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Highly Selective Synthetic Method for 1,6-Diols Bearing Enyne Functions: Development of 3,6-Dianion Reagent of 1,2-Hexadien-4-yne Using 1,6-Dibromo-2,4-hexadiyne and Indium

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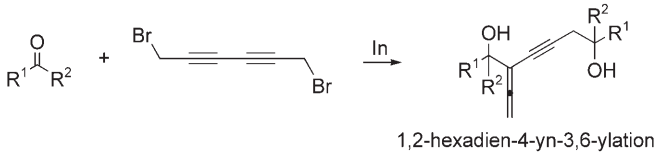
Abstract: The reaction of aldehydes and ketones with an organoindium reagent generated *in situ* from indium and 1,6-dibromo-2,4-hexadiyne in the presence of lithium iodide in tetrahydrofuran (THF) selectively produced 1,6-diols linked to an allenyne unit with complete regioselectivity and chemoselectivity through 1,2-hexadien-4-yn-3,6-ylation, indicating that the organoindium acted as the 3,6-dianion reagent of 1,2-hexadien-4-yne.

Keywords: 1,6-dibromo-2,4-hexadiyne; 1,6-diols; enynes; 1,2-hexadien-4-yn-3,6-ylation; indium

Indium has emerged as a useful metal in organic synthesis because of its intriguing chemical properties of reactivity, selectivity, and low toxicity.[1] On the basis of these properties of indium, efficient indium-mediated organic reactions have been developed and applied in environment-friendly organic reactions.[1] Their first synthetic applications have been found in allylation reactions of carbonyl compounds and their derivatives under aqueous and anhydrous Barbier conditions.[2] In addition, a range of indium-mediated processes have been found to be useful for Reformatsky reactions,[3] Michael addition reactions,[4] cross-coupling reactions,[5] allylic substitution reactions,[6] and addition of organoindium reagents to carbon-carbon multiple bonds and nitriles.[7] Indium has now demonstrated itself as the metal of choice for performing many of these reactions. A variety of *in situ* generated allylindiums, propargylindiums, and allenylindiums are of considerable value for regioselective and stereoselective allylation, propargylation, and allenylation to various carbonyl and imine compounds, leading to the corresponding alcohols[8] and amines.[9] Although many examples of the indium-mediated allylation and propargylation of simple carbonyl compounds have been reported,[8] as far as we are aware, no 1,2-hexadien-4-yn-3,6-ylation onto aldehydes and ketones through contemporary propargylation and allenylation in one-pot leading to an allenyne-1,6-diol has been published. As part of our continuing effort to expand the synthetic utility of indium, we now report highly selective 1,2-hexadien-4-yn-3,6-ylation using 1,6-dibromo-2,4-hexadiyne and indium (Scheme 1).



Scheme 1. Indium-mediated reaction of carbonyl compounds with 1,6-dibromo-2,4-hexadiyne.

Our initial study focused on the reactions of benzaldehyde with organoindium generated *in situ* from 1,6-dibromo-2,4-hexadiyne[10] and indium. The results are summarized in Table 1. Of the reaction conditions examined, the best results were obtained with 1.0 equiv. of benzaldehyde, 0.55 equivs. of 1,6-dibromo-2,4-hexadiyne, and 1.1 equivs. of indium in the presence of 1.1 equivs. of lithium iodide in THF at 25 °C for 1 h under a nitrogen atmosphere, producing selectively 1,6-diphenyl-2-vinylidenehex-3-yne-1,6-diol (**3a**) in 86 % yield through 1,2-hexadien-4-yn-3,6-ylation from contemporary propargylation and allenylation with complete regioselectivity (entry 10). Surprisingly, there are no traces of 1,8-diphenyl-octa-3,5-diyne-1,8-diol (**3b**) and 1,4-diphenyl-2,3-divinylidene-butane-1,4-diol (**3c**) through 2,4-hexadiyn-1,6-ylation and 1,2,4,5-hexatetraen-3,4-ylation, respectively, and **3d**, **3e** and **3f** formed in these reactions (Figure 1). The ^{1}H and ^{13}C NMR spectra of **3a** are consistent with a 1,6-diol structure possessing an allenyl as well as an alkynyl group. The *sp* and sp^2 resonances (400 MHz) of the allenyl group appear at 212.0 ppm (C_a) and 91.5 ppm (C_b), respectively. The *sp* resonance (400 MHz) of alkynyl group appears at 79.8 ppm (C_c)

