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Cyclization of 1-Bromo-2,7- and 1-Bromo-2,8-Enynes Mediated by Indium

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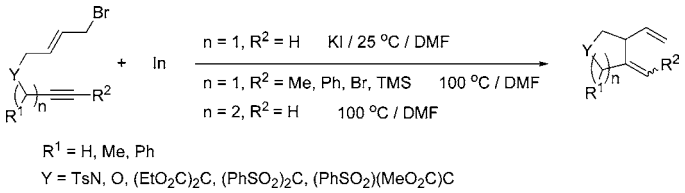
ABSTRACT



The cyclization of 1-bromo-2,7- and 1-bromo-2,8-enynes mediated by indium in DMF produced five- and six-membered cyclic compounds. Although KI was a necessary additive in the cyclization of terminal 1-bromo-2,7-enynes to give the desired products at 25 °C, reactions of terminal 1-bromo-2,8-enynes and internal 1-bromo-2,7-enynes with indium proceeded at 100 °C in DMF without KI. After cyclizations, subsequent cross-coupling reaction and iodolysis increase the usefulness of this reaction.

Organoindium reagents such as allylindiums, propargylindiums, and allenylindiums are of considerable value for regioselective and stereoselective allylation, propargylation, and allenylation of a variety of carbonyl and imine compounds to give the corresponding alcohols and amines.[1] Also, a range of indium-mediated organic reactions are useful for Reformatsky reactions,[2] Michael addition reactions,[3] cross-coupling reactions,[4] and allylic substitution reactions.[5] The intermolecular addition of organoindium reagents to C−C multiple bonds and nitriles are especially important synthetic tools for constructing 1,4-diene derivatives.[6] The reaction of allylindium with terminal alkynols and allenols in DMF at 100−140 °C produced the corresponding allylation products in good yields.[7] Although metal-catalyzed cyclizations have long been established as efficient methods for providing various types of cyclic compounds,[8] cyclization reactions involving organoindium reagents remain less-well explored. Despite the synthetic usefulness of intermolecular indium-mediated C−C bond formation,[1] the corresponding indium-mediated intramolecular cyclizations are mainly limited to Pd−In-mediated arylative cyclizations of allenyl carbonyl compounds,[9] intramolecular allylindation of ter-

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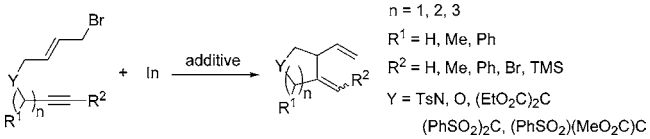
Scheme 1

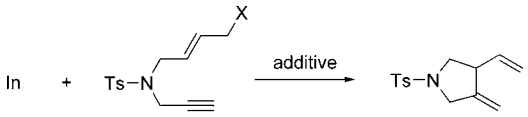


minal alkynes in aqueous media,[10] cyclizations of tethered propargyl bromides to carbonyl compounds,[11] atom-transfer cyclizations,[12] and cyclizations via *trans*-hydrometalation of alkynes by $InCl_3$ and DIBAL-H.[13] As part of the continuing effort to expand the synthetic utility of organoindium reagents,[14] we now report efficient intramolecular cyclizations of 1-bromo-2,7- and 1-bromo-2,8-enynes with indium (Scheme 1).

Our initial study focused on the use of *N*-(*E*)-4-bromo-2-butenyl-*N*-propargyl-*p*-toluenesulfonamide (**1a**) as a cyclization substrate (Table 1). Although treatment of **1a** with 1 equiv of indium did not produce the desired product **10** (25 °C, DMF, entry 4), heating **1a** at 80 °C gave **10** in 82% yield (entry 5). Reaction of **1b** with indium gave the desired product **10** in 80% yield (25 °C, 1 h, entry 6). Addition of potassium iodide (3 equiv) as an additive to **1a** gave the best result and afforded the carbocycle **10** in 83% yield (25 °C, 1 h, entry 9). We believe that KI is involved in the generation of allyl iodide derivatives during the cyclization reaction because indium-mediated cyclization of **1a** did not occur without KI at 25 °C for 1 h. DMF was the best solvent among several reaction media (DMF, THF, PhH, and $PhCH_3$) that were screened.

