup> with excellent results. The cyclizations proceeded rapidly, efficiently, and stereoselectively to afford the six chiral polycycles shown in Table 1. The use of 10 mol % of catalyst

**Table 1.** Six  $\text{InI}_2^+/\text{B}^-[\text{C}_6\text{H}_3-3,5-(\text{CF}_3)_2]_4$  (10 mol %) Catalyzed Polycyclization Reactions in  $\text{CH}_2\text{Cl}_2$  at  $-20^\circ\text{C}$

Entry	Substrate	Product	Yield, <sup>a,b</sup>
1			84
2			88
3			90
4			86
5			90
6			80

<sup>a</sup>Isolated yields of products fully characterized by NMR, IR and MS. <sup>b</sup>Reaction times with 0.1 M concentration of substrate were generally 30 min to 2 h, after which no starting material remained as determined by TLC analysis. <sup>c</sup>BIBS = di-*tert*-butylisobutylsilyl. <sup>d</sup>Cyclization occurred both *ortho* and *para* to the phenolic hydroxyl group.

resulted in complete reaction at  $-20^\circ\text{C}$  in conveniently short reaction times (30–120 min). The starting materials are readily available by a catalytic enantioselective route.<sup>1</sup> It is important to note that these and all other  $\text{InI}_2^+$ -catalyzed processes must be conducted with rigorous exclusion of moisture.

The scope of the  $\text{InI}_2^+$ -catalyzed cationic cyclization process is further illustrated by six additional examples involving achiral substrates that are outlined in Table 2. In each case the reactions are rapid at  $-20^\circ\text{C}$  with 5–10 mol % of catalyst and afford yields of 85% or better of purified product. The cyclizations in entries 1–3 all occur with complete diastereoselectivity and lead to racemic products. In principle, the use of a chiral cationic indium reagent with a suitable ligand could allow the direct construction of the chiral products shown in entries 1–3 of Table 2.

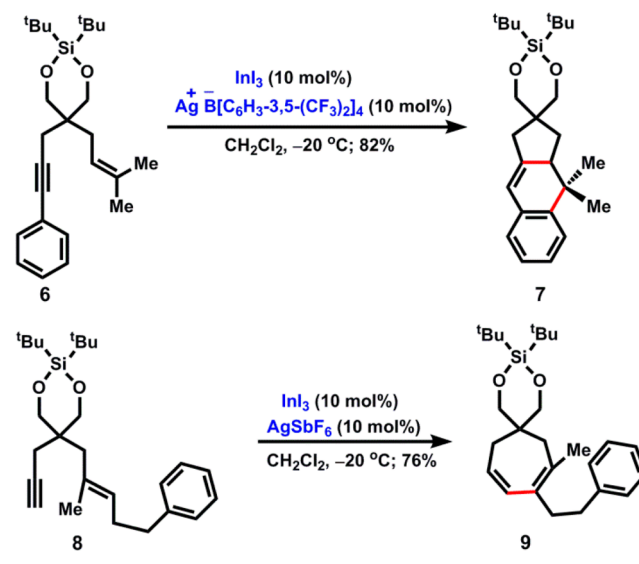
We have also investigated the synthesis of spiro ring systems using the three di-*tert*-butylsilyl-protected 1,3-diols, **6** and **8**, as shown in Scheme 3. In each case, smooth monocyclization was achieved to form the products **7** and **9** in good yield at  $-20^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$ .<sup>3,4</sup> In contrast to the cyclic silyl ethers **6** and **8**, the

**Table 2.** Six  $\text{InI}_2^+/\text{B}^-[\text{C}_6\text{H}_3-3,5-(\text{CF}_3)_2]_4$  (10 mol %) Catalyzed Polycyclization Reactions in  $\text{CH}_2\text{Cl}_2$  at  $-20^\circ\text{C}$

Entry	Substrate	Product	Yield, <sup>a,b</sup>
1			87
2			90
3			84
4			87
5			89
6			82

<sup>a</sup>Isolated yields of products fully characterized by NMR, IR and MS.

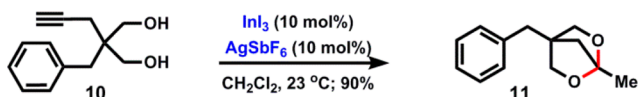
### Scheme 3. Formation of Spiro Rings



corresponding acetonides were unreactive under the same conditions, presumably because the cationic indium reagent coordinates preferentially with the acetonide oxygens. This limitation was somewhat surprising because of the satisfactory results obtained with other oxygen containing substrates (see Schemes 2 and 3 and Tables 1 and 2). The formation of the seven-membered ring in the cyclization **8** → **9** of Scheme 3, rather than the alternative six-membered carbocycle, is also of interest.<sup>5</sup>

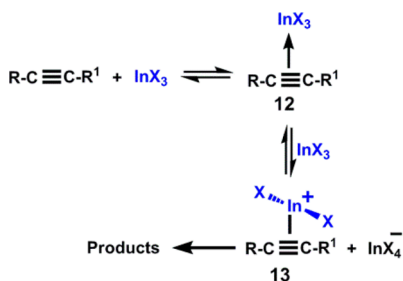
We have also shown that the activation of  $C\equiv C$  by  $InI_2^+$   $SbF_6^-$  (**1**) can be used for the conversion of acetylenic 1,3-diols to bridged cyclic ketals in a manner reminiscent of the gold-catalyzed formation of ketals from acetylenes,<sup>6</sup> as illustrated by the ketalization of acetylene **10** to **11** in Scheme 4. The cyclizations of **6** to **7** and **8** to **9** do not take place with AgBARF alone in  $CH_2Cl_2$  at  $-20^\circ C$ .