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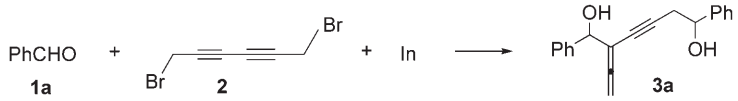
Table 1. Optimization of indium-mediated reaction of benzaldehyde with 1,6-dibromo-2,4-hexadiyne.[a]



Entry	Equiv. 1a	Equiv. 2	Equiv. In	Additive[b]	Solvent	Conc. [M]	T [°C]	t [h]	Yield [%][c]
1	0.5	0.75	1.0	-	THF	0.30	25	0.17	49(51)[d]
2	1.0	0.50	1.0	-	THF	0.30	25	0.17	26(20)[e]
3	1.0	0.75	1.0	-	THF	0.30	25	0.17	22
4	1.0	0.75	1.0	-	THF	0.30	0	0.17	30
5	1.0	0.75	1.0	-	THF	0.25	0	0.5	54
6	1.0	0.75	1.0	-	THF	0.30	0	0.5	70[f]
7	1.0	0.75	1.0	-	THF	0.25	0	0.5	76[f]
8	1.0	0.55	1.1	-	THF	0.20	25	1.0	63[f]
9	1.0	0.55	1.1	KI	THF	0.20	25	1.0	48[f]
10	1.0	0.55	1.1	LiI	THF	0.20	25	1.0	86[f][g]
11	1.0	0.55	1.1	LiI	THF	0.20	25	1.0	84[f][h]
12	1.0	0.55	1.1	LiI	DMF	0.20	25	1.0	60[f]

[a] Reactions were carried out under Grignard-type condition unless otherwise noted. Reaction was quenched with H_2O.
[b] Additive (1.1 equivs.) was used.
[c] Isolated yield.
[d] Recovery yield of **2**.
[e] Recovery yield of **1a**.
[f] Reaction was quenched with 10% HCl.
[g] Diastereomeric ratio = 1:1.
[h] Reaction was carried out under Barbier-type conditions.

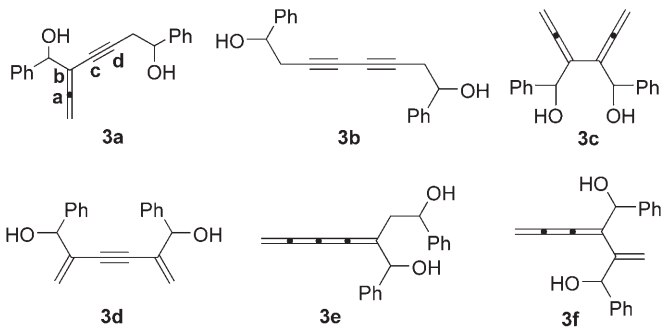


Figure 1. Possible isomeric products from the indium-mediated reaction of benzaldehyde with 1,6-dibromo-2,4-hexadiyne.

and 94.5 ppm (C_d), respectively, indicating that compound **3a** was produced selectively.

The diastereomeric ratio (1:1) of **3a** was determined by NMR interpretation of the MTPA diester (**4**) obtained from the reaction of **3a** with (*S*)-MTPA-Cl in 69% yield [Eq. (1)].[11]

THF (0.2 M solution, 86%) was the better than DMF (60%) (entry 10 *vs.* 12). The quenching of the reaction mixture using 10% HCl is highly essential for good results due to the solubility of indium salts (entry 4 *vs.* 6). The use of indium in less than 1.0–1.1 equivs. and 1,6-dibromo-2,4-hexadiyne in more than 0.55 equivs. resulted in lower yields. Lithium iodide as an additive is critically important for excellent yields (entry 8 *vs.* 9 *vs.* 10). 1,6-Diiodo-2,4-hexadiyne was detected in part in the ^{1}H NMR spectrum after treatment with lithium iodide in THF, indicating that iodide substituted bromide in 1,6-dibromo-2,4-hexadiyne and then, the corresponding iodide reacted smoothly with indium to produce the organoindium reagent.