The cyclizations of terminal 1-bromo-2,7- and 1-bromo-2,8-enynes mediated by indium are summarized in Table 2.

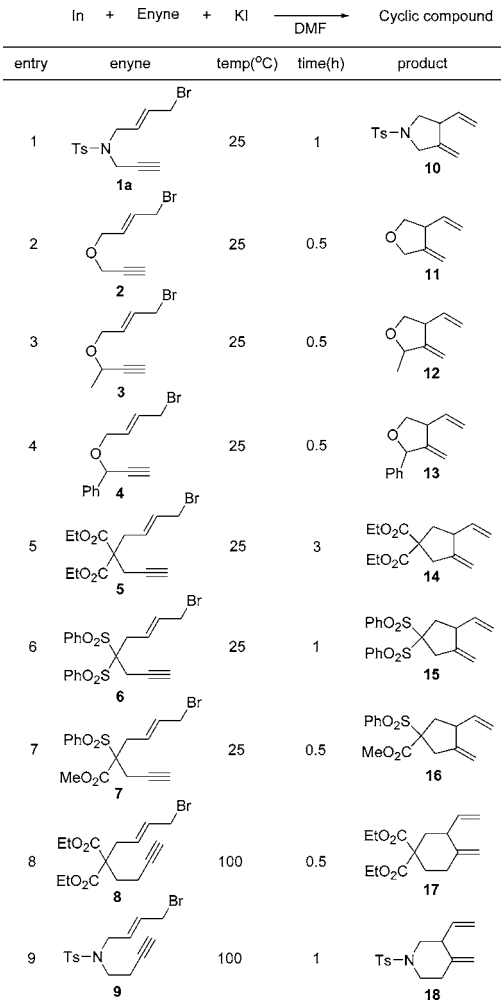
Table 1. Reaction Optimization



entry	X	additive	solvent	time (h)	temp (°C)	isolated yield (%)[a]
1	Br		THF	40	70	28
2	Br		PhH	5	50	0
3	Br		$PhCH_3$	12	80	0
4	Br		DMF	1	25	0
5	Br		DMF	1	80	82
6	I		DMF	1	25	80
7	Br	KI[b]	PhH	5	50	0
8	Br	KI[b]	$PhCH_3$	12	80	0
9	Br	KI[b]	DMF	1	25	83

[a] Reaction performed with 1 equiv of indium and 1 equiv of substrate. [b] Performed with 3 equiv of KI.

Table 2. Cyclization of Terminal 1-Bromo-2,7- and 1-Bromo-2,8-Enynes Mediated by Indium



[a] Reactions were performed with 1 equiv of indium and 3 equiv of KI unless otherwise noted. [b] Diastereomeric ratio. [c] KI was not used.

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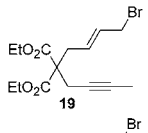
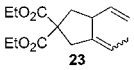
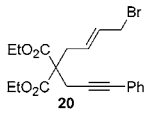
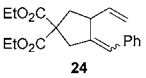
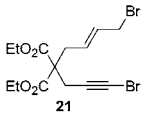
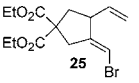
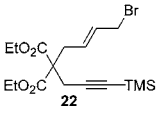
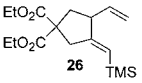
Table 3. Cyclization of Internal 1-Bromo-2,7-enynes Mediated by Indium[a]

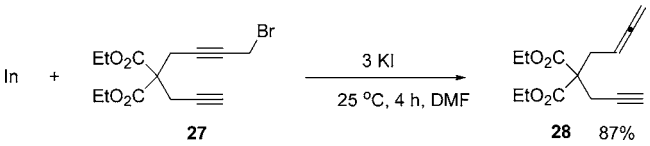
In + Enyne → (DMF) Cyclic compound

entry	enyne	temp(°C)	time(h)	product	isolated yield(%)[a]
1	 **19**	100	1	 **23**	60(1:3)[b]
2	 **20**	100	0.5	 **24**	55(1:1.6)[b]
3	 **21**	100	2	 **25**	45(9)[c]
4	 **22**	100	1	 **26**	63

[a] Reactions were performed with 1 equiv of indium unless otherwise noted. [b] Diastereomeric ratio. [c] Isolated yield of dehalogenated compound **14**.

