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Selective Indium-Mediated 1,2,4-Pentatrien-3-ylation of Carbonyl Compounds for the Efficient Synthesis of Vinyl Allenols

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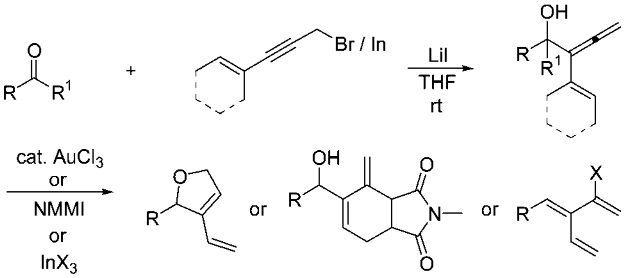
ABSTRACT



A highly selective synthetic method of functionalized vinyl allenols was developed from the reactions of various carbonyl compounds with organoindium reagent in situ generated from indium and 1-bromopent-4-en-2-yne derivatives. Treatment of vinyl allenols with gold catalyst, dienophile, or indium trihalide produced the functionalized dihydrofuran, cyclohexene, or 2-halo-1,3-diene derivatives in good to excellent yields.

In view of the usefulness of functionalized dienes in organic synthesis, a number of reagents have been developed for the 1,3-butadien-2-ylation of carbonyl compounds.[1] However, the synthetic method of functionalized 1,3-dienes possessing extended double bonds such as vinyl allene and bis(allene) is still rare in organic reactions. Because so much is now known about the Diels−Alder reaction,[2] we were convinced that when we developed an efficient synthetic route to vinyl allenes and bis(allenes), this reaction would prove useful for the synthesis of six-membered carbocycles

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bearing *exo*-methylene groups. Moreover, recent progress of transition metal-catalyzed multicomponent reactions and cyclizations using vinyl allenes,[3] vinyl allenols, and bis(allenes)[4] led us to the development of convenient and selective synthetic methods to these compounds. In the pursuit of an ongoing program of indium-mediated organic reactions,[5] we reported the efficient synthetic method of vinyl allenes through Pd-catalyzed cross-coupling reactions using allenylindium reagent.[3f] Recently, we required a diverse range of vinyl allenols in connection with Diels−Alder reactions,[6] Pd-catalyzed multicomponent reactions,[3g] and Au-catalyzed cyclizations.[7] The addition of organozinc and organomagnesium reagents obtained from the corresponding bromide to carbonyl compounds suffers from poor regioselectivity.[8] Organochromium reagents, though effective in reacting with carbonyl compounds to afford vinyl allenols, were derived from toxic CrCl$_n$ (n = 2 and 3) and have not shown good functional group tolerance due to the use of LAH.[9] LDA-mediated selective addition reaction requires vinylidenecyclopropanes, which are difficult to prepare.[10] As part of our continuing efforts to expand the synthetic utility of vinyl allenes,[3f,g] vinyl allenols, and bis(allenes),[11] we now report highly selective 1,2,4-pentatrien-3-ylation reactions from the reaction of carbonyl compounds with organoindium reagents in situ generated from indium and 1-bromopent-4-en-2-yne derivatives, producing vinyl allenols in good to excellent yields (Scheme 1).

Scheme 1. Selective 1,2,4-Pentatrien-3-ylation to Carbonyl Compound

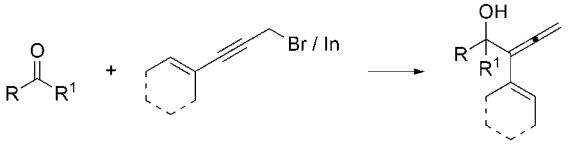
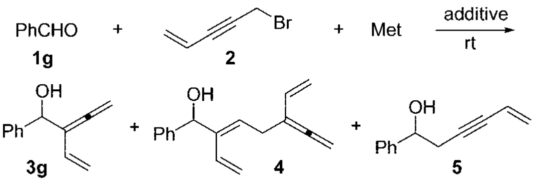


