Stereoselective Synthesis of 4-Alkyl- or 4-Aryl-3-ethoxycarbonyl-2-halo-1,3-dienes from the Reaction of Allenols Having Ethoxycarbonyl Group with Indium Trihalide

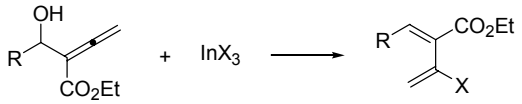
Jae-Myung A and Phil Ho Lee*

*Department of Chemistry and Institute for Molecular Science and Fusion Technology, Kangwon National University, Chuncheon 200-701, Korea. *E-mail: phlee@kangwon.ac.kr*

Received November 20, 2008, Accepted December 9, 2008

Key Words: Allenol, 2-Halo-1,3-diene, Indium trihalide, Selectivity

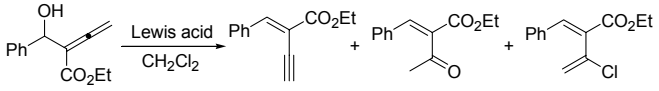
Because Diels-Alder reaction represents an extremely versatile tool in organic synthesis, reactions leading to 1,3-diene formation are often key steps in a wide range of organic processes.[1] Especially, 2-halo-1,3-dienes are very important compounds due to the further functionalization of vinyl halide after or before Diels-Alder reaction. A few methods have been developed for the synthesis of 2-halo-1,3-dienes. Bäckvall *et al.* described stereoconvergent synthesis of (*Z*,*E*)-2-bromo-1, 3-dienes from Pd(II)-catalyzed S_N2' reactions of α-allenic acetates.[2] Ma *et al.* reported S_N2'-type addition-elimination reactions of 1-aryl-2,3-allenols with LiX to provide 2-halo-1,3-dienes[3] and stereoselective addition-elimination reactions of 3-(methoxycarbonyl)-1,2-allen-4-ols with MX (M: Na, Li, K. X: Cl, Br, I).[4] In addition, Cho *et al.* developed indium trihalide-mediated S_N2' reaction of alkyl- or aryl-substituted allenols, producing 2-halo-1,3-dienes.[5] Recently, we developed not only the efficient synthetic method of a variety of allenols having ethoxycarbonyl group[6] but also Diels-Alder reaction of 2-azetidinone having 1,3-butadien-2-yl[7] and 1,2,4,5-hexatetraen-3-yl group.[8] During the course of our research program aimed at finding new indium-mediated organic reactions,[9] we became interested in the stereoselective synthesis of 2-halo-1, 3-dienes from allenols having an ethoxycarbonyl group. Herein, we report a stereoselective synthetic method of 3-ethoxycarbonyl-2-halo-1,3-dienes from the reaction of α-hydroxyalkyl allenic esters possessing ethoxycarbonyl group with indium trihalide (Scheme 1).



R = alkyl, aryl X = Cl, Br, I

Scheme 1. Reaction of α-hydroxyalkyl allenic esters possessing ethoxycarbonyl group with indium trihalide

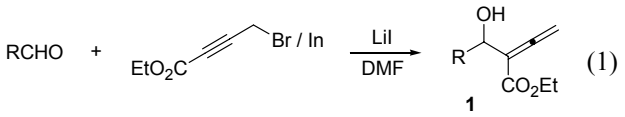
Table 1. Treatment of allenols with Lewis acids[a]



Entry	Lewis Acid	Temp (℃)	Time (h)	Yield (%)[b]		
				2	**3**	**4a**
1	TMSOTf[c]	0	5	55	20	
2	$In(OTf)_3$	25	5	37	16	
3	BF_3OEt_2	0	0.17	17	44	
4	$ZnCl_2$	25	24			(95)[d]
5	$AlCl_3$	25	10			23(23)[e]
6	AgOTf	25	3			57[f]

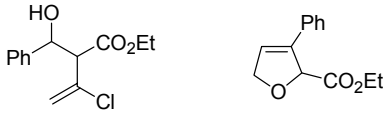
[a]Lewis acid (1 equiv) was used. [b]Isolated yield. [c]TMSOTf (0.2 equiv) was used. [d]**1a**. [e]Ethyl 2-benzhydroxyl-3-chloro-3-butenoate (**5**). [f]3-Ethoxycarbonyl-2-phenyl-2,5-dihydrofuran (**6**).