To demonstrate the efficiency and scope of the present method, we applied this reaction system to a variety of aldehydes and ketones to obtain 2-vinylidenehex-3-yne-1,6-diol derivatives. The results are summarized in Table 2.[11] Under the optimized conditions, aliphatic aldehydes such as acetaldehyde, butyralde-

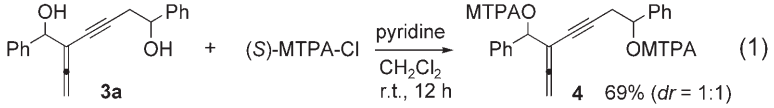


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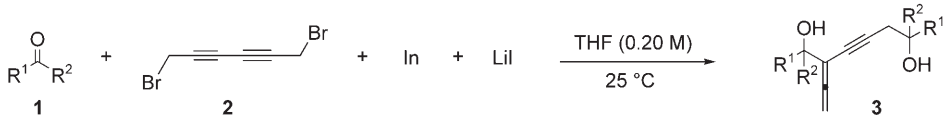
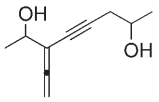
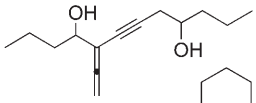
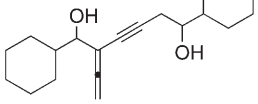
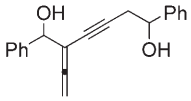
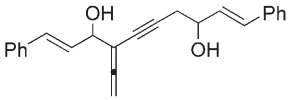
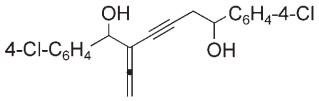
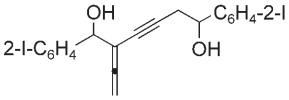
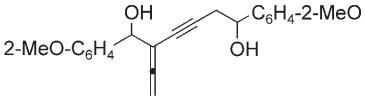
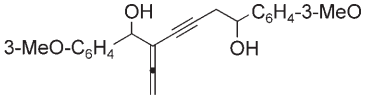
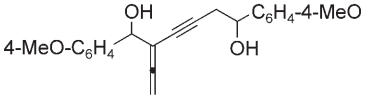
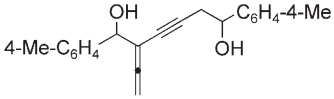
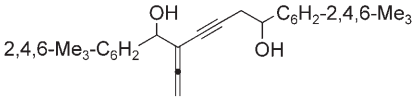
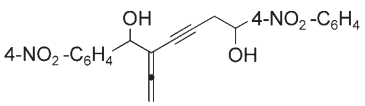
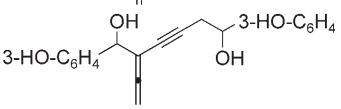
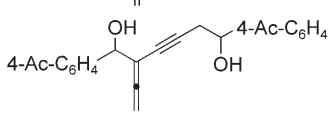
Table 2. Indium-mediated reaction of carbonyl compounds with 1,6-dibromo-2,4-hexadiyne.[a]



1 **2** **3**

Entry	R^1	R^2	*t* [h]	Product		Yield [%]
1	Me	H	1		**3g**	84
2	*n*-Propyl	H	1		**3h**	85
3	*c*-C_6H_{11}	H	1		**3i**	78
4	Ph	H	1		**3a**	86[b]
5	*t*-C_6H_5CH=CH	H	1		**3j**	70
6	4-Cl-C_6H_4	H	1		**3k**	86
7	2-I-C_6H_4	H	4		**3l**	77
8	2-MeO-C_6H_4	H	8		**3m**	82[c]
9	3-MeO-C_6H_4	H	6		**3n**	78
10	4-MeO-C_6H_4	H	3		**3o**	81
11	4-Me-C_6H_4	H	4		**3p**	87[c]
12	2,4,6-Me_3-C_6H_2	H	34		**3q**	82[c]
13	4-NO_2-C_6H_4	H	0.25		**3r**	95
14	3-HO-C_6H_4	H	8		**3s**	80
15	4-Ac-C_6H_4	H	8		**3t**	82

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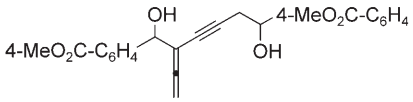
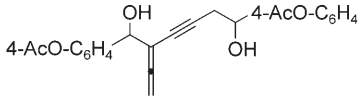
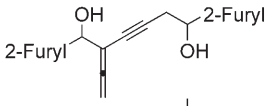
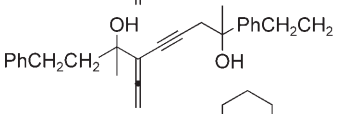
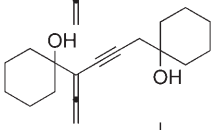
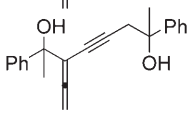
Entry	R^1	R^2	t [h]	Product		Yield [%]
16	4-MeO_2C-C_6H_4	H	7		**3u**	92
17	4-AcO-C_6H_4	H	24		**3v**	69[d]
18	2-Furyl	H	2		**3w**	91
19	$PhCH_2CH_2$	Me	7		**3x**	67[e]
20	— $(CH_2)_5$ —		7		**3y**	73[e]
21	Ph	Me	20		**3z**	68[e]