Table 1. Reaction Optimization of 1,2,4-Pentatrien-3-ylation[a]



entry	Met	additive (equiv)	solvent	time (h)	yield[b] (%) 3g	4	5
1	In		DMF	1	74	8	6
2	In	LiCl (3)	DMF	3	57	1	12
3	In	LiI (3)	DMF	1	69	3	5
4	In		THF	1	27	29	12
5[c]	In		THF	1		73	16
6	In	LiI (3)	THF	2	79	7	3
7[d]	In	LiI (3)	THF	3	51		7
8	**In**	**LiI (1)**	**THF**	**2**	**88**		**8**
9	In	LiI (1)	H$_2$O	4	52		11
10	Mg		Et$_2$O	1	42		42
11[e]	Zn	LiI (1.5)	THF	2	45		40

[a] **1g** was added to organoindium reagent derived from metal (1 equiv) and **2** (1 equiv) under Grignard-type conditions unless otherwise noted. [b] Ratios were determined by ^{1}H NMR analysis after isolation. [c] In (2 equiv) and **2** (2 equiv) were used. [d] Barbier-type conditions. [e] Zn (1.5 equiv) and **2** (1.5 equiv) were used.

Our initial study focused on the reactions of benzaldehyde (**1g**) with organoindium reagent in situ generated from 1-bromopent-4-en-2-yne (**2**)[12] and indium (Table 1). Reaction of **1g** with organoindium reagent in DMF at 25 °C gave **3g** (74%), **4** (8%), and **5** (6%) (entry 1). The model reaction afforded the vinyl allenol **3g** in 57% and 69% yields in the presence of additives (3 equiv) such as LiCl and LiI, respectively (entries 2 and 3). Although **3g** was produced in 27% yield in THF without additive (entry 4), the vinyl allenol **3g** was obtained in 79% yield in the presence of LiI (3 equiv) in THF (entry 6). We attempted the present reaction under the Barbier-type conditions, producing **3g** in 51% yield (entry 7). Of the reaction conditions examined, the best results were obtained with **1g** (1 equiv), **2** (1 equiv), and indium (1 equiv) in the presence of LiI (1 equiv) in THF at 25 °C for 2 h under a nitrogen atmosphere, affording selectively **3g** in 88% yield and **5** in 8% yield (entry 8). 1-Iodopent-4-en-2-yne was detected in part in ^{1}H NMR after treatment of **2** with LiI in THF-d_8, indicating that iodide anion substituted bromide in **2** and then the corresponding iodide smoothly reacted with indium to produce organoindium reagent. The high selectivity of the present reaction using organoindium reagents was compared to Grignard and organozinc reagents. Subjecting **1g** to **2** and Mg in Et$_2$O gave **3g** (42%) and **5** (42%) (entry 10). Similar results were obtained in the case of Zn (1.5 equiv) in the presence of LiI in THF, indicating that organoindium reagent was superior to other organometallic

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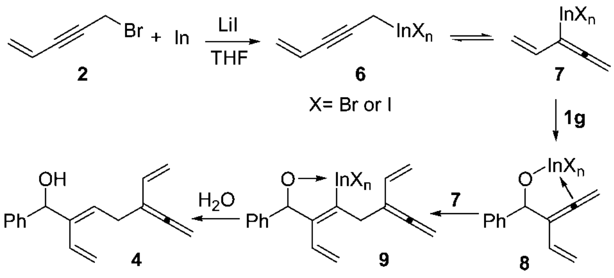
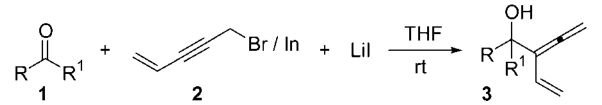
reagents (entry11). Formation of **4** could be explained by 1,2,4-pentatrien-3-ylation to the carbonyl group of **1g** followed by additional 1,2,4-pentatrien-3-ylation to the terminal double bond of the allenyl group (Scheme 2). On the basis of the result that the yield of **4** was increased by 29% without an additive (entry 4), exposure of **1g** to organoindium reagent in situ generated from **2** (2 equiv) and indium (2 equiv) in THF without LiI resulted in the selective formation of **4** in 73% yield (entry 5).