First, reaction of α-hydroxyalkyl allenic esters with a variety of Lewis acids were examined (Table 1). α-Hydroxyalkyl allenic esters were regioselectively obtained from the reaction of various aldehydes with organoindium reagent generated in situ from indium and ethyl 4-bromobutynoate in the presence of LiI in DMF (eq. 1).[6]



(1)

Treatment of **1a** with TMSOTf, $In(OTf)_3$, and $BF_3{\cdot}OEt_2$ gave the mixture of ethyl (*E*)-2-ethynyl cinnamate (**2**) and ethyl (*E*)-2-acetylcinnamate (**3**) (entries 1-3). Although $ZnCl_2$ did not react with **1a** (entry 4), $AlCl_3$ gave ethyl (*Z*)-2-(1'-chlorovinyl)cinnamate (**4a**) in 23% yield and ethyl 2-benzhydroxyl-3-chloro-3-butenoate (**5**) in 23% yield (entry 5). In the case of AgOTf, 3-ethoxycarbonyl-2-phenyl-2,5-dihydrofuran (**6**) was produced in 57% yield (entry 6).



Next, we examined the reaction of **1a** with indium trihalide as Lewis acid (Table 2). Treatment of **1a** with 1 equiv of $InCl_3$ produced 2-chloro-1,3-diene **4a** (*Z*:*E* = 36:1) in 71% yield and **3** in 6% yield at 25 °C for 5 h in CH_2Cl_2 (entry 1). The stereochemistry (*Z*/*E*) of generated double bond was determined by comparison to the corresponding methyl ester.[4] The chemical shift of vinyl proton on benzylic position of *Z*-**4a** (δ 7.70) was downfield than that (δ 7.21) of *E*-**4a.**

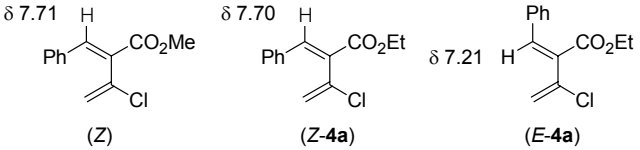
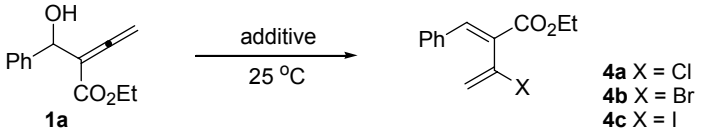


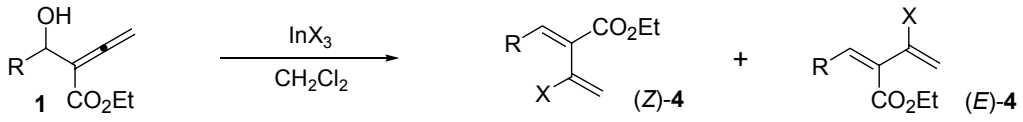
Table 2. Reaction optimization of allenols with indium trihalide

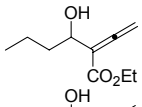
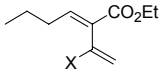
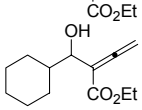
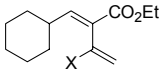
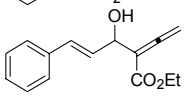
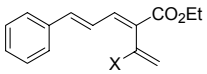
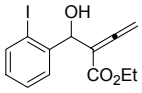
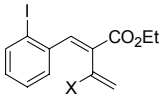
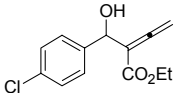
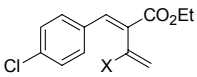
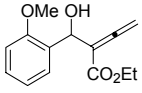
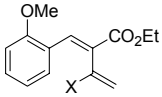
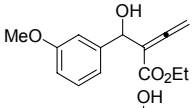
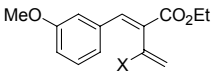
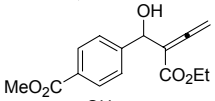
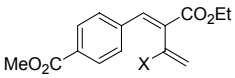
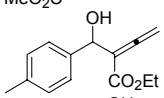
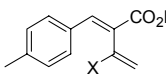
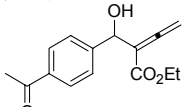
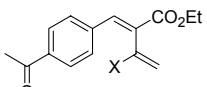


