

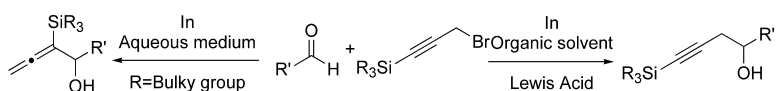
Communication

Indium-Mediated Reaction of Trialkylsilyl Propargyl Bromide with Aldehydes: Highly Regioselective Synthesis of Allenic and Homopropargylic Alcohols

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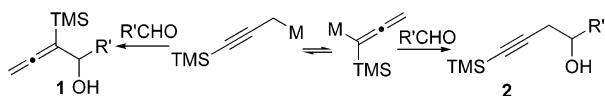
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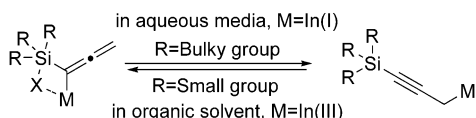
Tuning the regioselectivity of the reaction of propargylmetals with carbonyl compounds toward the synthesis of either allenic alcohols or homopropargylic alcohols remains an important challenge in organic synthesis.^{1,2} Recently, Chan and Li reported the first indium-mediated reaction of aldehydes with trimethylsilyl propargyl bromides in aqueous media, with the allenic alcohol as the major product in low to moderate selectivities.^{3,4} Herein, we report a general strategy using the indium-mediated reaction of trialkylsilyl propargyl bromides with various aldehydes to obtain either the allenic alcohols or homopropargylic alcohols in high regioselectivities (Scheme 1).

Scheme 1



On the basis of our observation that indium complexes may chelate with silicon group⁵ and observation by others that indium complexes in organic and aqueous media are likely different species,⁶ and the dramatic solvent effects on the propargylation and allenylation with metallic tin,⁷ we hypothesized that the judicious choice of solvent and steric and chelation effects may provide us with the designed conditions to select a product of choice (Scheme 2).

Scheme 2



To prove our hypothesis, we first focused on the indium-mediated reaction of propargyl bromide under anhydrous conditions. The results are shown in Table 1.

Contrary to the reported results obtained in water,^{3,4} excellent regioselectivities can be obtained when the reactions were carried out in THF in the presence of catalytic amount of indium tribromide or indium trifluoride. The reaction was found to proceed faster in the presence of InF₃ as compared to InBr₃ (entries 4 and 8). This type of reaction is limited to silicon-containing propargyl bromides as shown in Table 1 that phenyl propargyl bromide afforded the homopropargylic alcohols in low selectivities (entry 5). Furthermore, the reactions of triisopropyl silyl propargyl bromide and diphenyl-*tert*-butyl silyl propargyl bromide also furnished the homopropargylic alcohols, albeit in lower yields (entries 9 and 10). It is also important to note that two equivalents of the indium reagent are essential to obtain high regioselectivity (entry 7). With the unveiling of 0.1 equiv InBr₃ or 0.1 equiv InF₃ and 2 equiv of trialkylsilyl propargyl bromide in THF as important criteria to obtain the trialkylsilyl homopropargylic alcohol adduct, we extended the reaction to various aldehydes. The results are shown in Table 2.

Table 1. Indium-Mediated Reactions of Nonyl Aldehyde with Propargyl Bromide in Organic Solvents^a

entry	R	solvent	yield ^b % (3:4)
1	TMS	THF, rt, 20 h	86 (57:43)
2	TMS	THF/reflux, 20 h	89 (72:28)
3	TMS	THF/rt, (10 mol % InBr ₃), 20 h	90 (63:37)
4	TMS	THF/reflux, (10 mol % InBr ₃), 20 h	95 (99:1)
5	Ph	THF/reflux, (10 mol % InBr ₃), 20 h	65 (12:88)
6	TMS	CH ₂ Cl ₂ /reflux, (10 mol % InBr ₃), 19 h	88 (99:1)
7	TMS	THF/reflux, (10 mol % InF ₃), 9 h	75 (87:13) ^c
8	TMS	THF/reflux, (10 mol % InF ₃), 9 h	93 (99:1)
9	TIPS	THF/reflux, (10 mol % InF ₃), 9 h	58 (99:1)
10	TBDPS	THF/reflux, (10 mol % InF ₃), 9 h	35 (99:1)

^a Except where indicated, all reactions were carried out on 0.5 mmol scale with aldehyde:bromide:indium = 1:2:2. ^b Isolated yield. ^c Reaction was carried out with aldehyde:bromide:indium = 1:1:1.

Table 2. Indium-Mediated Propargylation of Aldehydes with Trimethylsilylpropargyl Bromide^a

entry	aldehyde	5	I (5:6) yield ^b %	II (5:6) yield ^b %
1	hydrocinnamaldehyde	a	85 (99:1)	89 (99:1)
2	cinnamaldehyde	b	89 (99:1)	92 (99:1)
3	cyclohexanecarbaldehyde	c	90 (99:1)	94 (99:1)
4	benzaldehyde	d	92 (99:1)	92 (99:1)
5	nonyl aldehyde	e	95 (99:1)	93 (99:1)

I: In/10mol% InBr₃, THF, reflux, 20h
II: In/10mol% InF₃, THF, reflux, 9h

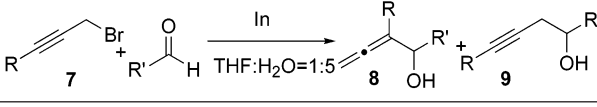
^a All reactions were carried out in THF on 0.5 mmol scale with aldehyde:trimethylsilylpropargyl bromide:indium = 1:2:2. ^b Isolated yield.