Scheme 2. Plausible Mechanism for Formation of 1-Phenyl-2,5-divinyl-2,5,6-heptatrien-1-ol



To demonstrate the efficiency and scope of the present method, we applied this reaction system to a variety of carbonyl compounds to obtain vinyl allenols (Table 2). Under the optimized conditions, formaldehyde gave the vinyl allenol **3a** in moderate yield (61%) mainly due to volatility (entry 1). Treatment of 1-butanal and cyclohexanecarbaldehyde with indium and **2** in the presence of LiI selectively produced **3b** and **3c** in 81% and 91% yields, respectively (entries 2 and 3). Ethyl glyoxalate reacted with the organoindium reagent to give **3d** in 82% yield (entry 4). Reactions of ethyl pyruvate and ethyl benzoylformate with the indium reagent gave the vinyl allenols (**3e** and **3f**) in 70% and 71% yields, respectively (entries 5 and 6). In the case of various aromatic aldehydes, electronic variation on the aromatic substituents, such as methyl, methoxy, hydroxyl, acetyl, methoxycarbonyl, bromide, and iodide groups, did not diminish the efficiency and selectivity of indium-mediated 1,2,4-pentatrien-3-ylation (entries 8−18). Organoindium reagent in situ generated from indium and **2** in the presence of LiI smoothly added to methyl-, methoxy-, and 3,4-(methylenedioxy)benzaldehyde to produce the desired products in good yields (75−84% yields) (entries 8, 9, and 11−13). 2,4,6-Trimethylbenzaldehyde reacted with organoindium reagent to provide **3j** in 49% yield for 2 h (entry 10). It is noteworthy that protection of a hydroxyl group on the substrates is not necessary as demonstrated by the reaction of 3-hydroxybenzaldehyde (entry 14). Addition of the organoindium reagent to 4-acetylbenzaldehyde led to the selective formation of **3o** in 82% yield (entry 15). Methyl 4-formylbenzoate reacted with organoindium reagent to result in the exclusive formation of **3p** in 88% yield (entry 16). Indium reagent was treated with 3-bromo- and 2-iodobenzaldehyde to afford **3q** and **3r** selectively in good yields (entries 17 and 18). 2-Furfural and 3-pyridinecarboxaldehyde turned out to be compatible with the employed reaction conditions (entries 19 and 20). Exposure of acetophenone to organoindium reagent provided **3u** in 45% yield (entry 21).

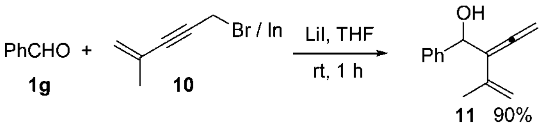
Table 2. Reactions of Carbonyl Compounds with Indium and 1-Bromopent-4-en-2-yne[a]



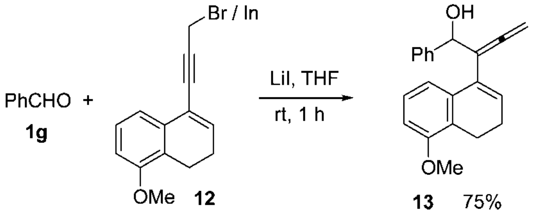
entry	R	R¹		time (h)		yield (%)[b]
1	H	H	**1a**	2	**3a**	61 (1)[c]
2	*n*-Bu	H	**1b**	2	**3b**	81
3	C_6H_{11}	H	**1c**	2	**3c**	91 (3)[c]
4	EtO_2C	H	**1d**	2	**3d**	82 (8)[c]
5	EtO_2C	CH_3	**1e**	2	**3e**	70
6	EtO_2C	Ph	**1f**	2	**3f**	71 (3)[c]
7	Ph	H	**1g**	2	**3g**	88 (8)[c]
8	4-Me-C_6H_4	H	**1h**	1	**3h**	77 (7)[c] (3)[d]
9	2-Me-C_6H_4	H	**1i**	1	**3i**	75 (8)[c] (5)[d]
10	2,4,6-Me$_3$-C_6H_2	H	**1j**	2	**3j**	49 (2)[c] (34)[e]
11	4-MeO-C_6H_4	H	**1k**	2	**3k**	82 (4)[c] (4)[d]
12	3-MeO-C_6H_4	H	**1l**	2	**3l**	84 (8)[c] (2)[d]
13	3,4-(OCH_2O)-C_6H_3	H	**1m**	2	**3m**	83 (5)[c]
14	3-HO-C_6H_4	H	**1n**	2	**3n**	80 (6)[c]
15	4-Ac-C_6H_4	H	**1o**	1	**3o**	82 (6)[c]
16	4-MeO$_2$C-C_6H_4	H	**1p**	1	**3p**	88
17	3-Br-C_6H_4	H	**1q**	1	**3q**	86 (4)[c]
18	2-I-C_6H_4	H	**1r**	1	**3r**	89 (7)[c]
19	2-furyl	H	**1s**	2	**3s**	90 (2)[c]
20	3-pyridyl	H	**1t**	1	**3t**	93 (2)[c]
21	Ph	CH_3	**1u**	4	**3u**	45 (20)[e]