Entry	InX_3 (equiv)	Additive (equiv)	Solvent	Time (h)	Yield (%)[a]
1	$InCl_3$(1)	-	CH_2Cl_2	5	71(36:1)[b](6)[c]
2	$InCl_3$(0.34)	-	CH_2Cl_2	10	51(50:1)[b](15)[c](10)[d]
3	$InBr_3$(1)	-	CH_2Cl_2	2	84(39:1)[b]
4	InI_3(1)	-	CH_2Cl_2	2	79(55:1)[b]
5	-	LiCl(3)	CH_2Cl_2	10	0
6	$InCl_3$(0.1)	LiCl(3)	CH_2Cl_2	20	0
7	$InCl_3$(0.1)	LiCl(3)	DMF	10	0
8	$InCl_3$(1)	-	benzene	10	47(182:1)[b]
9	$InCl_3$(1)	-	CH_3CN	10	0
10	$InCl_3$(1)	-	DMF	10	0
11	**$InCl_3$(1.5)**	**-**	**CH_2Cl_2**	**4**	**81(78:1)[b]**
12	**InI_3(1.5)**	**-**	**CH_2Cl_2**	**1**	**89(35:1)[b]**

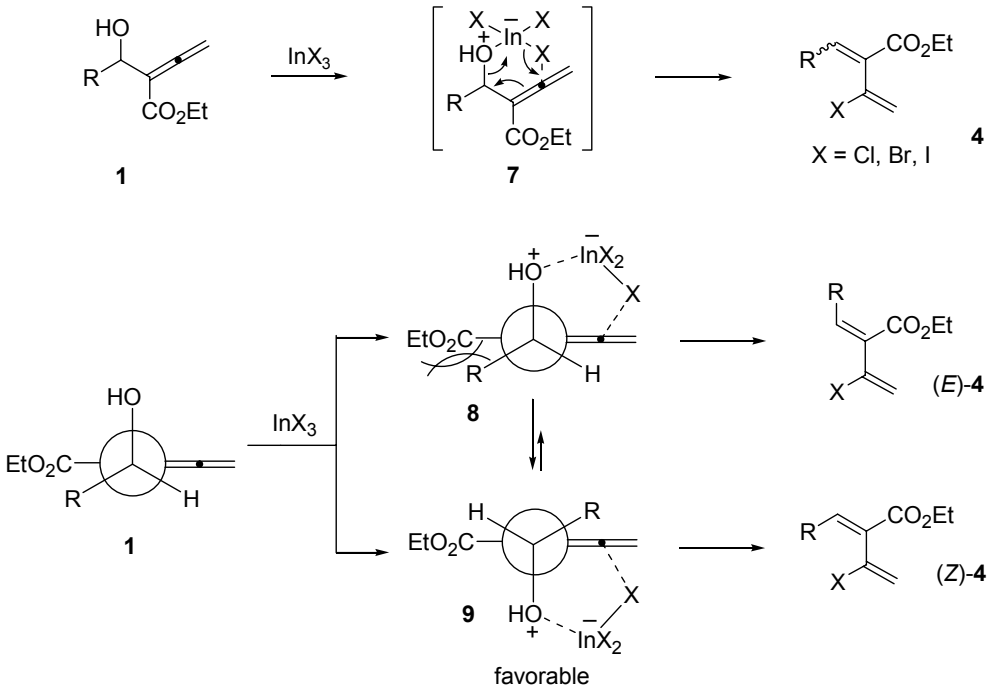
[a]Isolated yield. [b]*Z/E* ratio. [c]Ethyl 2-acetylcinnamate (**3**). [d]**1a**.