Scheme 4. Acetylenic Ketalization



The  $InI_2^+ X^-$  reagents **1** and **2** are of interest not only for synthetic purposes but also with regard to their structure. It would seem likely that the  $InI_2^+$  cation is a linear structure with sp bonding between indium and iodine. Such a structure with two vacant p-orbitals could reasonably be expected to coordinate with  $C\equiv C$  as a bidentate ligand, i.e., in a crisscrossed geometry in which each vacant p-orbital of indium interacts with one of the orthogonal  $\pi$ -orbitals of the triple bond. Such an interaction would explain the selective activation of  $C\equiv C$  in the presence of  $C=C$  as reported herein.<sup>7</sup>

It is also possible that the same mode of complexation could be involved in the cyclizations catalyzed by  $InBr_3$  and  $InI_3$  alone. In such an event, the participation of two  $InX_3$  molecules would seem logical by the pathway shown in Scheme 5, in

Scheme 5. Cationic Pathway for  $InX_3$ -Promoted Activation of  $C\equiv C$ 

which direct cyclization is induced by a cationic complex of the triple bond with  $InI_2^+$ , not  $InI_3$ . The results summarized in Scheme 2 (above) demonstrate clearly that the cyclization via a complex of type **13** occurs faster than that via **12**.

The activation of a nonliganded, Lewis acidic metal halide by silver(I) to effect cationic  $\pi$ -cyclizations is unprecedented, to the best of our knowledge. In contrast, there are many reports of Ag(I)-activation of phosphine coordinated palladium(II) halides (e.g., for cationic intramolecular Heck reactions<sup>10</sup> or Diels–Alder reactions<sup>11</sup>), coordinated Cu(II),<sup>12</sup> coordinated bromoboranes,<sup>13</sup> and bisphosphino-coordinated Au(I) complexes.<sup>14</sup>

This possibility is further supported by recent DFT calculations on transition state energetics for the cycloisomerization of 1,6-ynynes by  $InCl_3$ .<sup>8</sup>

The generation of other cationic metal halide with two low-lying vacant orbitals, as exemplified herein by  $InI_3 \rightarrow InI_2^+$ , may be possible and deserves study.

Our investigations on cationic indium(III) halides and their applications in catalysis and synthesis are continuing.

## ■ ASSOCIATED CONTENT

### Supporting Information

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

## ■ AUTHOR INFORMATION

### Corresponding Author

corey@chemistry.harvard.edu

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are grateful to Pfizer, Inc. and Gilead Sciences for a postdoctoral fellowship to K.S. and to Dr. S.-L. Zheng from Harvard University for the X-ray crystallographic analysis.<sup>9</sup> We thank Sigma-Aldrich for gifts of chemicals and Harrison A. Besser for experimental assistance.

## ■ REFERENCES

- (1) Surendra, K.; Qiu, W.-W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724.
- (2) Qiu, W.-W.; Surendra, K.; Corey, E. J. *Org. Lett.* **2011**, *13*, 5893.
- (3) Cristina, N.-O.; Patricia, P.-G.; Elena, H.-G.; Thorsten, L.; Cristina, R.; Salome, L.; Christophe, B.; Antonio, R.; Diego, J.; Antonio, M. E. *J. Am. Chem. Soc.* **2008**, *130*, 269.
- (4) The trans formations **6**  $\rightarrow$  **7** and **8**  $\rightarrow$  **9** have previously been reported using catalysis by  $Au(I)Cl$  and  $AgSbF_6$ .
- (5) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.
- (6) Antonioti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2010**, *127*, 9976.
- (7) We have also observed the generation of  $InBr_2^+$  using  $AgSbF_6$  and cyclizations with this reagent such as **4**  $\rightarrow$  **5**. The use of 0.5 equiv of  $AgSbF_6$  and 1.0 equiv of  $InI_3$  leads to a distinctly less reactive form of cationic indium(III) and argues against the possibility that the reactions described herein are mediated by  $In_2I_5^+$ .
- (8) Zhuo, L.-G.; Zhang, J.-J.; Yu, Z.-X. *J. Org. Chem.* **2014**, *79*, 3809.
- (9) See the Supporting Information for details.
- (10) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.
- (11) Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1841.
- (12) See Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407.
- (13) Hayashi, Y.; Rhode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502.
- (14) (a) Matsumoto, Y.; Selim, K. B.; Nakanishi, H.; Yamada, K.-I.; Yamamoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2010**, *51*, 404. (b) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888.