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Indium-Mediated Regio- and Chemoselective Synthesis of α-Hydroxyalkyl Allenic Esters and Gold-Catalyzed Cyclizations to Ethyl 2-Naphthoate Derivatives

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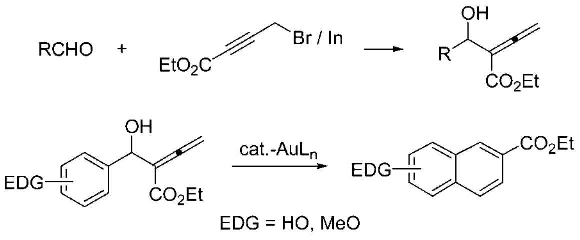
ABSTRACT



The regio- and chemoselective synthetic method of functionalized α-hydroxyalkyl allenic esters was developed from the reactions of various aldehydes with organoindium reagent generated in situ from indium and ethyl 4-bromobutynoate. The α-hydroxyalkyl allenic esters possessing electron-donating groups were cyclized to ethyl 2-naphthoate derivatives through intramolecular *C*-alkylation catalyzed by gold salts.

The functionalized α-hydroxyalkyl allenic esters composed of allenic alcohol and allenic ester play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals but also as useful building blocks in synthetic chemistry.[1] For this reason, the efficient synthesis of substituted α-hydroxyalkyl allenic esters continues to attract the interest of synthetic chemists. Recently, α-hydroxyalkyl allenic esters were prepared in good yields (59−83%) from the modified reactions of aldehydes with 3-(methoxycarbonyl)propargyl bromide using $SnCl_2$ and NaI in DMPU.[1d] However, these reactions needed the toxic stannous chloride and a long reaction time (14−36 h) in the absence of light. Aldol reactions of allenic esters with aldehydes gave the α-hydroxyalkyl allenic esters, whereas functional group tolerance and product yields were unsatisfactory due to the basic reaction conditions.[1b] The allenic alcohols bearing an ethoxycarbonyl group at the α-position were provided by the 1,6-cuprate addition to acceptor-substituted enynes followed by the oxidation of titanium enolates with dimethyl dioxirane in a two pot process.[2] Although the allenic alcohols were obtained through the indium-mediated reactions of trialkylsilylpropargyl bromide with aldehydes, the product yields were moderate (45−71%) and the corresponding

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(1) (a) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621. (b) Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1983**, *58*, 5952. (c) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805. (d) Deng, Y.; Jin, X; Ma, S. *J. Org. Chem.* **2007**, *72*, 5901.

(2) (a) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186. (b) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1. (c) Krause, N.; Laux, M.; Hoffmann-Röder, A. *Tetrahedron Lett.* **2000**, *41*, 9613. (d) Krause, N., ; Zelder, C. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: New York, 2000; Vol. 2, p 645.

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homopropargylic alcohols were produced as side products.[3] In addition, the bulky groups, such as triisopropylsilyl and *tert*-butyldiphenylsilyl groups, at the γ-position of propargyl bromide were necessarily required. Despite recent progress,[4,5] these results have led us to investigate the preparative methods of functionalized α-hydroxyalkyl allenic esters. In continuation of our studies directed toward the development of efficient indium-mediated reactions,[6] we described herein an efficient synthetic method of functionalized α-hydroxyalkyl allenic esters. Also, treatment of α-hydroxyalkyl allenic esters possessing electron-donating groups with gold catalyst unexpectedly led to the formation of ethyl 2-naphthoate derivatives through intramolecular *C*-alkylation (Scheme 1).

Scheme 1. Preparation of α-Hydroxyalkyl Allenic Esters and Their Cyclization to Naphthoates

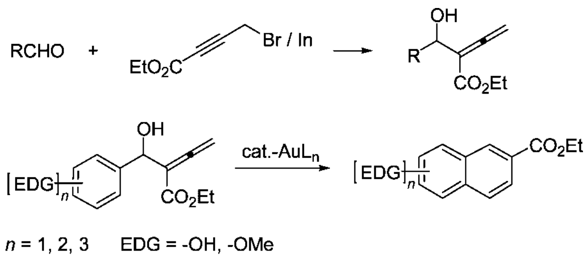
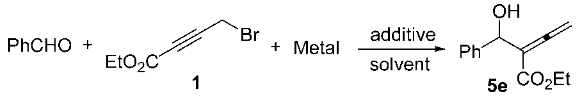