Table 3. Synthesis of halo-1,3-dienes from allenols[a]



Entry	**1**		Temp (°C)	Time (h)	Product		X	Yield (%)[b]
1		**1b**	80	1		**4d**	Br[c]	69(Z)
2			80	1		**4e**	I[c]	71(25:1)
3		**1c**	40	10		**4f**	Cl[c]	62(32:1)
4			40	10		**4g**	Br[c]	65(58:1)
5		**1d**	25	2		**4h**	Cl	72(Z)
6			25	0.5		**4i**	Br	85(19:1)
7		**1e**	25	15		**4j**	Cl	67(4:1)
8			25	7		**4k**	Br	74(23:1)
9			25	7		**4l**	I	74(7:1)
10		**1f**	25	5		**4m**	Cl	72(Z)
11			25	2		**4n**	Br	84(Z)
12			25	1		**4o**	I	74(24:1)
13		**1g**	25	4		**4p**	Cl[c]	71(Z)
14			25	0.5		**4q**	Br[c]	80(25:1)
15		**1h**	25	3		**4r**	Cl	70(50:1)
16			25	1		**4s**	Br	79(53:1)
17		**1i**	25	10		**4t**	Cl[c]	71(17:1)
18			25	10		**4u**	Br	77(17:1)
19		**1j**	25	3		**4v**	Cl	71(76:1)
20			25	0.5		**4w**	Br	88(33:1)
21		**1k**	25	10		**4x**	Cl[d]	47(26:1)
22			25	10		**4y**	Br[d]	59(27:1)

[a]Reactions were carried out with InX_3 (1 equiv) in CH_2Cl_2. [b]Ratio in parenthesis indicates ratio of *Z/E* isomer determined from NMR. [c]InX_3 (1.5 equiv) was used. [d]InX_3 (2 equiv) was used.



Scheme 2. A plausible mechanism

Compound **1a** was reacted with 1 equiv of $InBr_3$ and InI_3 to afford 2-bromo-1,3-diene **4b** (84%, *Z*:*E* = 39:1) and 2-iodo-1, 3-diene **4c** (79%, *Z*:*E* = 55:1), respectively (entries 3 and 4). The use of catalytic amount of $InCl_3$ (0.34 equiv) provided **4a** in 51% yield (*Z*:*E* = 50:1) (entry 2). Reaction of **1a** with LiCl (3 equiv) without InX_3 did not proceed in CH_2Cl_2 (entry 5). Combination of catalytic amount of $InCl_3$ (0.1 equiv) and LiCl (3 equiv) in CH_2Cl_2 or DMF was not effective for the reaction with **1a** (entries 6 and 7). Dichloromethane was the best solvent among several reaction media screened (DMF, benzene, and CH_3CN). Although the use of benzene as a solvent gave good *E*/*Z* selectivity (182:1) at 25 °C for 10 h (entry 8), the starting material **1a** did not completely disappear even at reflux condition. Of the reactions screened, the best results were obtained from the reaction of **1a** with 1.5 equiv of $InCl_3$ (1.5 equiv), and InI_3 (1.5 equiv), and $InBr_3$ (1.0 equiv) producing **4a** and, **4c**, and **4b** in 81% (*Z*:*E* = 78:1) and, 89% (*Z*:*E* = 35:1), and 84% (*Z*:*E* = 39:1) yields (entries 11, and 12, and 3).

To demonstrate the efficiency and scope of the present method, we carried out the reactions of a variety of α-hydroxyalkyl allenic esters **1** with indium trihalide (Table 3). Reaction of **1b** obtained from butanal with 1.5 equiv of $InBr_3$ and InI_3 afforded stereoselectively 2-halo-1,3-dienes **4d** and **4e** in 69% (*Z* only) and 71% (*Z*:*E* = 25:1) yields at 80 °C for 1 h, respectively (entries 1 and 2). Treatment of **1c** with $InCl_3$ and $InBr_3$ gave rise to the desired products **4f** (*Z*:*E* = 32:1) and **4g** (*Z*:*E* = 58:1) in good yields (entries 3 and 4). Allenic ester **1d** derived from cinnamaldehyde reacted with indium trihalide (1 equiv) to produce stereoselectively 2-halo-1,3-dienes **4h** and **4i** in 72% % (*Z* only)and 85% (*Z*:*E* = 19:1) yields, respectively (entries 5 and 6). Electronic as well as steric variations on the aromatic substituents, such as iodide, chloride, methoxy, methoxycarbonyl, and methyl, displayed little effect on the reaction efficiency and selectivity (entries 7-20). We were pleased to obtain selectively (*Z*)-2-chloro and 2-bromo-1,3-diene (**4m** and **4n**) from the reaction of **1f** with $InCl_3$ and $InBr_3$ (entries 10 and 11). However, *Z*-selectivity (*Z*:*E* = 24:1) was a little lower in the case of InI_3 (entry 12). Although the reactions worked equally well with α-hydroxyalkyl allenic ester **1i** possessing methoxycarbonyl group to give the desired products (**4t** and **4u**) in 71% and 77% (*Z*:*E* = 17:1) yields (entries 17 and 18), α-hydroxyalkyl allenic ester **1k** having ketone group produced 2-halo-1,3-dienes (**4x** and **4y**) in a little low yields (47% and 59%), indicating that indium trihalide might complex with ketone group (entries 21 and 22).[10]