In all cases, the homopropargylic alcohols were obtained with excellent selectivities in high yields. No allenic alcohols were observed in all these cases.

Next, to suppress the possible chelation of the silicon with the halide of indium and inspired by the results of T. H. Chan,³ C. J. Li,⁴ and Hammond,⁸ we decided to explore the reaction with more bulky trialkylsilyl propargyl bromides in aqueous media. The results are summarized in Table 3.

In all these cases, the allenic alcohols were obtained in moderate to good yields with high selectivities. It is also important to note that addition of the aldehyde first followed by bromide afforded the product in higher yield.

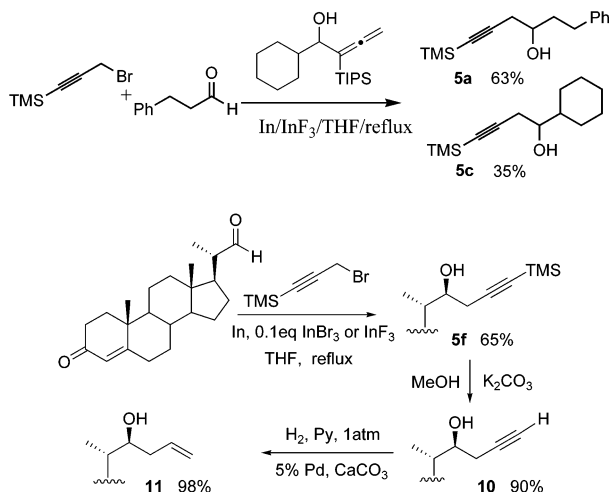
The following observations are of mechanistic interest: (1) The reaction with InF₃ is faster than with InBr₃. (2) A mixture of homopropargylic and allenic alcohols is formed initially with the homopropargylic alcohol observed as the major product. Refluxing

Table 3. Indium-Mediated Reactions of Aldehydes with Trialkylsilyl Propargyl Bromides^a


entry	aldehyde	R = TIPS yield % (8:9)	R = TBDPS yield % (8:9)
1	nonyl aldehyde	52 (95:5) a	45 (95:5) f
2	hydrocinnamaldehyde	71 (93:7) b	50 (90:10) g
3	cinnamaldehyde	46 (92:8) c	52 (97:3) h
4	cyclohexanecarbaldehyde	61 (95:5) d	56 (95:5) i
5	benzaldehyde	59 (96:4) e	55 (96:4) j

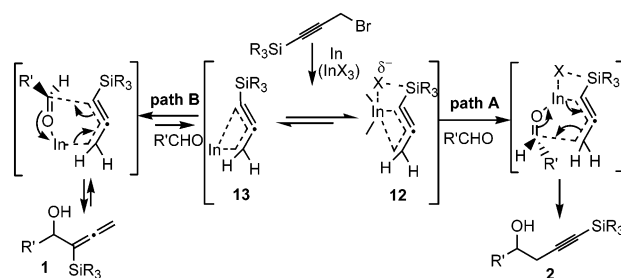
^a All reactions were carried out on 0.25 mmol scale with aldehyde: trialkylsilylpropargyl bromide:indium = 1:2:2. ^b Isolated yield.

the reaction longer afforded only the homopropargylic alcohols. (3) It is important to note that two equivalent of propargyl bromide was necessary to obtain high selectivity. (4) A cross-over experiment was carried out as shown in Scheme 3. After the reaction, column chromatography provided the crossover product **5c** in 35% yield in addition to the indium-coupling product. (5) Stereochemical studies using steroidal aldehyde with trimethylsilyl propargyl bromide and indium/indium trifluoride in THF resulted in the formation of the Cram's product.⁹ (6) No allenic product was obtained with the reaction of homopropargyl alcohol and aldehydes.

Scheme 3

All these suggest that silicon may be playing a key role in this reaction, most probably facilitating the retro cleavage of allenic alcohol or/and shifting the equilibrium of the indium species toward the formation of species **12** due to the coordination with the halogen of the indium (Scheme 4). The preferential formation of species **12** coupled with the retro cleavage of the allenic alcohol to form the aldehyde¹⁰ which further reacts with the excess organoindium reagent resulted in the selective formation of the thermodynamically more stable homopropargylic alcohols.

On the other hand, the indium species generated in aqueous media using more bulky silicon will preferentially form species **13** which reacts with aldehydes to form the kinetically favored allenic alcohols. The preferential formation of species **13** is probably due

Scheme 4

to the steric repulsion of indium complex (which complexes to water molecules) with the bulky silicon group.

In conclusion, we have developed a general strategy to obtain either the allenic alcohols or homopropargylic alcohols in high regioselectivities via the indium-mediated reaction of trialkylsilyl propargyl bromides with various aldehydes. This method is extremely easy. By just changing the silyl group and the reaction conditions, both the allenic and homopropargylic alcohols can be obtained in high regioselectivities. Furthermore, mechanistic studies have revealed that silicon plays an important role in the high regioselectivities. These studies pave the way for the design of an enantioselective version for the synthesis of allenic alcohols and homopropargylic alcohols. Further application of this concept to the control stereochemistry in other systems is in progress.

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Supporting Information Available: Spectroscopic and analytical data for all compounds and the representative procedure (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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