Table 1. Optimization for the Reaction of Benzaldehyde with Metal and Ethyl 4-Bromobutynoate[a]



entry	metal	additive (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	In		THF	60	10	32[c]
2	In		DMF	60	10	38[c]
3	In	LiI (3.0)	THF	25	5	0[d]
4	In	KI (3.0)	THF	25	6	45
5	In	LiI (3.0)	THF/H_2O	25	4	58
6	In	LiI (3.0)	DMF/H_2O	25	4	29[c]
7	In	KI (3.0)	DMF	25	6	72
8	**In**	**LiI (3.0)**	**DMF**	**25**	**5**	**90 (86)**[e]
9	Mg		THF	25	12	0
10	Zn		THF	25	12	38[f]

[a] Reactions were performed with benzaldehyde (1 equiv) and organometallic reagent generated in situ from the reaction of metal (1 equiv) with **1** (1.5 equiv) under Grignard-type condition. [b] GC yields obtained on the basis of 2-methoxynaphthalene as an internal standard. [c] Benzaldehyde was mainly recovered. [d] TLC is messy. [e] Isolated yields. [f] Isolated yield of ethyl 5-hydroxy-5-phenyl-2-butynoate.

Reactions of benzaldehyde with indium and ethyl 4-bromobutynoate (**1**)[7] were initially examined (Table 1). Treatment of benzaldehyde with organoindium reagent generated in situ from indium and **1** selectively produced α-hydroxybenzyl allenic ester **5e** in 32% (THF) and 38% (DMF) yields, respectively (entries 1 and 2). The use of additives, such as lithium iodide and potassium iodide, affected the reaction time and product yields. Potassium iodide in DMF afforded the allenic ester in 72% yield (entry 7). Of the reactions screened, the best results were obtained with organoindium reagent generated in situ from the reaction of indium (1 equiv) with ethyl 4-bromobutynoate (1.5 equiv) in the presence of lithium iodide (3 equiv) in DMF at 25 °C for 5 h under a nitrogen atmosphere, producing exclusively allenic ester **5e** in 86% yield with complete regioselectivity (entry 8). Grignard-type addition reaction provided the better results rather than one of Barbier type. DMF was the best solvent among several reaction media (THF, DMF, THF−H_2O and DMF−H_2O). Subjecting benzaldehyde to **1** and Mg in THF did not give **5e** (entry 9). In the case of Zn, propargylation product (ethyl 5-hydroxy-5-phenyl-2-butynoate) was only produced in 38% yield (entry 10). Ethyl 4-iodobutynoate was detected in part in ^{1}H NMR after treatment with lithium iodide in DMF, indicating that iodide replaced bromide in ethyl 4-bromobutynoate, and then the corresponding iodide reacted smoothly with indium to produce organoindium reagent.

The ^{1}H NMR (400 MHz, DMF-d_7, 25 °C) spectrum of organoindium reagents showed two signals (δ 4.01 and 3.88) for the methylene group, indicating that two types of propargylindium reagent (**2**, ratio = 2.62:1 for 30 min, 2.40:1 for 45 min, 1.86:1 for 60 min) were produced and the corresponding allenylindium reagents (**3**) were not formed (Table 2).

To demonstrate the efficiency and scope of the present method, we applied the organoindium reagent to a variety of aldehydes (Table 3). Indium reagent was treated with formaldehyde to selectively afford allenic ester **5a** in 82% yield (entry 1). In the case of butanal and cyclohexane−carbaldehyde, the corresponding allenic esters **5b** and **5d** were obtained in 83% and 82% yields, respectively (entries 2 and 4). Electronic variations on the aromatic substituents did not diminish largely the efficiency and selectivity (entries 6−19). Reaction of 2,4,6-trimethylbenzaldehyde with the organoindium reagent provided the corresponding product

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(3) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042.