Although mechanism for the reaction of allenol with indium trihalide has not been firmly established, the present reaction can be described as in Scheme 2. First, indium trihalide coordinates with allenol **1** to form a six membered cyclic transition state **7** and then, subsequent S_N2' attack of the halide ion to the center carbon of allene resulted in 2-halo-1,3-dienes **4**. The major isomer (*Z*)-**4** might be produced through more favorable transition state **9** compared to **8** due to steric interaction between aryl or alkyl and ethoxycarbonyl group.

In summary, we have developed an efficient synthetic method of *Z*-selective 3-ethoxycarbonyl-2-halo-1,3-dienes from the reaction of allenols possessing ethoxycarbonyl group with indium trihalides in CH_2Cl_2. Because 3-ethoxycarbonyl-2-halo-1,3-dienes can be applied to further functionalization such as Diels-Alder reactions and metal-catalyzed cross-coupling reactions, these results should provide more opportunities for the discovery of efficient and selective organic reactions.

Experimental Procedure

Synthetic procedure of allenyl alcohols (1a)[6]: Ethyl 4-bromobutynoate (95.5 μL, 0.75 mmol) was added to a suspension

of indium (57.4 mg, 0.5 mmol) and LiI (200.8 mg, 1.5 mmol) in DMF (2.0 mL). After being stirred for 30 min at room temperature, benzaldehyde (50.7 μL, 0.5 mmol) was added and then, the reaction mixture was stirred for 5 h. The reaction mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combine organic layers were washed with brine. The resulting organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:5) to give ethyl 2-(hydroxyphenylmethyl) buta-2,3-dienoate (93.8 mg, 86%).

Synthetic procedure of ethyl 2-(1-chlorovinyl)cinnamate (4a): Allenyl alcohol **1a** (65.5 mg, 0.3 mmol) was added to a solution of $InCl_3$ (66.5 mg, 0.3 mmol) in CH_2Cl_2 (1.2 mL) at room temperature. After being stirred for 5 h, the reaction was quenched with $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2. The extracts were was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:5) to give ethyl (*Z*)-2-(1-chlorovinyl)cinnamate (50.0 mg, 71%).

Ethyl (*Z*)-2-(1-chlorovinyl)cinnamate (4a-*Z*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.66-7.64 (m, 2H), 7.40-7.37 (m, 3H), 5.61 (d, *J* = 1.5 Hz, 1H), 5.36 (d, *J* = 1.5Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 141.9, 134.1, 133.5, 130.5, 130.1, 129.8, 128.9, 118.9, 61.5, 14.2; IR (film) 2981, 1715, 1649, 1608, 1448, 1253, 1200, 777 cm^{-1}; LRMS (EI) : *m/z* calcd. For $C_{13}H_{13}ClO_2$: 236.06, found: 236.09.

Ethyl (*E*)-2-(1-chlorovinyl)cinnamate (4a-*E*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.33 (m, 5H), 7.21 (s, 1H), 5.59 (d, *J* = 2.2 Hz, 1H), 5.53 (d, *J* = 2.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 141.9, 134.1, 133.9, 130.1, 129.8, 128.9, 128.5, 115.9, 61.8, 13.7; IR (film) 2981, 1715, 1649, 1608, 1448, 1253, 1200, 777 cm^{-1}; LRMS (EI) : *m/z* calcd. For $C_{13}H_{13}ClO_2$: 236.06, found: 236.09.

