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Atom Transfer Cyclization Catalyzed by $InCl_3$ via Halogen Activation

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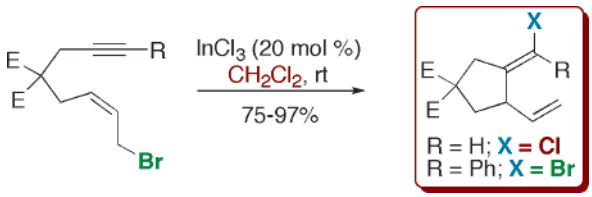
ABSTRACT



Indium trichloride was found to be an efficient catalyst for the cyclization of allylic halides and alkynes with atom transfer in methylene chloride. Mechanistic evidence supports a cationic reaction pathway with Lewis acid activation of the allylic halogen. Concomitant nucleophilic attack by the alkyne and trapping with halide led to atom transfer cyclization products. Depending on alkyne substitution, a bromine atom was transferred from the substrate or a chlorine atom was transferred from the solvent.

Atom transfer radical processes are well-known in polymerization and cyclization reactions.[1] They proceed via chain mechanisms and may be initiated by a variety of organic or inorganic radical initiators. Transition metals are known to affect cyclizations with halogen or group transfer taking place.[2] $InCl_3$ has been reported to promote the cyclization of allylstannanes onto alkynes with the intermediacy of organoindium intermediates as well.[3] We have discovered a facile and efficient $InCl_3$-catalyzed cyclization of allylic bromides onto alkynes with concomitant halogen atom transfer from the substrate or from the solvent that does not proceed via a radical pathway nor through organoindium intermediates. Indeed, the mechanistic evidence supports a cationic cyclization via mild halogen activation by Lewis acidic indium salts that has heretofore never been proposed. Herein, we disclose the results of our investigation of this remarkable transformation.

The utility of indium metal and its salts has been well demonstrated, most notably in the indium-mediated allylation of carbonyl compounds.[4] Allyl indium has been shown to react with alkynes via carbometalation reactions.[5,6] Indium and indium derivatives are reducing agents for a variety of

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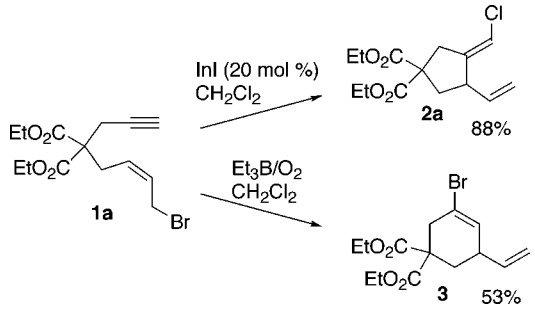
functional groups,[7] and indium reagents have been utilized for cross coupling of organic halides[8] and other reductive couplings.[9] In these applications, single electron transfer processes are likely involved. Indium-mediated radical reactions are also well established and have been utilized in atom transfer cyclizations.[10]

We have previously disclosed that low-valent indium(I) iodide in halogenated solvents initiated a cyclization reaction of **1a** to **2a** with halogen atom transfer from the solvent[11] (Scheme 1) along with a trace of the bromo analogue **4a**.

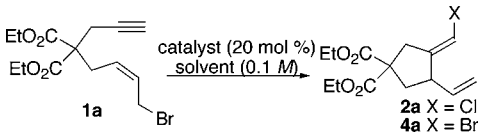
Scheme 1



We envisioned this process to proceed by initial single electron transfer similar to other indium-initiated radical reactions. Recently, Salter has reported the same cyclization utilizing stoichiometric indium metal in halogenated solvents,[12] and his results are also suggestive of the involvement of radical and/or organoindium intermediates. With In(0), yields were modest (generally <50%) and the reaction was slow (16−18 h). In contrast, our reaction was complete in less than 3 h with only 20 mol % of InI and yields were significantly improved. We hypothesized that InI was a better radical initiator for this reaction than In(0) as it could be slightly more soluble in organic solvents. However, the mechanism remained elusive. Hence, we undertook a study to further understand the atom transfer reaction. To attain support for a radical mechanism, we subjected **1a** to standard radical initiation conditions with Et_3B/O_2[13] and were surprised to find that the 6-endo cyclization product **3** was formed exclusively with only bromine atom transfer and no incorporation of chloride from solvent. Thus, it was unlikely the transformation of **1a** to **2a** proceeded via a radical pathway.