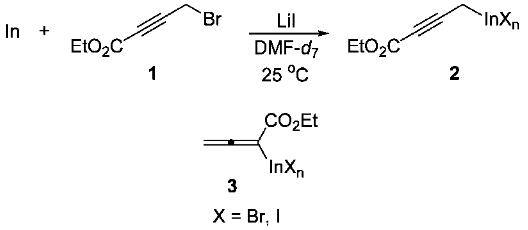
(4) (a) Hopf, H.; Bohm, I.; Kleinschroth, J. *Org. Synth.* **1982**, *60*, 41. (b) Oehlsehlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587. (c) Brandsma, L.; Verkruijisse, H. In *Preparative Polar Organometallic Chemistry I*; Springer: Berlin, 1987; pp 61−64. (d) Isaac, M. B.; Chan, T.-H. *Chem. Commun.* **1995**, 1003. (e) Masuyama, Y.; Ito, A.; Fukuzawa, M.; Terada, K.; Kurusu, Y. *Chem. Commun.* **1998**, 2025. (f) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (g) Masuyama, Y.; Watabe, A.; Ito, A.; Kurusu, Y. *Chem. Commun.* **2000**, 2009. (h) Krause, N.; Hoffmann-Röder, A.; Cansius, J. *Synthesis* **2002**, 1759. (i) Hoffmann-Röder, A., ; Krause, N. In *Modern Allene Chemistry*; Krause, N., ; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1,pp 51−92 and 493−592.

(5) For allenylmagnesium halide and allenyllithium, see: (a) Babudri, F.; Florio, S. *Synthesis* **1986**, 638. (b) Shinokubo, H.; Miki, H.; Yokoo, T.; Oshima, K.; Utimoto, K. *Tetrahedron* **1995**, *51*, 11681. (c) Weyershausen, B.; Nieger, M.; Dötz, K. H. *Organometallics* **1998**, *17*, 1602. (d) Hoffmann-Röder, A., ; Krause, N. In *Modern Allene Chemistry, Vol. 1*, (Eds.; Krause, N., ; Hashmi, A. S. K., Eds.;Wiley-VCH: Weinheim, 2004; pp 497−499 and pp 509−510.

(6) (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (b) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901. (c) Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem.−Eur. J.* **2007**, *13*, 5197.

(7) MacInnes, I.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1077.

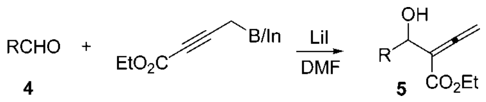
Table 2. NMR Study of the Reaction of Indium with Ethyl 4-Bromo-2-butynoate in the Presence of LiI in DMF-d_7



	$-CH_2-$	
time (min)	ppm (δ)	ratio
30	4.01, 3.88	2.62:1
45		2.40:1
60		1.86:1

5g in 85% yield regardless of the steric effect (entry 7). Although the reactions worked equally well with 3- and 4-methoxybenzaldehyde (entries 8 and 9) to give the desired products (**5h** and **5i**) in 80% and 89% yields, 3,5-dimethoxy- and 3,4,5-trimethoxybenzaldehyde produced the allenic esters (**5j** and **5l**) in 70% and 71% yields due to the electronic nature of methoxy groups (entries 10 and 12). 3,4-(Methylenedioxy)benzaldehyde also produced α-hydroxyalkyl allenic esters in 93% yield (entry 11). It is noteworthy that protection of hydroxyl group on substrates is not necessary as demonstrated by the reaction of 3-hydroxylbenzaldehyde (entry 13). Moreover, the present reaction proceeded to furnish the allenic ester **5n** in 68% yield despite the presence of two hydroxyl groups on the aromatic ring (entry 14). Aromatic aldehydes having electron-withdrawing groups, such as 4-acetyl, 4-methoxycarbonyl, and 4-nitro groups, reacted with organoindium reagents to result in the exclusive formation of α-hydroxyalkyl allenic esters in excellent yields under the optimum conditions (entries 15−17). A range of 4-chloro- and 2-iodobenzaldehyde readily participated in these indium-mediated addition reactions (entries 18 and 19). Surprisingly, no propargylic addition products are formed in any reactions. The reactions of aldehydes, such as **4i**, **4n**, and **4s**, with 3-(methoxycarbonyl)propargyl bromide using $SnCl_2$ and NaI in DMPU for 24 h under the absence of light produced **5i**, **5n**, and **5s**, in 62%, 52%, and 50% yields, respectively. These results indicate that the organoindium reagent is more reactive than organotin reagent. However, ketones have thus far failed.