Ethyl (*Z*)-2-benzylidene-3-bromo-but-3-enoate (4b-*Z*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (m, 2H), 7.63 (s, 1H), 7.41-7.38 (m, 3H), 5.85 (d, *J* = 1.7 Hz, 1H), 5.78 (d, *J* = 1.7 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 141.2, 133.5, 131.3, 130.8, 130.1, 128.6, 123.9, 123.1, 61.6, 14.2; IR (film) 2980, 1715, 1644, 1604, 1448, 1253, 1200, 691 cm^{-1}.

Ethyl (*E*)-2-benzylidene-3-bromo-but-3-enoate (4b-*E*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (m, 2H), 7.63 (s, 1H), 7.41-7.38 (m, 3H), 5.88 (d, *J* = 1.74 Hz, 1H), 5.85 (d, *J* = 1.74 Hz, 1H), 4.30 (q, *J* = 7.14 Hz, 2H), 1.21 (t, *J* = 7.14 Hz, 3H); IR (film) 2980, 1715, 1644, 1604, 1448, 1253, 1200, 691 cm^{-1}.

Ethyl (*Z*)-2-benzylidene-3-iodo-but-3-enoate (4c-*Z*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.50 (s, 1H), 7.42-7.38 (m, 3H), 6.20 (d, *J* = 1.5 Hz, 1H), 6.12 (d, *J* = 1.5 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.37(t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 139.2, 134.3, 133.7, 131.7, 131.1, 129.9, 128.6, 98.6, 61.5, 14.2; IR (film) 2980, 1712, 1635, 1597, 1447, 1250, 1199, 690 cm^{-1}.

Ethyl (*E*)-2-benzylidene-3-iodo-but-3-enoate (4c-*E*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.42-7.38 (m, 3H), 7.00 (s, 1H), 6.43 (d, *J* = 1.5 Hz, 1H), 6.20 (d, *J* = 1.5 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 139.2, 134.3, 133.7, 131.7, 131.1, 129.9, 128.4, 98.6, 61.5, 14.2; IR (film) 2980, 1712, 1635, 1597, 1447, 1250, 1199, 690 cm^{-1}.

Acknowledgments. This paper is dedicated to Professor Byung Tae Cho on the occasion of his honorable retirement. This work was supported by the KOSEF through the NRL Program funded by the MOST (No. M10600000203-06J0000-20310) and by the KOSEF (R01-2006-000-11283-0). The NMR was obtained from the central instrumental facility in Kangwon National University. We thank Professor Sukbok Chang and Dr. Young Seo Cho for proofreading this manuscript. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the MS data.

References

1. (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1990. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 315. (c) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179. (d) Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243. (e) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.
2. Horváth, A.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120.
3. Ma, S.; Wang, G. *Tetrahedron Lett.* **2002**, *43*, 5723.
4. Deng, Y.; Jin, X.; Ma, S. *J. Org. Chem.* **2007**, *72*, 5901.
5. Cho, Y. S.; Jun, B. K.; Pae, A. N.; Cha, J. H.; Koh, H. Y.; Chang, M. H.; Han, S.-Y. *Synthesis* **2004**, *16*, 2620.
6. Park, C.; Lee, P. H. *Org. Lett.* **2008**, *10*, 3359.
7. Lee, K.; Lee, P. H. *Chem. Eur. J.* **2007**, *13*, 8877.
8. Yu, H.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 5183.
9. (a) Park, J.; Kim, S. H.; Lee, P. H. *Org Lett.* **2008**, *10,* 5067. (b) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (c) Lee, K.; Lee, P. H. *Org. Lett.* **2008**, *10*, 2441. (d) Lee, K.; Lee, P. H. *Tetrahedron Lett.* **2008**, *49*, 4302. (e) Lee, W.; Kang, Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 4326. (f) Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 1165. (g) Lee, K.; Lee, P. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 487. (h) Lee, J.-Y.; Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 1929. (i) Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 17. (j) Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem. Eur. J.* **2007**, *13*, 5197. (k) Lee, P. H.; Lee, K.; Kang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1139.
10. Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8846.