We surveyed several catalysts and conditions for the cyclization of **1a** to **2a** and found that the reaction was promoted by Lewis acids rather than by reductive metals. As shown in Table 1 (entry 1), $InCl_3$ was an extremely effective catalyst for the cyclization affording 97% yield of **2a** along with a trace of brominated **4a**.[14] Increasing the concentration affected both the yield and the Cl/Br ratio (entries 2−4). As the reaction became more concentrated, the amount of Br transfer from the substrate relative to Cl transfer from solvent increased. The yield diminished with increasing concentration suggesting that Br transfer from the

Table 1. Atom Transfer Cyclization



entry	catalyst	solvent	t (h)	yield %	**2a/4a**[a]
1	$InCl_3$	CH_2Cl_2	4	97	29:1
2	$InCl_3$	CH_2Cl_2 (0.5 M)	12	64	7:1
3	$InCl_3$	CH_2Cl_2 (1.0 M)	12	45	5:1
4	$InCl_3$	CH_2Cl_2 (10 M)	12	16	1:2
5	$InCl_3$	CH_2ClCH_2Cl	24	58	29:1
6	$InCl_3$	CCl_4	18	34[b]	4:6
7	$InCl_3$	$CHCl_3$	18	0	
8	$InBr_3$	CH_2Cl_2	3	89	29:1
9	$In(OTf)_3$	CH_2Cl_2	18	dec	
10	AuOTf	CH_2Cl_2	18	0[c]	
11	AgOTf	CH_2Cl_2	18	0[d]	
12	$InCl_3$	CH_2Br_2	3	81	0:100
13	$InCl_3$	CH_2I_2	3	8[e]	10:1[f]
14	$Zn(OTf)_2$	CH_2Cl_2	16	0	
15	$SnCl_4$	CH_2Cl_2	16	dec	
16	$Fe(ClO_4)_3$	CH_2Cl_2	16	0	

[a] Measured by ^{1}H NMR. [b] 42% of starting material recovered. [c] 90% of starting material recovered. [d] 92% of starting material recovered. [e] 72% of starting material recovered. [f] Ratio reflects I/Br ratio, respectively.

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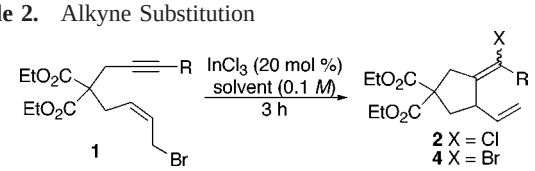
(13) The same product was obtained in low yield by treating the substrate with benzoyl peroxide in refluxing benzene.

(14) A trace of **3** (<1%) was also detected.

substrate may be difficult. The reaction would proceed in dichloroethane (entry 5) but was less effective in CCl_4 and would not proceed at all in $CHCl_3$ (entry 6). The reaction also failed completely in nonhalogenated solvents (H_2O, MeOH, CH_3CN, toluene, THF). $InBr_3$ performed equally well, whereas $In(OTf)_3$ resulted in decomposition of the substrate (entries 8 and 9). Other metals that are known to activate alkynes[15−17] were examined. Au (entry 10) and Ag (entry 11) salts did not catalyze any reaction of **1a**. Thus, it appears $InCl_3$ is not promoting the reaction through alkyne activation. With $InCl_3$, halogen transfer from dibromomethane and diiodomethane was also observed (entries 12 and 13); however, the yield diminished significantly in the latter case. As Zn(2+) salts have been reported to activate allyl chlorides for cycloaddition onto alkynes,[18] we examined a few other Lewis acids. Surprisingly, no reaction ensued when $Zn(OTf)_2$ was employed (entry 14). $SnCl_4$ resulted, and decomposition of the substrate and $Fe(ClO_4)_3$ was ineffective.

We next examined the influence of substitution on the alkyne, and the results are summarized in Table 2. This had

Table 2. Alkyne Substitution



entry	R	solvent	yield %	**2**/**4**[a]	*E*/*Z*[a]
1[b]	**a** H	CH_2Cl_2	97	29:1	*E* only
2	**a** H	CH_2Br_2	81	0:100	*E* only
3	**b** Me	CH_2Cl_2	89	4:1	*E* only[c]
4	**b** Me	CH_2Br_2	87	0:100	15:1
5	**c** *n*-Bu	CH_2Cl_2	75	1:2	3:1
6	**c** *n*-Bu	CH_2Br_2	80	0:100	5:1
7	**d** Ph	CH_2Cl_2	79	0:100	14:1
8	**d** Ph	CH_2Br_2	85	0:100	5:1
9[d]	**e** D	CH_2Cl_2	82	>30:1	*E* only
10[d]	**e** D	CH_2Br_2	95	0:100	*E* only
11	**a** H	CD_2Cl_2	82	>30:1	*E* only
12[e]	**a** H	CH_2Cl_2	82	29:1	*E* only
13[e]	**a** H	CH_2Br_2	81	0:100	*E* only
14[e]	**d** Ph	CH_2Cl_2	75	0:100	13:1
15[e]	**d** Ph	CH_2Br_2	96	0:100	5:1