Table 3. Reactions of Various Aldehydes with Indium and Ethyl 4-Bromobutynoate[a]



entry	R		time (h)	yield[b] (%)
1	H	**a**	10	82
2	*n*-Pr	**b**	7	83
3	$PhCH_2CH_2$	**c**	7	79
4	*c*-C_6H_{11}	**d**	7	82
5	Ph	**e**	5	86
6	4-Me-C_6H_4	**f**	5	88
7	2,4,6-Me_3-C_6H_2	**g**	10	85
8	3-MeO-C_6H_4	**h**	10	80
9	4-MeO-C_6H_4	**i**	20	89
10	3,5-$(MeO)_2$-C_6H_3	**j**	12	70
11	3,4-(OCH_2O)-C_6H_3	**k**	14	93
12	3,4,5-$(MeO)_3$-C_6H_2	**l**	12	71
13	3-HO-C_6H_4	**m**	5	65
14	3,5-$(HO)_2$-C_6H_3	**n**	8	68
15	4-Ac-C_6H_4	**o**	2	84
16	4-MeO_2C-C_6H_4	**p**	2	87
17	4-NO_2-C_6H_4	**q**	3	80
18	4-Cl-C_6H_4	**r**	5	84
19	2-I-C_6H_4	**s**	5	69

[a] Reactions were performed with aldehyde (1 equiv) and organoindium generated in situ from the reaction of indium (1 equiv) with **1** (1.5 equiv) in the presence of lithium iodide (3.0 equiv) in DMF. [b] Isolated yields.

Next, we tried to cyclize α-hydroxyalkyl allenic esters to obtain a variety of dihydrofuran derivatives. In general, allenic alcohols in the presence of gold salt catalysts provided 2,5-dihydrofuran derivatives.[8] However, treatment of allenic esters possessing electron-donating groups, such as methoxy and hydroxyl group, on the aromatic ring with gold catalyst unexpectedly produced ethyl 2-naphthoate derivatives (Table 4).[9] Allenic ester **5h** having 3-methoxyphenyl group was treated with 5 mol % of $(Ph_3P)AuCl$ and 5 mol % of $AgBF_4$ to give ethyl methoxy-2-naphthoate in 54% yield (**6a**:**6b** = 1:3.5) through *C*-alkylation and 2-(3-methoxyphenyl)-3-ethoxycarbonyl-2,5-dihydrofuran in 33% yield through *O*-alkylation (entry 1). This result implies that nucleophilicity of aromatic ring bearing methoxy group is more strong than one of hydroxy group at the benzylic position toward gold-activated allene. As far as we are aware, there is no report on the preparation of naphthalene derivatives through intramolecular *C*-alkylation of allenic alcohols catalyzed by gold salts. When the cyclization of **5h** was performed with 5 mol % of AgOTf and $AgBF_4$ in CH_2Cl_2, cyclization product did not produce. These blank tests clearly indicate that $(Ph_3P)AuCl$ is required for the cyclization to proceed. To clarify the reaction course, the reaction of **5h** with 5 mol % of triflic acid and trifluoroacetic acid instead of $(Ph_3P)AuCl$ and $AgBF_4$ was investigated. However, no cyclization product was obtained. Addition of organoindium reagent to aldehydes and sequential treatment of allenic esters with gold salt catalysts in one pot did not produce the naphthalene derivatives due to lack of harmony of solvents (DMF and CH_2Cl_2). Exposure of allenol **5j** possessing dimethoxyphenyl group to 5 mol % of $(Ph_3P)AuCl$ and 5 mol % of AgOTf led to the formation of the naphthalene derivative **6c** in 81% yield (entry 2). Under the optimal conditions, allenic ester **5l** having trimethoxyphenyl group gave ethyl 2-naphthoate

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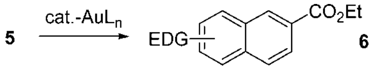
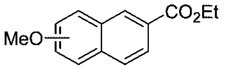
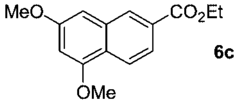
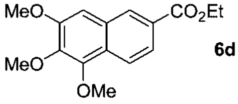
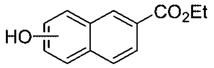
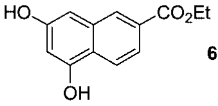
(8) (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (b) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (c) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485. (d) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. (e) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2006**, *71*, 8658. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

(9) Skouta, R.; Li, C.-J. *Can. J. Chem.* **2008**, *86*, 616.