The terminal 1,6-enyne **2** reacted with indium in the presence of 3 equiv of KI in DMF at 25 °C for 30 min to afford 3-methylene-4-vinyl tetrahydrofuran **11** in 90% yield (entry 2). Under the same conditions, propargyl ether **3** was cyclized to give the desired product **12** in 95% yield (dr = 1:3.1) (entry 3). When the malonate-branched terminal 1,6-enyne **5** was treated with indium in the presence of KI, **14** was obtained in 77% yield (entry 5). Similarly, intramolecular cyclization of the bis(sulfone)- and phenylsulfonyl acetate-branched terminal 1,6-enynes (**6** and **7**) proceeded smoothly to produce cyclopentane derivatives (**15** and **16**) in good yields (entries 6 and 7). This indium-mediated cyclization was then extended to synthesize cyclohexane derivatives. Although terminal 1-bromo-2,8-enyne **8** was not cyclized at 25 °C even in the presence of KI,[15] heating enyne **8** at 100 °C for 30 min with indium produced **17** in 70% yield in the absence of KI in DMF (entry 8). Cyclization of *N*-(*E*)-4-bromo-2-butenyl-*N*-4-pentynyl-*p*-toluenesulfonamide to prepare a cycloheptane derivative met with failure under the present conditions.

Scheme 2

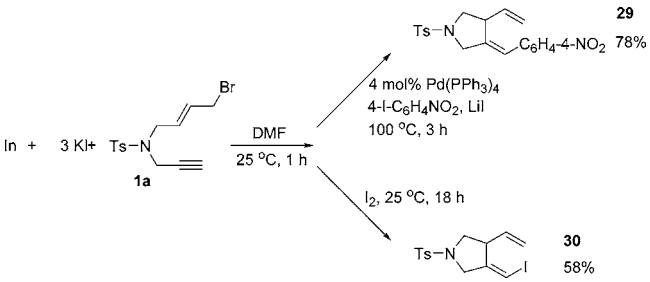


Encouraged by these results, we next examined the cyclization of internal 1-bromo-2,7-enynes (Table 3). Exposure of **19** to indium in DMF at 100 °C produced the desired product **23** in 60% yield (dr = 1:3) (entry 1). Although KI was used as an additive at 25 °C in this reaction, **23** was not produced.[15] Phenyl, bromo, and trimethylsilyl groups as substituents did not affect the cyclization, and cyclopentane derivatives were obtained in good yields (entries 2−4).

On the basis of the results above, the cyclization of diethyl 4-bromo-2-butyn-1-yl propargyl malonate (**27**) under a variety of reaction conditions was attempted. Unfortunately, the cyclized compound was not produced, but diethyl 2,3-butadien-1-yl propargyl malonate (**28**) was obtained in 87% yield (Scheme 2).

After *N*-(*E*)-4-bromo-2-butenyl-*N*-propargyl-*p*-toluenesulfonamide (**1a**) was treated with indium in the presence of KI in DMF at 25 °C for 1 h, addition of 4 mol % Pd(PPh$_3$)$_4$, LiI (3 equiv), and 1-iodo-4-nitrobenzene (3 equiv) to the reaction mixture gave coupling product **29** in 78% yield. Subsequent iodolysis (3 equiv of I$_2$, 25 °C, 18 h) under the same reaction conditions produced vinyl iodide **30** in 58% yield (Scheme 3).

Scheme 3



In summary, we have demonstrated that cyclization of 1-bromo-2,7- and 1-bromo-2,8-enynes mediated by indium produced five- and six-membered cyclic compounds in good yield. KI was a necessary additive in the cyclization of

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(15) Although starting material disappeared on TLC in the presence of KI (3 equiv) at 25 °C, the desired product was not obtained and a complicated TLC was observed.

terminal 1-bromo-2,7-enynes to give the desired products at 25 °C. Treatment of terminal 1-bromo-2,8- and internal 1-bromo-2,7-enynes with indium afforded cyclic compounds in good yields without KI at 100 °C in DMF. After cyclizations, subsequent cross-coupling reaction and iodolysis increase the usefulness of the present reaction. Further studies to explain the utility and mechanism of this reaction are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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