[a] Measured by ^1H NMR. [b] Reaction run for 4 h. [c] For X = Cl, E/Z was not determined for the brominated product. [d] Reaction run for 18 h. [e] The *trans*-allyl bromide substrate was utilized.

an influence on both the *E*/*Z* ratio of the product and the amount of incorporation of halogen from the solvent vs halogen from the substrate. Particularly noteworthy is entry 7 with phenyl-substituted alkyne. Even in dichloromethane, only brominated product was obtained. Substrate **1e** (entries 9 and 10) with deuterium substituted on the alkyne was examined. Cyclization proceeded well with complete retention of the deuterium. This suggests that a vinyl organoindium intermediate is likely not present after the reaction, and no insertion in the alkyne C−D bond occurs. Furthermore, use of CD_2Cl_2 solvent (entry 11) resulted in no incorporation of deuterium in the product. The geometry of the allyl bromide had no effect on the reaction as demonstrated by entries 12−15. Utilizing substrates with the *E*-olefin performed identically to substrates with the *Z*-olefin.

The data suggest an ionic or polar concerted mechanism in which the Lewis acid activates the allylic bromide (Figure 1). In the case where R = H, the reaction probably proceeds

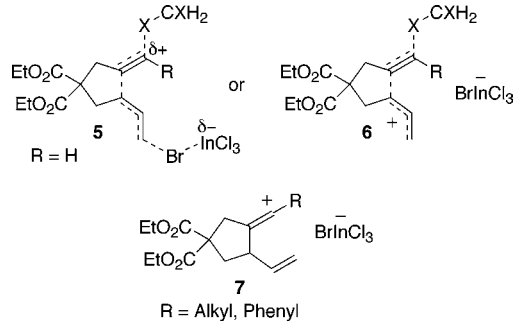


Figure 1. Possible cyclization modes.

in a concerted fashion with halogen trapping from the solvent.[19,20] This could occur concurrent with activation of the allyl bromide (**5**) or through a discreet allyl carbocation (**6**). Nevertheless, alkyne cyclization is likely to be concerted with halide attack as the reaction affords *only* the *E*-isomer. If the alkyne is more substituted, a more stabilized vinyl carbocation such as **7** could be produced. Thus, halogen transfer could come from solvent, an indium-ate complex, or from another allyl bromide substrate and *E*/*Z* selectivity would vary depending on substitution and size of the halogen source. This would explain the change in the *E*/*Z* ratio observed upon alkyne substitution.

The *E* selectivity of substrate **1a** also contrasts with the Salter report. Whereas we observed the formation of only one isomer, with In(0), a mixture of isomers was obtained

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(17) Hf Lewis acids catalyze the intramolecular allylsilation of alkynes via alkyne activation: Imamura, K.-i.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339.

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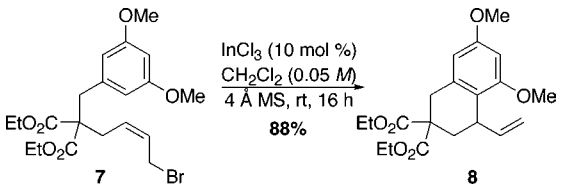
(20) Overman has shown that nucleophiles accelerate the reaction of alkynes with cations: Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612.

in ratios ranging from 3:1 to 10:1 (*E*/*Z*) with terminal alkyne substrates. It is likely that In(0) reacts with the allyl bromide substrate to form an allyl indium intermediate. This could generate, through disproportionation,[21] In(III) salts that would catalyze the cationic cyclization of bromide substrate as we have observed. The *Z*-isomer may arise through a competing indium-ene cyclization of the allyl indium intermediate. In our reaction, the formation of organoindium species with $InCl_3$ would be highly unlikely.

To garner even more evidence for allylic halide activation and a cationic pathway, we examined the reaction of **7** (Scheme 2) under the $InCl_3$-catalyzed conditions in dichloromethane. If the reaction proceeds through a cationic mechanism, other nucleophiles besides alkynes should participate in the cyclization. Indeed, the arene cyclized smoothly at room temperature to form the Friedel−Crafts allylation product **8** in high yield. This provides further support against alkyne activation in the atom transfer cyclization.

Scheme 2



In conclusion, we have demonstrated a facile and efficient atom transfer cyclization of alkynes and allylic bromides utilizing $InCl_3$ as the catalyst. The reaction appears to proceed via a cationic halogen activation mechanism with halogen transfer from the solvent or from the substrate. Additionally, similar halogen activation effectively leads to remarkably mild Friedel−Crafts-type cyclizations. We are currently examining the scope and limitations of this electrophilic substitution reaction, and our results will be reported in due course.

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

OL052802A

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