Table 4. Synthesis of Naphthalene Derivatives via Gold-Catalyzed Cyclization of Allenic Ester[a]

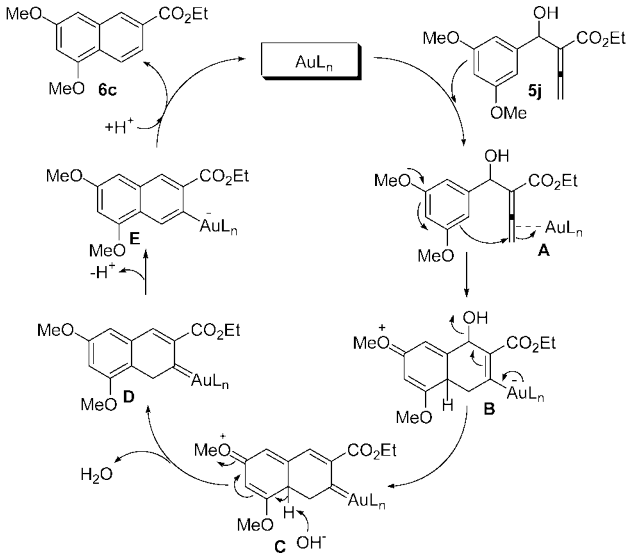


entry	reactant	product		yield (%)[a]
1[b]	**5h**		**6a** **6b**	54(1:3.5)[c](33)[d]
2[e]	**5j**		**6c**	81
3[b]	**5l**		**6d**	38
4[e]	**5m**		**6e** **6f**	76(1:3.2)[f](21)[g]
5[e]	**5n**		**6g**	64

[a] Isolated yields. [b] 5 mol % of (Ph_3P)AuCl and 5 mol % of $AgBF_4$ were used in CH_2Cl_2 at 25 °C for 1 h. [c] Ratio of **6a** (5-MeO) and **6b** (7-MeO). [d] 2-(3-Methoxyphenyl)-3-ethoxycarbonyl-2,5-dihydrofuran. [e] 5 mol % of (Ph_3P)AuCl and 5 mol % of AgOTf were used in CH_2Cl_2 at 25 °C for 1 h. [f] Ratio of **6e** (5-OH) and **6f** (7-OH). [g] 2-(3-Hydroxyphenyl)-3-ethoxycarbonyl-2,5-dihydrofuran.

in 38% yield due to the methoxy group at the 4-position (entry 3). In the case of allenol **5m**, ethyl hydroxy-2-naphthoate was produced in 76% yield (**6e**:**6f** = 1: 3.2) together with 2-(3-hydroxyphenyl)-3-ethoxycarbonyl-2,5-dihydrofuran in 21% yield with 5 mol % of (Ph_3P) AuCl and 5 mol % of AgOTf (entry 4). Allenic ester **5n** was treated with gold catalyst, producing exclusively ethyl 5,7-dihydroxy-2-naphthoate (**6g**) in 64% yield (entry 5). Although the mechanism of 2,5-dihydrofuran formation from allenic alcohols has been reported,[8] the mechanism of the cyclization to naphthalene derivatives has not been established. A plausible reaction pathway is described in Scheme 2. Thus, coordination of the gold catalyst to terminal double bond in allene **5j** results in the formation of the intermediate **A** which, upon nucleophilic attack of the carbon on aromatic ring, is cyclized to the σ-gold complex **B**. Dehydration of **C** followed by protodeauration of **E** affords the naphthalene derivative **6c** and releases the gold catalyst into the catalytic cycle. At present, the exact nature of the catalytically active gold species is unknown.

Scheme 2. Plausible Mechanism of Synthesis of Naphthalene Derivatives



In summary, we have developed a regio- and chemoselective synthetic method of functionalized α-hydroxyalkyl allenic ester derivatives from the reaction of various aldehydes with organoindium reagent generated in situ from indium and ethyl 4-bromobutynoate. The functionalized α-hydroxyalkyl allenic esters possessing electron-donating groups were cyclized to naphthalene derivatives through intramolecular *C*-alkylation catalyzed by gold salts.

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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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