[a] Reactions were carried out with indium (1 equiv), **2** (1 equiv), and LiI (1 equiv) in THF at 25 °C. [b] Isolated yields. [c] Propargylation products. [d] Compounds similar to **4** produced from sequential allenylation to aldehyde followed by to allene. [e] Recovery yields of carbonyl compound.

With these results in hand, we applied the present method to enynyl bromide possessing alkyl substituents. We were pleased to obtain selectively vinyl allenol **11** in 90% yield from the reaction of **1g** with organoindium reagents in situ generated from **10** and indium (eq 1).[13] Treatment of **1g** with **12** and indium selectively produced the vinyl allenol **13** in 75% yield (eq 2).[14]



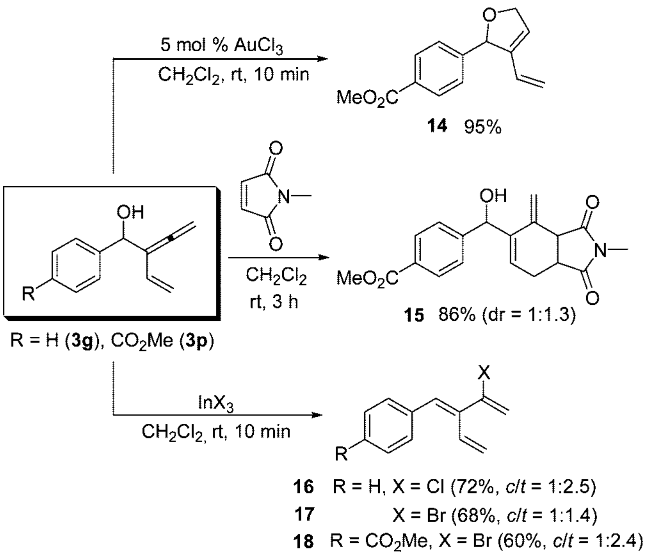
(1)



(2)

Next, we examined further functionalization of vinyl allenols (Scheme 3). Treatment of **3p** with 5 mol % of $AuCl_3$ in CH_2Cl_2 produced dihydrofuran **14** in 95% yield. The Diels−Alder reaction of vinyl allenol **3p** with *N*-methylma-

Scheme 3. Functionalization of Vinyl Allenols



leimide afforded adduct **15** (dr = 1:1.3) in 86% yield. Vinyl allenols **3g** and **3p** reacted with indium trihalide to give 2-halo-3-vinyl-1,3-butadiene derivatives (**16**−**18**) in good yields.

In summary, we have demonstrated that the reaction of carbonyl compounds with organoindium reagents in situ generated from indium and 1-bromopent-4-en-2-yne derivatives in THF at 25 °C selectively produced vinyl allenols in good to excellent yields, indicating that 1-bromopent-4-en-2-yne acted as synthon of 3-anion of 1,2,4-pentatriene. The present reaction has shown good functional group tolerance. Treatment of vinyl allenols with gold catalyst, dienophile, or indium trihalide cleanly provided the functionalized dihydrofuran, cyclohexene, or 2-halo-1,3-diene derivatives, respectively.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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