[a] In (1.1 equivs.), LiI (1.1 equivs.), and **2** (0.55 equivs.) were used.
[b] Diastereomeric ratio = 1:1.
[c] In (2.2 equivs.), LiI (2.2 equivs.), and **2** (1.1 equivs.) were used.
[d] Reaction was carried out at 0 °C.
[e] In (3.3 equivs.) and **2** (1.65 equivs.) were used. LiI was not used.

hyde, and cyclohexanecarbaldehyde regioselectively gave 1,6-diol derivatives linked to the allenyne unit in 78–85 % yields (entries 1–3). Treatment of *trans*-cinnamaldehyde with 1,6-dibromo-2,4-hexadiyne and indium produced the desired 1,6-diol compound in 70 % yield (entry 5). In the cases of various aromatic aldehydes, electronic variation on the aromatic substituents such as chloride, iodide, methoxy, methyl, nitro, hydroxy, ketone, methoxycarbonyl, and acetoxy did not diminish the efficiency and selectivity (entries 6–17). It is noteworthy that protection of a hydroxy and ketone group on substrates is not necessary as demonstrated by the reaction of 3-hydroxybenzaldehyde (entry 14) and 4-acetylbenzaldehyde (entry 15). 2,4,6-Trimethylbenzaldehyde reacted with the 1,6-dianionic indium reagent to afford the desired product in 82 % yield after 34 h due to the steric effect (entry 12). Heteroatoms turned out to be compatible with the employed reaction conditions (entry 18). The reaction worked equally well with aliphatic ketones such as 4-phenyl-2-butanone and cyclohexanone (entries 19 and 20). Reaction of acetophenone with organoindium gave the 1,6-diol linked to allenyne in 68 % yield (entry 21). All of the above reactions selectively gave 1,6-diols having an allenyne functional group between the hydroxy groups in good to excellent yields with complete regioselectivity and chemoselectivity.

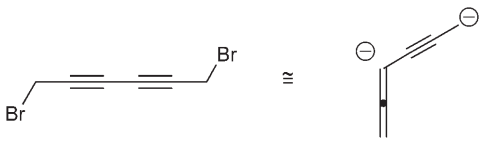


Figure 2. Synthon of the 3,6-dianion of 1,2-hexadien-4-yne.

In summary, we have shown that the reaction of aldehydes and ketones with the organoindium reagent generated *in situ* from indium and 1,6-dibromo-2,4-hexadiyne in the presence of lithium iodide in DMF produced 1,6-diols linked to allenyne in good to excellent yields through 1,2-hexadien-4-yn-3,6-ylation from contemporary propargylation and allenylation with complete regioselectivity and chemoselectivity, indicating that 1,6-dibromo-2,4-hexadiyne acted selectively as a synthon of the 3,6-dianion of 1,2-hexadien-4-yne (Figure 2).

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Experimental Section

Typical Experimental Procedure for 1,2-Hexadien-4-yn-3,6-ylation

Indium (63.0 mg, 0.55 mmol) and lithium iodide (74 mg, 0.55 mmol) in dry THF (1.5 mL) were slowly added to 1,6-dibromo-2,4-hexadiyne (65.0 mg, 0.275 mmol) in dry THF (1 mL) at room temperature under a nitrogen atmosphere. After stirring for 10 min, benzaldehyde (53.0 mg, 0.5 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with 10% HCl (2 mL). The aqueous layer was extracted with ether (3× 10 mL), and combined organic phase were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/2, $R_f = 0.3$) to give *1,6-diphenyl-2-vinylidenehexa-3-yne-1,6-diol*; yield: 63.0 mg (86%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.25 (m, 10H), 5.21 (s, 1H), 5.10 (s, 2H), 4.75 (t, $J = 6.3$ Hz, 1H), 2.69 (d, $J = 6.3$ Hz, 2H), 2.27 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) Isomer A: $\delta = 212.04$, 142.45, 141.33, 128.43, 128.30, 128.01, 127.88, 126.35, 125.69, 94.54, 91.51, 79.76, 75.02, 74.26, 72.31, 30.62; Isomer B: $\delta =$ 212.04,142.45, 141.33, 128.43, 128.30, 128.01, 127.88, 126.33, 125.69, 94.54, 91.51, 79.76, 75.00, 74.24, 72.31, 30.62; IR (film): $\nu = 3419$, 3026, 2921, 2217, 1514, 1043 cm^{-1}; HR-MS (EI): $m/z = 290.1306$, calcd for $C_{20}H_{18}O_2$ (M^+): 290.1307.

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